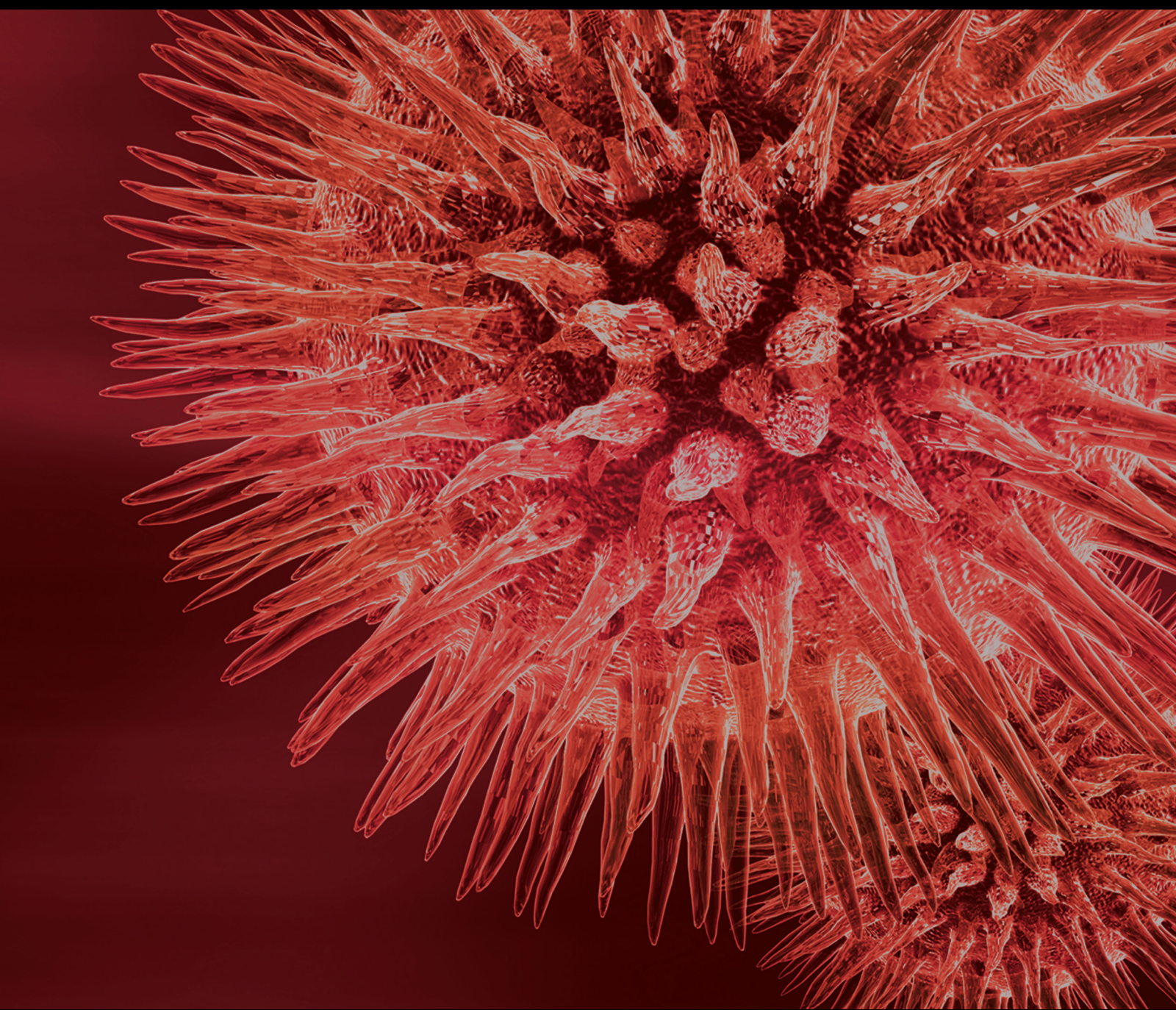
BioMed Research International

Innovative Techniques to Enhance Musculoskeletal Surgery Outcomes

Lead Guest Editor: Berardo Di Matteo
Guest Editors: Elizaveta Kon, Peter Angele, and Christian Lattermann



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Editorial

Innovative Techniques to Enhance Musculoskeletal Surgery Outcomes

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In the last 15 years, orthopaedic practice has been revolutionized by the amazing progresses made in the field of biotechnologies, which led to the introduction of innovative therapeutical approaches aimed at minimizing surgical distress for patients and, at the same time, providing better healing chances for many musculoskeletal diseases [1]. Beside the great enthusiasm for novel strategies represented by the use of biomaterials and biologic agents, such as autologous growth factors [2] and stem cells [3], there has been also an increasing awareness on the necessity of better understanding the mechanisms of pathology, improving our diagnostic skills, and identifying positive and negative prognostic factors [4]. In fact, not only is the "therapeutic success" based on the treatment itself, but it is the result of a more complex interaction of factors: an early diagnosis, a proper timing for starting the treatment, and the specific patient features which could determine either a satisfactory or poor outcome. This multifactorial approach is usually regarded as "patient profiling" and represents the pinnacle of the "personalized medicine" which is the ultimate goal of current research in all medical specialties [5]: providing a treatment "tailored" to the specific needs of the patients in order to maximize the benefit and reduce potential side effects. Therefore, the focus of clinicians has shifted from the pathology as a stand-alone entity to the concept of "pathology within a specific patient": based on this conception, it is not only the disease that changes the "homeostasis" of the patient, but the patient himself can influence the course of the pathology in a favourable or negative manner, depending on his/her particular features [6, 7]. The challenge is always to understand how to take advantage of the "pros" and how to get rid of the "cons."

This was the idea that led us to propose the present special issue, whose title reflects the curiosity of all the guest editors towards the potential ways to enhance the outcomes of musculoskeletal surgery. The title is very broad, and we expected contributions coming from very different areas, ranging from basic traumatology to elective surgery and also preclinical experiments. This was a conscious choice, since we believe that sharing ideas from a wide range of different clinical scenarios could be a winning method to provide fruitful stimuli to the readers, avoiding excessive subspecialization: sometimes to find solutions you have to raise your eyes from the microscope and take a wider look around you. We believe that innovative strategies in one particular field might perhaps be applied in completely different situations, and therefore it would have been interesting to include in the same special issue perspectives coming from basic researchers, traumatologists, spine surgeons, sports medicine surgeons, and so on. We are truly glad to have received such a great interest, which is testified by a total of 15 papers accepted. Looking at the topics proposed in the whole issue, four main areas can be identified: (1) biomarkers and molecular pathways (for early diagnosis or as potential therapeutic target); (2) computer aided surgery and patient-specific implants; (3) biomaterials and biologic agents for tissue regeneration; (4) evaluation of prognostic factors after surgery. All the major fields related to the "personalization"

of the treatment have been covered, with very interesting contributions. Regarding biomarkers and molecular pathways, four papers have been included in the issue: one investigated the role of serum biomarkers in predicting heart-related complications following hip fracture, one dealt with synovial procalcitonin for the detection of periprosthetic joint infection, one focused on ACL reconstructive surgery, and, lastly, there was an interesting review on the role of Wnt-pathway in the pathogenesis of OA. Looking at computer aided surgery and patients' specific implants, we have papers dealing with innovative frames for pelvic fracture stabilization and 3D-printed PEEK hardware. In the field of biomaterials and regenerative medicine we included an animal trial on Achilles tendon collagen scaffold and a clinical trial investigating the potential of PRP in stimulating healing of partial ACL rupture. Considering papers on "prognostic factors," we included one multicentric trial presenting a score to predict tibial fracture healing time, one systematic review on radial head fractures, one retrospective trial investigating the failure predictors in pediatric forearm fractures, and one pilot study which revealed particular histological features of the articular capsule of patients affected by glenohumeral instability.

Perhaps some readers will be bewildered by the variability of the topics included, but we believe this is actually the strength of our issue, which offered a panoramic overview on the many different innovative approaches to the treatment of disparate musculoskeletal conditions. Therefore, it should be considered a starting point for future, more focused insights on specific pathologies, in the attempt of strengthening the conviction that the outcomes of innovative treatments are strictly related to the timing of diagnosis and the patients' intrinsic features. The mere "technological" improvement will not provide better results if not accompanied by the understanding of the disease mechanisms and the factors playing a crucial role in its progress.

Conflicts of Interest

All the guest editors declare that they do not have any conflicts of interest with regard to the content of the special issue. With regard to other disclosures (without any relation to the aforementioned special issue), E. Kon is a consultant for Cartiheal LTD (Israel).

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We would like to thank all the authors whose efforts made the accomplishment of the present special issue possible.

Berardo Di Matteo
Peter Angele
Christian Lattermann
Elizaveta Kon

References

[1] B. Di Matteo, F. Perdisa, N. Gostynska, E. Kon, G. Filardo, and M. Marcacci, "Meniscal Scaffolds - Preclinical Evidence to Support their Use: A Systematic Review," *The Open Orthopaedics Journal*, vol. 9, no. 1, pp. 143–156, 2015.

[2] G. Filardo, E. Kon, B. Di Matteo et al., "Leukocyte-poor PRP application for the treatment of knee osteoarthritis," *Joints*, vol. 1, no. 3, pp. 112–120, 2014.

[3] J. Zellner, G. Pattappa, M. Koch et al., "Autologous mesenchymal stem cells or meniscal cells: what is the best cell source for regenerative meniscus treatment in an early osteoarthritis situation?" *Stem Cell Research & Therapy*, vol. 8, no. 1, 2017.

[4] J. D. King, G. Rowland, A. G. Villasante Tezanos et al., "Joint Fluid Proteome after Anterior Cruciate Ligament Rupture Reflects an Acute Posttraumatic Inflammatory and Chondrodegenerative State," *Cartilage*, p. 194760351879000, 2018.

[5] A. Alyass, M. Turcotte, and D. Meyre, "From big data analysis to personalized medicine for all: challenges and opportunities," *BMC Medical Genomics*, vol. 8, no. 1, 2015.

[6] C. Selmi, E. Kon, M. D. Santis et al., "How advances in personalized medicine will change rheumatology," *Personalized Medicine*, vol. 15, no. 2, pp. 75–78, 2018.

[7] M. Borro, M. Simmaco, A. Aceti et al., "H2020 and beyond: Skip discrepancy between theory and practice of personalized medicine. a position paper by the Italian society of personalized medicine," *Current Pharmaceutical Biotechnology*, vol. 17, no. 10, pp. 926–929, 2016.

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Clinical Study

Use of a Biomimetic Scaffold for the Treatment of Osteochondral Lesions in Early Osteoarthritis

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Guest Editor: Christian Lattermann

The aim of this study is to investigate clinical and radiographic outcomes of a biomimetic scaffold for the treatment of osteochondral knee lesions in patients with early OA. Study population was represented by 26 patients with a mean age of 44 years affected by early OA. Inclusion criteria were two episodes of knee pain for more than 10 days in the last year, Kellgren-Lawrence OA grade 0 or I or II, and arthroscopic findings of cartilage defects. Nineteen patients had a previous surgery, 11 of which were revision surgeries of osteochondral unit. All patients were treated with a biomimetic scaffold with a tri-layered structure of type I equine collagen and magnesium-enriched hydroxyapatite. Clinical outcomes were evaluated using the IKDC, Lysholm, VAS, KOOS, and Tegner scores at baseline and at an average follow-up of 35 months. Magnetic resonance imaging (MRI) was performed at follow-up time in 19 patients. Clinical outcomes showed significant improvement in VAS, Lysholm, IKDC subjective score, and KOOS subscales in 69% of the patients. Complication rate of this cases series was 11%, with no surgical failure, although 31% of patients did not reach a significant improvement and were thus considered as clinical failure. MRI analysis showed integration of the scaffold only in 47% of the patients, with partial regeneration of the subchondral bone. No correlation between clinics and radiological images was found. The use of a biomimetic osteochondral scaffold in the setting of an early OA, alone or associated with other procedures, appeared to be a valid and safe option, able to provide good and stable clinical outcomes with high patient's satisfaction and low complication rate.

1. Introduction

Osteoarthritis (OA) is one of the most common orthopaedic conditions, generally affecting patients over 50 years old, with joint pain and decreased function [1]. This disorder, chronic and degenerative in nature, presents early phases with signs and symptoms that in recent years were classified under the term "early OA" (EOA). EOA, as described by Luyten et al. [2] is characterized by at least two episodes of joint pain for more than 10 days in the last year, radiographic Kellgren-Lawrence classification up to grade 2, and arthroscopic findings of ICRS cartilage defects grade III or IV with softening and swelling of the surrounding cartilage. The main concern of this condition is often the young age of the affected patients, which represents an issue for joint metal replacement. Thus, EOA patients could benefit from a biological treatment approach to restore the articular surface and avoid or at least delay prosthetic resurfacing. In this light, the greatest

challenge is represented by the unfavorable environment characterizing OA joints, which was shown to significantly decrease the potential of traditional chondral and osteochondral regenerative procedure [3, 4]. Thus, surgeons need to consider both the aim to allow a full and prompt return to expected activity and the need to treat the articular cartilage defect with an effective treatment, in the attempt to arrest, or at least delay, the progression of the disease.

OA degeneration involves the entire osteochondral unit. Thus, to address both cartilage and the subchondral bone, biphasic scaffolds have been developed and recently gained increasing credit for the treatment of osteochondral lesions. Several in vitro and in vivo experiments [5–7] showed good tissue formation even without the addition of cells: the scaffold appeared to induce in situ regeneration through cells from bone marrow, leading to the formation of cartilage-like tissues. Moreover, several clinical studies [8–13] demonstrated its feasibility, efficacy, and safety, and good results maintained from short- to medium-term follow-ups. More recently, they were proposed to restore the osteochondral unit also in more complex cases, like tibial plateau fracture [14] and osteonecrosis [15], and even in patients presenting an osteochondral defect in the setting of EOA, with promising preliminary clinical results [16]. Nevertheless, results in such challenging indication for scaffold implantation are still sparse and preliminary.

Thus, the aim of this study was to assess the safety of the procedure, and the clinical and imaging outcomes of a biphasic biomimetic scaffold for the treatment of osteochondral defects in the setting of EOA.

2. Materials and Methods

The study population is represented by patients affected by knee early osteoarthritis (EOA) and treated with an osteochondral scaffold implantation. The inclusion criteria for treatment, according to the criteria defined by Luyten et al. [2], were knee pain with at least two episodes of pain for more than 10 days in the last year, Kellgren-Lawrence grading less than or equal to 2 degrees, and arthroscopic findings of cartilage lesions of III or IV degree of ICRS with at least surrounding softening and swelling of the cartilage. Exclusion criteria were lesions on the tibial plateau, osteochondritis dissecans (OCD), and patients with uncorrected (not treated) lower limb malalignment >5° and instability of the knee. Patients presenting infectious, neoplastic, metabolic, and inflammatory pathologies, as well as those not able to comply with the required postoperative rehabilitation regimen, were also excluded from this study.

All patients have been treated with a biomimetic scaffold with a tri-layered structure that reproduced the osteochondral tissue (MaioRegen, Finceramica SpA, Faenza, Italy). The lower layer consists of a mineralized blend of type I equine collagen (30%) and hydroxyapatite (70%) reproducing the subchondral bone layer. The intermediate layer (tide mark-like) consists of a combination of type I collagen (60%) and hydroxyapatite (40%), whereas the superficial layer consists of type I collagen and has a smooth surface to mimic the cartilage surface.

2.1. Surgical Procedure. The surgical procedure was performed with the patient under general or spinal anesthesia and in the supine position with a pneumatic tourniquet around the proximal thigh. An arthroscopic joint evaluation was performed to confirm the diagnosis of EOA. The defects were exposed through a medial, mini-arthrotomic, paratendineous approach for the medial femoral condyle and trochlea lesions. In case of patellar lesion, a medial parapatellar approach was used; after capsulotomy, the patella was everted in order to visualize and to treat the osteochondral lesion; after implantation, the medial retinaculum of the patella was sutured in order to avoid postoperative patellar maltracking. Regardless of the surgical approach, the chondral defect was prepared with an osteotome and the arthroscopic shaver, by removing the sclerotic subchondral bone layer. A 7 mm deep lodging with perpendicular sides was created to allow for press-fit fixation of the implant [8]. Stability was then visually and manually tested by cyclic flexion-extension of the knee, both before and after tourniquet removal. If additional stability was required, a modified surgical technique was used, applying fibrin glue to cover the scaffold surface and the host-scaffold interface while avoiding the presence of fibrin glue between the bottom of the scaffold and subchondral bone. Fibrin glue can protect the superficial layer, which is the most susceptible to the proinflammatory factors of the joint environment. However, cases with significant synovial inflammation were considered contraindicated for surgery.

2.2. Post-Surgery Rehabilitation and Evaluation. Patients were hospitalized for an average of 3 days and maintained the knee in full extension with a brace for 7 days. Then patients started the rehabilitation program based on the progressive recovery of range of motion (ROM), quadriceps strength, and the weight bearing according to the associated surgery and the location of the chondral defect treated. Overall, partial weight bearing was allowed at 6 weeks for 2 weeks in cases of femorotibial lesion treated, whereas partial weight bearing was allowed at 2 weeks for 2 weeks in cases of patellofemoral lesion treated. Proprioceptive exercises began at full weight bearing recovery.

Patients were evaluated at a mean follow-up of 35 months. The clinical outcome was evaluated using the International Knee Documentation Committee score (IKDC) [17], Lysholm score [18], Visual Analogue Scale (VAS) [19], Knee injury and Osteoarthritis Outcome Score (KOOS) [20], and Tegner score for preoperatory (baseline status) and follow-up visit. Any kind of adverse event was recorded at the follow-up visit. The operation was deemed to have failed if the patient needed reoperation because of symptoms due to primary defects. For failed patients, the last clinical evaluation before reoperation was considered for final evaluation. Besides surgical failures, patients without a clinically significant improvement (10 IKDC subj points) with respect to the basal evaluation were considered clinical failures [21].

MRI evaluation was performed using a 1.5-T superconducting magnet (General Electric Co, Fairfield, Connecticut) with a dedicated quadrature detection knee coil (Quadknee; diameter, 18 cm). The following sequences were used for graft

evaluation: sagittal fast spin echo, proton density weighted with fat saturation, sagittal dual fast spin echo T2 weighted and proton density weighted, and axial fast imaging employing steady-state acquisition, axial 3-dimensional gradient echo with fat suppression and axial fast spin echo, and proton density weighted with fat saturation. The MOCART scoring system [22] was applied for the evaluation of the grafts. All imaging evaluations were blindly performed by an orthopaedic surgeon and a musculoskeletal radiologist experienced in cartilage regeneration procedures. After an initial independent assessment, all images were reviewed in consensus.

2.3. Statistical Methods. All continuous data are expressed in terms of mean ± SD, and categorical variables are expressed as proportions or percentages. The Kolmogorov Smirnov test was performed to test normality of continuous variables. Repeated Measures GLM with post hoc Sidak correction for multiple comparisons was performed to compare normally distributed scores at the different follow-up times. The Friedman nonparametric test with Wilcoxon Test post hoc test with Holm correction for multiple comparisons was performed to compare not normally distributed scores at the different follow-up times. The ANOVA test was performed to assess the between-group differences of continuous and normally distributed and homoscedastic data; the Mann Whitney test was used otherwise. The Spearman rank Correlation was used to assess correlations between scores and continuous data. Fisher's exact test was performed to investigate the relationships between grouping variables [23]. The analysis on the MRI findings was evaluated by the Monte Carlo method for small samples. For all tests $p<0.05$ was considered significant.

3. Results

The study group consisted in 26 cases (18 males, 8 females). Mean age was 43.8 ± 11.2 years and mean BMI was 27.3 ± 4.3; 15 patients were affected on the right knee and 11 on the left knee, and the mean time since symptoms onset was 20.0 ± 14.9 months; 18 patients presented a IV degree and 8 patients a III degree of ICRS chondral lesion, respectively. The sites of the lesions were medial femoral condyle (n=17), trochlea (n=6), and patella (n=3). Etiology was rated as microtraumatic or degenerative in 19 cases and posttraumatic (not acute setting) in 7 cases. Only 9 were active amateur sport patients. Nineteen patients had at least one previous surgery, 11 of which related to chondral or osteochondral categories. In particular, 2/3 patients with patellar lesions had undergone previous surgical procedures (3 and 7 surgeries, respectively). Most of the patients (n=18) had undergone one or more associated surgical procedures: 9 tibial osteotomies and 1 femoral osteotomy, 5 patellar realignments, 2 medial meniscal transplantations, 2 ACL reconstructions, 2 synovial debridements, 1 microfracture (in another site), and 1 medial and 1 lateral meniscectomy.

At follow-up VAS score showed a marked reduction in pain, decreasing from a mean of 67.5 ± 30.3 points preoperatively to mean 36.4 ± 25 points at the follow-up ($p < .0005$) (Figure 1). Lysholm Knee mean score increased from 44.1 ± 23.2 preoperatively to 73.4 ± 18.5 postoperatively ($p < .0005$) (Figure 2). IKDC subjective score showed an improvement in the mean scores, from 36.2 ± 20.5 to 57.0 ± 18.2 ($p < .0005$) (Figure 3), and KOOS score as well showed a significant improvement in all subscales: KOOS Pain from 56.3 ± 27.4 to 78.0 ± 17.0 ($p < .0005$), KOOS Symptoms from 61.9 ± 24.3 to 72.5 ± 15.6 ($p = .006$), KOOS ADL from 60.6 ± 25.0 to 81.7 ± 17.9 ($p < .0005$), KOOS Sport from 27.5 ± 28.6 to 50.8 ± 28.5 ($p < .0005$), and KOOS QOL from 32.3 ± 25.9 to 47.2 ± 22.8 ($p = .012$) (Figure 4). A lower and not significant improvement was shown for Tegner score, passing from 3.8 ± 1.7 to 4.4 ± 1.3 at follow-up ($p = .088$), without reaching the preinjury level of 6.2 ± 2.0 ($p < .0005$).

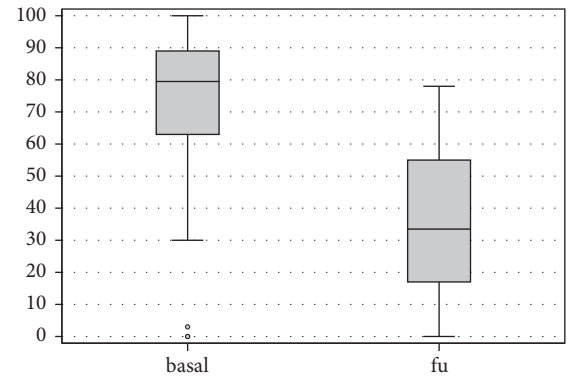

Figure 1: VAS score at basal level and at final follow-up.

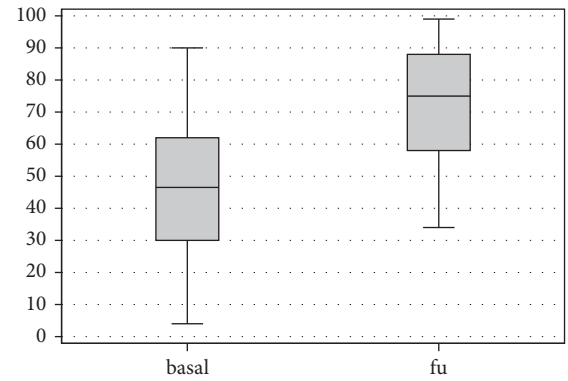

Figure 2: Lysholm score at basal level and at final follow-up.

Previous surgical procedures were found to be significantly correlated with a worse outcome in KOOS pain ($p = .025$), KOOS sport ($p = .036$), KOOS QOL ($p = .030$), and IKDC ($p = .038$). No significant statistical correlation was found between clinical outcomes and patients sex, age, BMI, preoperative pain duration, smoking, sport activity, lesion location, and combined surgery.

Complication rate of this cases series was 11%, being represented by 1 case of scaffold resorption and 2 cases of joint stiffness (1 CFM and 1 trochlea); the latter patients underwent a second surgery for arthroscopic arthrolysis. No patient failed according to the surgical definition, while considering

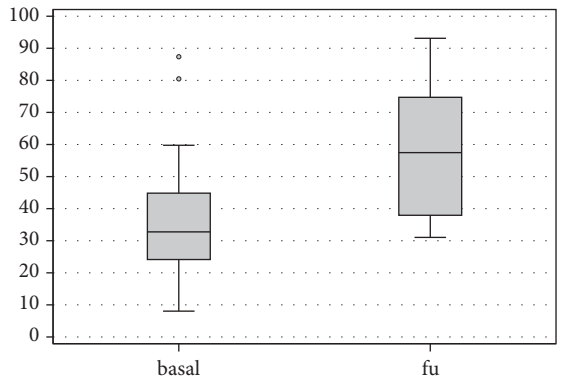

Figure 3: IKDC subjective outcome at basal level and at final follow-up.

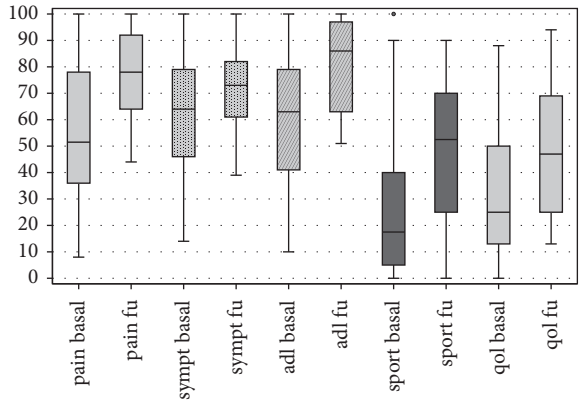

Figure 4: KOOS subscales at basal level and at final follow-up.

clinical failures only 69.2% of patients reached a clinical significant improvement evaluated with the IKDC subjective score and 30.8% of patients did not reach a significant improvement and were thus considered as clinical failure.

Finally, 19 knees were evaluated with high resolution MRI at follow-up. The MOCART evaluation showed a complete filling of the cartilage area in 63.2% of the lesions, complete integration of the graft in 47.4% of cases, intact repair tissue surface in 31.6% of the cases, homogeneous structure of the repair tissue in 42.1% of cases, and iso-intense graft signal intensity score with the adjacent native cartilage in 64.8% of the cases in both dual T2-FSE and 3D-GE-FS sequences. Moreover, the subchondral bone appearance was considered normal in 42.1%, whereas the lamina was not intact in all the cases. Finally, adhesions and effusion were shown in 26.3% and 57.9% of the cases, respectively. The mean total MOCART score was 65.0 ± 16.4. No correlation was found in this series between MOCART variables and the clinical findings.

4. Discussion

The most important finding of the present study is that the treatment with an osteochondral biomimetic scaffold in patients affected by EOA provides symptoms relief and function improvement at mid-term follow-up.

The clinical utility of osteochondral scaffold implantation has been previously established in a setting of nonosteoarthritic joints with focal chondral defects [8–13]. Evidence has been provided also on its use for more complex cases which entail a progressive degenerative joint environment, like tibial plateau fractures [14], and spontaneous osteonecrosis of the knee [15]. Nevertheless, there are still few evidences about the possibility to treat with success an osteochondral lesion in an already degenerated joint. Other regenerative treatments, like autologous chondrocyte implantation and matrix-assisted autologous chondrocyte transplantation, have shown less satisfactory results when applied to degenerative lesions or OA, with a high rate of failures at mid-term follow-up [3, 24]. The reason could be found in some preclinical evidences. In fact, the cytokines produced by the chondrocytes near the implant and the altered joint environment might cause dedifferentiation or apoptosis of the implanted bioengineered scaffold seeded with cells, and this might affect the results [25]. The intra-articular changes taking place in OA processes, which cause pain and effusion due to the presence of synovitis, matrix degradation, and subchondral bone changes, represent unfavorable conditions for tissue regeneration, as supported by some preclinical studies. In an animal model on goats, Saris et al. [26] showed a negative influence of a disturbed intra-articular environment on the cartilage formation, with decrease of histological, biochemical, and macroscopic parameters after tissue engineering. Similarly, Ozsoy et al. [27] showed in an experimental osteochondral defect model in rabbits a poorer outcome related to the disturbed homeostasis and the negative effects in chronic degenerative stages. Moreover, Rodrigo et al. [28] showed that the synovial fluid from the knees of patients with chronic cartilage lesions may exert an inhibitory effect, causing a negative healing environment which may impair chondrogenesis. Furthermore, tissue engineering applied to the treatment of articular degenerative lesions presents some additional problems: healthy tissues are key to provide stable sides for the implant, whereas in a degenerative process the surrounding areas may be involved, thus limiting the stability and integration of the graft.

On the other hand, some authors showed that regenerative procedures may still produce satisfactory results also in joints affected by degenerative changes. Hollander et al. [29] observed tissue regeneration even for implants in OA joints, and laboratory studies confirmed the potential usefulness of regenerative procedures in joints with degenerative lesions, even when the OA process has already started [30, 31], thus suggesting that OA does not completely inhibit the regeneration process, justifying a possible clinical use [30]. Nowadays, the only study reporting clinical results of an osteochondral scaffold in the EOA setting [16] reported a significant improvement at short-term follow-up in 23 patients diagnosed with EOA after failure of conservative management, with best results obtained for patients younger than 40 years. However, those age-related conclusions have to be considered with caution, since it has been proven that the influence of age could be related only on a score bias, as shown by a recent study where score standardization led to this difference to become not significant [32], opening to the

possibility to address such osteochondral lesions also in older patients.

The cohort of 26 patients analyzed in the current study demonstrated a significant improvement between pre- and postoperative score evaluated with VAS, IKDC, KOOS, and Lysholm scores, proving a satisfactory subjective outcome in patients regardless of age. The Tegner score showed instead a not significant improvement. This could be partially explained considering that the study population suffered from a chronic condition that led to surgery after several years, in which the activity level was already lower than presymptoms levels; moreover, as the time passed, the same patients would physiologically perform at a lower intensity simply due to aging, therefore providing a worst outcome. Data gathering about complications and adverse effects was wide and comprehensive, both in the perioperative timeframe and at the follow-up trough analysis of the medical records. A complication rate of about 11% was found, represented by one case of resorption of the scaffold and two cases of joint stiffness requiring new surgery. Similar results were obtained by other study groups [33, 34]. No surgical failures were recorded during study follow-up, but 30% of these patients did not show a clinically significant improvement after treatment, which should be considered when considering this treatment indication for EOA patients [3].

This study described for the first time the MRI evaluation of the use of this biomimetic osteochondral scaffold in a EOA setting, showing less favorable results with respect to what was observed clinically: although imaging results did not correlate with the clinical outcome, only half of the patients showed complete graft integration and only one-third intact repair tissue surface. Moreover 26% and 58% of adhesion and effusion are higher rates compared to what was reported in the literature. To this regard the literature actually provides contrasting evidence. In a pilot study on 28 patients [33], the 2-year follow-up showed complete filling of the defect and integration of the border zone in 70% of the lesions, but subchondral lamina and bone were intact only in a minority of cases, not correlating with the good clinical results, and suggesting that MOCART score is not so reliable for the evaluation of the osteochondral unit as it is for the chondral layer alone. In another study by the same group, the total MOCART score of 45 cases was stable between 12 and 24 months of follow-up (72.9 ± 13.6 and 70.8 ± 13.2, respectively), and again no correlation was found between MOCART total score and the clinical parameters [16]. Different results have been published more recently by Christensen et al. [34]; using specific acquisitions and software algorithms they reported absence of defect filling, integration, and subchondral healing/restoration, utilizing MRI but also CT evaluation, despite positive clinical outcomes. The contrast about imaging and clinical results, and the absence of correlation with clinical outcomes, could be explained in consideration of the fact that current MRI scoring systems were developed for the evaluation of the chondral layer and therefore have lower specificity and sensibility in evaluating a complex organ as the osteochondral unit. Moreover, the most specific MRI acquisitions are not standard nor of easy interpretation, nor economic or available everywhere, and this can create several difficulties in comparing results of different papers. CT imaging could be suitable for the subchondral bone but fails in the needed goal of properly addressing both cartilage and subchondral bone with the same accuracy and efficacy. While the imaging findings show the limits of this osteochondral regenerative solution, especially in the EOA setting, further studies are needed to understand the significance of this findings in terms of clinical outcome.

This study presents some limitations: first of all, the small number of patients analyzed, although being the largest survey described in the literature on EOA, limits the significance of the results, being probably the reason why no correlation was found between patients' characteristics and clinical outcomes. Secondarily, such a brief follow-up, despite being sufficient to prove a clinical improvement, is obviously not optimal to evaluate the survivorship of the implant in this kind of challenging joints, which face a high risk of prosthetic replacement. Moreover, the high number of combined procedures may further jeopardize the results of the scaffold. However, knees affected by EOA are only seldom affected by a mere cartilage issue, whereas the large majority of EOA knees are affected by complex morbidity, like axial deviation, instability, meniscal lesions, etc. Thus, the patients documented in this study reflect those found in the common clinical practice. All comorbidities have to be addressed to increase the possibility of a positive outcome. Such combined biological and mechanical approach already demonstrated good results at short/medium follow-up in patients affected by unicompartmental OA eligible for prosthetic resurfacing [35–37]. The safety of performing multiple combined surgeries was further underlined in this study, where also patients with previous and combined surgeries achieve a marked clinical improvement with absence of short-term surgical failures or severe adverse events. While future biomaterial/technical improvement could further improve the potential of osteochondral implants, this treatment approach proved to be useful and could be considered a suitable option to address osteochondral lesions in patients affected by EOA.

5. Conclusion

The use of a biomimetic osteochondral scaffold in the setting of an EOA, alone or associated with other procedures, appeared to be a valid and safe option, able to provide good and stable clinical outcomes with high patient's satisfaction and low complication rate. Further studies on larger cohorts and with longer follow-up are need to better understand the potential of this scaffold and, of particular importance in the EOA setting, the efficacy in delaying prosthetic replacement.

Data Availability

The clinical and radiological outcome data used to support the findings of this study are restricted by the Ethic Committee in order to protect patients' privacy. Data are available from the corresponding author for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

Giuseppe Filardo received institutional support from Finceramica Faenza Spa (Italy), Fidia Farmaceutici Spa (Italy), CartiHeal (2009) Ltd (Israel), EON Medica SRL (Italy), IGEA Clinical Biophysics (Italy), BIOMET (USA), and Kensey Nash (USA).

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References

[1] J. W. J. Bijlsma, F. Berenbaum, and F. P. J. G. Lafeber, "Osteoarthritis: an update with relevance for clinical practice," *The Lancet*, vol. 377, no. 9783, pp. 2115–2126, 2011.

[2] F. P. Luyten, M. Denti, G. Filardo, E. Kon, and L. Engebretsen, "Definition and classification of early osteoarthritis of the knee," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 20, no. 3, pp. 401–406, 2012.

[3] G. Filardo, F. Vannini, M. Marcacci et al., "Matrix-assisted autologous chondrocyte transplantation for cartilage regeneration in osteoarthritic knees: results and failures at midterm follow-up," *The American Journal of Sports Medicine*, vol. 41, no. 1, pp. 95–100, 2013.

[4] L. de Girolamo, E. Kon, G. Filardo et al., "Regenerative approaches for the treatment of early OA," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 24, no. 6, pp. 1826–1835, 2016.

[5] E. Kon, M. Delcogliano, G. Filardo et al., "Orderly osteochondral regeneration in a sheep model using a novel nano-composite multilayered biomaterial," *Journal of Orthopaedic Research*, vol. 28, no. 1, pp. 116–124, 2010.

[6] E. Kon, A. Mutini, E. Arcangeli et al., "Novel nanostructured scaffold for osteochondral regeneration: Pilot study in horses," *Journal of Tissue Engineering and Regenerative Medicine*, vol. 4, no. 4, pp. 300–308, 2010.

[7] A. Tampieri, M. Sandri, E. Landi et al., "Design of graded biomimetic osteochondral composite scaffolds," *Biomaterials*, vol. 29, no. 26, pp. 3539–3546, 2008.

[8] E. Kon, G. Filardo, A. Di Martino et al., "Clinical results and MRI evolution of a nano-composite multilayered biomaterial for osteochondral regeneration at 5 years," *The American Journal of Sports Medicine*, vol. 42, no. 1, pp. 158–165, 2014.

[9] F. Perdisa, E. Kon, A. Sessa et al., "Treatment of Knee Osteochondritis Dissecans With a Cell-Free Biomimetic Osteochondral Scaffold: Clinical and Imaging Findings at Midterm Follow-up," *The American Journal of Sports Medicine*, vol. 46, no. 2, pp. 314–321, 2018.

[10] E. Kon, G. Filardo, M. Brittberg et al., "A multilayer biomaterial for osteochondral regeneration shows superiority vs microfractures for the treatment of osteochondral lesions in a multicentre randomized trial at 2 years," *Knee Surgery, Sports Traumatology, Arthroscopy*, pp. 1–12, 2017.

[11] F. Perdisa, G. Filardo, A. Sessa et al., "One-Step Treatment for Patellar Cartilage Defects with a Cell-Free Osteochondral Scaffold: A Prospective Clinical and MRI Evaluation," *The American Journal of Sports Medicine*, vol. 45, no. 7, pp. 1581–1588, 2017.

[12] M. Delcogliano, A. Menghi, G. Placella et al., "Treatment of osteochondritis dissecans of the knee with a biomimetic scaffold. A prospective multicenter study," *Joints*, vol. 2, no. 3, pp. 102–108, 2014.

[13] M. Berruto, M. Delcogliano, F. De Caro et al., "Treatment of large knee osteochondral lesions with a biomimetic scaffold: Results of a multicenter study of 49 patients at 2-year follow-up," *The American Journal of Sports Medicine*, vol. 42, no. 7, pp. 1607–1617, 2014.

[14] E. Kon, G. Filardo, G. Venieri, F. Perdisa, and M. Marcacci, "Tibial plateau lesions. Surface reconstruction with a biomimetic osteochondral scaffold: Results at 2 years of follow-up," *Injury*, vol. 45, no. 6, pp. S121–S125, 2014.

[15] M. Berruto, P. Ferrua, F. Uboldi et al., "Can a biomimetic osteochondral scaffold be a reliable alternative to prosthetic surgery in treating late-stage SPONK?" *The Knee*, vol. 23, no. 6, pp. 936–941, 2016.

[16] A. Di Martino, E. Kon, F. Perdisa et al., "Surgical treatment of early knee osteoarthritis with a cell-free osteochondral scaffold: Results at 24 months of follow-up," *Injury*, vol. 46, pp. S33–S38, 2015.

[17] J. J. Irrgang, A. F. Anderson, A. L. Boland et al., "Development and validation of the international knee documentation committee subjective knee form," *The American Journal of Sports Medicine*, vol. 29, no. 5, pp. 600–613, 2001.

[18] Y. Tegner and J. Lysholm, "Rating systems in the evaluation of knee ligament injuries," *Clinical Orthopaedics and Related Research*, vol. 198, pp. 43–49, 1985.

[19] U.-D. Reips and F. Funke, "Interval-level measurement with visual analogue scales in internet-based research: VAS generator," *Behavior Research Methods*, vol. 40, no. 3, pp. 699–704, 2008.

[20] E. M. Roos, H. P. Roos, L. S. Lohmander, C. Ekdahl, and B. D. Beynnon, "Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 28, no. 2, pp. 88–96, 1998.

[21] G. Filardo, L. Andriolo, F. Balboni, M. Marcacci, and E. Kon, "Cartilage failures. Systematic literature review, critical survey analysis, and definition," *Knee Surgery, Sports Traumatology, Arthroscopy*, 2014.

[22] S. Marlovits, G. Striessnig, C. T. Resinger et al., "Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging," *European Journal of Radiology*, vol. 52, no. 3, pp. 310–319, 2004.

[23] G. Filardo, E. Kon, B. di Matteo, P. Pelotti, A. di Martino, and M. Marcacci, "Platelet-rich plasma for the treatment of patellar tendinopathy: clinical and imaging findings at medium-term follow-up," *International Orthopaedics*, vol. 37, no. 8, pp. 1583–1589, 2013.

[24] G. Filardo, E. Kon, A. D. Martino et al., "Second-generation arthroscopic autologous chondrocyte implantation for the treatment of degenerative cartilage lesions," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 20, no. 9, pp. 1704–1713, 2012.

[25] J. A. Martin and J. A. Buckwalter, "The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repair," *The Journal of bone and joint surgery America*, vol. 85, 2, pp. 106–110, 2003.

[26] D. B. F. Saris, W. J. A. Dhert, and A. J. Verbout, "The discrepancy between old and fresh defects in cartilage repair," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 85, no. 7, pp. 1067–1076, 2003.

[27] M. H. Ozsoy, S. Aydogdu, D. Taskiran et al., "The effects of early or late treatment of osteochondral defects on joint homoeostasis: An experimental study in rabbits," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 17, no. 6, pp. 578–589, 2009.

[28] J. J. Rodrigo, J. R. Steadman, G. Syftestad, H. Benton, and J. Silliman, "Effects of human knee synovial fluid on chondrogenesis in vitro.," *American Journal of Knee Surgery*, vol. 8, no. 4, pp. 124–129, 1995.

[29] A. P. Hollander, S. C. Dickinson, T. J. Sims et al., "Maturation of tissue engineered cartilage implanted in injured and osteoarthritic human knees," *Tissue Engineering Part A*, vol. 12, no. 7, pp. 1787–1798, 2006.

[30] C. Cavallo, G. Desando, A. Facchini, and B. Grigolo, "Chondrocytes from patients with osteoarthritis express typical extracellular matrix molecules once grown onto a three-dimensional hyaluronan-based scaffold," *Journal of Biomedical Materials Research Part A*, vol. 93, no. 1, pp. 86–95, 2010.

[31] T. Tallheden, C. Bengtsson, C. Brantsing et al., "Proliferation and differentiation potential of chondrocytes from osteoarthritic patients.," *Arthritis research & therapy*, vol. 7, no. 3, pp. R560–568, 2005.

[32] G. Filardo, L. Andriolo, A. Sessa et al., "Age is not a contraindication for cartilage surgery: A critical analysis of standardized outcomes at long-term follow-up," *The American Journal of Sports Medicine*, vol. 45, no. 8, pp. 1822–1828, 2017.

[33] E. Kon, M. Delcogliano, G. Filardo, M. Busacca, A. Di Martino, and M. Marcacci, "Novel nano-composite multilayered biomaterial for osteochondral regeneration: A pilot clinical trial," *The American Journal of Sports Medicine*, vol. 39, no. 6, pp. 1180–1190, 2011.

[34] B. B. Christensen, C. B. Foldager, J. Jensen, N. C. Jensen, and M. Lind, "Poor osteochondral repair by a biomimetic collagen scaffold: 1- to 3-year clinical and radiological follow-up," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 24, no. 7, pp. 2380–2387, 2016.

[35] R. E. Rosenberger, A. H. Gomoll, T. Bryant, and T. Minas, "Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older," *The American Journal of Sports Medicine*, vol. 36, no. 12, pp. 2336–2344, 2008.

[36] A. H. Gomoll, R. W. Kang, A. L. Chen, and B. J. Cole, "Triad of cartilage restoration for unicompartmental arthritis treatment in young patients: meniscus allograft transplantation, cartilage repair and osteotomy.," *The Journal of Knee Surgery*, vol. 22, no. 2, pp. 137–141, 2009.

[37] M. Marcacci, S. Zaffagnini, E. Kon et al., "Unicompartmental osteoarthritis: an integrated biomechanical and biological approach as alternative to metal resurfacing," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 21, no. 11, pp. 2509–2517, 2013.

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Clinical Study

Percutaneous Total Endoscopic Resection of Partial Articular Processes for Treatment of Lateral Crypt Stenosis and Lumbar Spinal Stenosis: Technical Report and Efficacy Analysis

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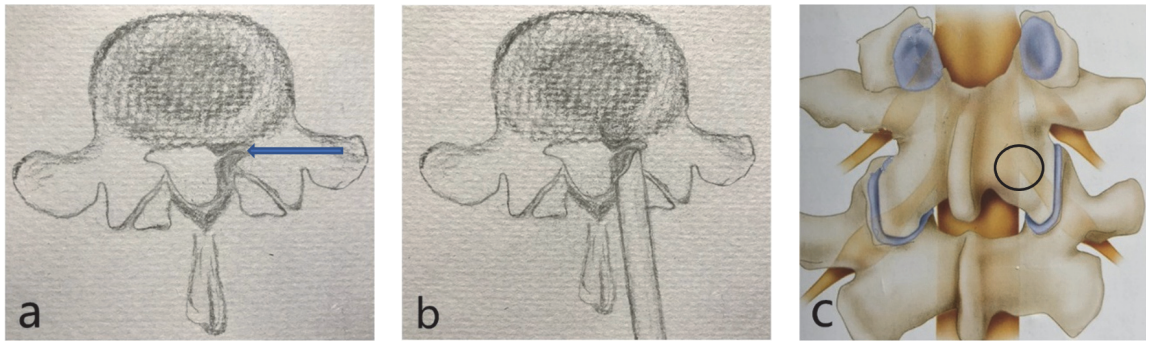
Objective. To observe the clinical curative effect of posterior total endoscopic precision decompression for the treatment of single-segment lateral crypt lumbar spinal stenosis (LSS). *Method*. A total of 27 patients with single-segment LSS satisfying the inclusion criteria were recruited from July 2013 to September 2015. There were 18 cases of unilateral stenosis of the $L_{4\text{-}5}$ segments and 9 cases of unilateral stenosis of the L_5-S_1 segment. All patients were treated via the posterior approach with the precise lateral crypt decompression technique. Precise decompression was performed on the narrow areas causing clinical symptoms. Clinical efficacy was assessed at 3 days, 3 months, 6 months, and 2 years after surgery. Low-back pain and sciatic nerve pain assessed by visual analog scale (VAS) score and the functional Oswestry Disability Index (ODI) were used to evaluate lumbar function, and modified MacNab score criteria were used to investigate long-term efficacy. *Result*. All patients completed the operation successfully, and the follow-up time was 2 years. The VAS score of lumbago was lower after than before surgery (preoperative: 6.96±0.90; postoperative: 2.04±1.02, $P<0.05$). The VAS score of sciatica was also lower after than before surgery (preoperative: 7.19±0.88, postoperative: 1.93±0.92, $P<0.05$), and the ODI was improved at the last follow-up (29.62±4.26) % compared with before surgery (80.07±3.98) %. The MacNab efficacy evaluation showed improvement at the end of the follow-up period: 20 cases were excellent, 6 cases were good, and 1 case was satisfactory, with a good/excellent rate of 96%. No surgical site infections, iatrogenic nerve root injuries, epidural hematomas, or other complications occurred. *Conclusion*. Total endoscopic decompression of posterior facet arthrodesis for the treatment of single-segment lateral crypt LSS has the advantages of safety, reduced recurrence and trauma, and a satisfactory curative effect. This trial is registered with ChiCTR1800015628.

1. Foreword

Lumbar spinal stenosis (LSS) is one of the most common degenerative diseases encountered in spinal surgery. According to the anatomical classification, there are four types of LSS: central, lateral, intervertebral, and intervertebral foramen [1]. The lateral recess type is due to its special anatomical position; located in the upper articular process, the anterior and posterior walls are limited, and the anterior wall is formed by the fibrous ring of the intervertebral disc, while the posterior wall is formed by the small joint [2]. The most common pathological basis of lateral crypt stenosis is hypertrophic osteoarthritis, followed by intervertebral disc fibrosis and endplate osteophyte growth [3, 4] (Figure 1(a)). The lateral recess is located at the entrance of the nerve root into the nerve root canal. Lateral recess stenosis leads to compression of the nerve roots, which is associated with the presence of lumbago and/or sciatica as clinical symptoms. Early-stage patients usually use NSAIDs, physiotherapy, nerve blocks, or epidural steroid injections, along with changes in their lifestyle, multidisciplinary rehabilitation, and other conservative treatments [5]. Surgical treatment is needed for patients in whom conservative treatments are not effective [6]. The purpose of surgical treatment is to decompress the lateral recess and relieve the nerve roots. A variety of surgical procedures have been used to treat lateral recess stenosis, ranging from standard open laminectomy to minimally invasive decompression [7–15]. Traditional treatment methods



(a) (b) (c)

Figure 1: (a) Left lateral crypt stenosis. (b), (c) Operational area of arthroscopic and total endoscopic precision decompression techniques.

mainly focus on complete decompression, such as by opening the laminar window, decompressing the vertebral disc, and removing the intervertebral disc. Sometimes, the ideal therapeutic effect can be achieved by intervertebral fusion or internal fixation [16, 17]. However, total laminectomy decompression of the spinal cord destroys the stability of the spine, and lumbar instability, spondylolisthesis, and chronic low-back pain may occur after surgery [18]. In recent years, minimally invasive techniques to access the lumbar vertebrae, intervertebral disc mirrors, endoscopic techniques, and minimally invasive intervertebral foramen bone graft fusion, among others, have been developed and widely applied in the treatment of LSS and have achieved good clinical effects [19, 20]. Among them, percutaneous endoscopic decompression (PED) is an effective decompression under the endoscope for reduced volume of spinal canal due to degeneration, including the treatment of herniated discs, hypertrophied and ligamentum flavum, and facet joints, narrow lateral recesses, or nerve root canals. PED has gradually become a common treatment method for lumbar spinal canal stenosis [21]. PED technology is mainly based on the narrow area, and the approach can be either via the intervertebral entry or intervertebral orifice. The intervertebral foramen approach can be used to decompress lateral recess stenosis at the intervertebral pore level. There is no effective approach for the decompression of lateral recess stenosis at the pedicle level. At the same time, due to blocking by the high iliac bone in some patients, 20% of patients are not suitable for endoscopic decompression using the intervertebral foramen approach. Because of the special anatomical position of the lateral crypt, it is necessary to remove part of the articular joint to achieve complete decompression endoscopically operation. Additionally, to achieve a vertebral plate gap for endoscopy, a high-speed grinding drill or a laminar rongeur can be used to remove part of the inside edge of the laminar or articular process; the endoscopic operation range is small, and the lateral crypt presents certain difficulties to relieving the stress of this condition. We treated patients with $L_{4\text{-}5}$, L_5-S_1 single-segment lateral LSS by applying posterior facet arthrodesis total endoscopic crypt decompression (Figures 1(b) and 1(c)), and we obtained a good clinical curative effect.

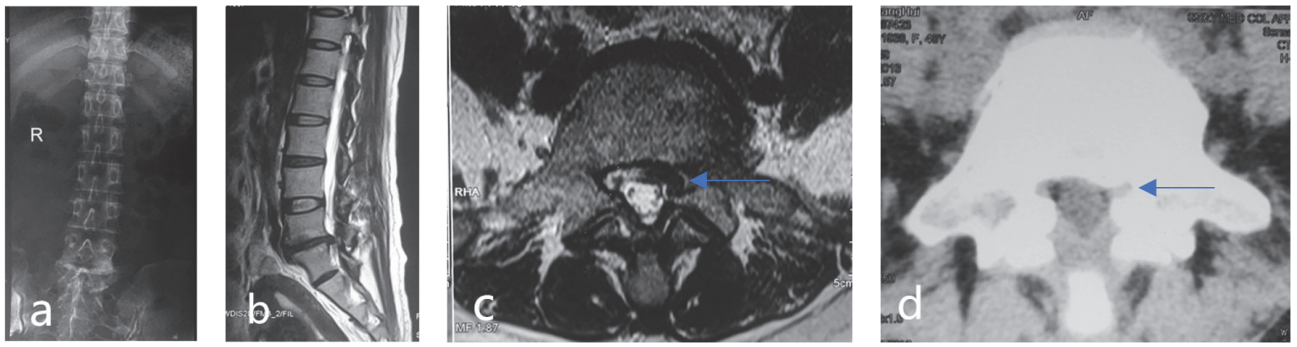
2. Materials and Methods

2.1. General Information. The inclusion criteria were as follows: aged 56 to 73 years presenting with low-back pain, lower-limb radiative pain, muscle weakness, and/or paresthesia; computed tomography (CT) and/or magnetic resonance imaging (MRI) results indicating that the affected segment was unilateral $L_{4\text{-}5}$or L_5-S_1; conservative treatments received for 3 to 6 months.

The exclusion criteria were as follows: cauda equina syndrome leading to complete urinary dysfunction; central spinal canal stenosis; lumbar hyperextension flexion X-rays suggesting lumbar spondylolisthesis or instability in the surgical segment; spinal deformities, spinal fractures, ankylosing spondylitis, spinal tuberculosis, spinal infection, or spinal tumors; symptoms of cervical spondylosis; coagulation dysfunction; and abnormal mental behavior.

A total of 27 patients were enrolled according to the inclusion and exclusion criteria. There were 19 males and 8 females aged 56 to 73 years, with an average age of 61.1 years. There were 18 cases involving the $L_{4\text{-}5}$ segments and 9 cases involving the single side of L_5-S_1. The 27 patients showed low-back pain and sciatica. Twenty-one patients had leg sensory disorders. Lower-extremity muscle weakness was observed in 5 patients, and 1 patient showed decreased tendon reflexes (Figure 2).

2.2. Surgical Methods. Continuous epidural anesthesia was applied to patients in the prone position. Intraoperative X-ray fluoroscopy was used to locate the lesion segment. The center of the articular process under the segment of interest or the most obvious site of stenosis was targeted by the puncture needle. X-ray fluoroscopy was used to confirm placement of the puncture needle toward the lower articular process. An approximately 6-mm-long skin incision was made with the guide needle. The guide wire was then inserted into the expansion tube and the work sleeve to the joint process. Imaging examination was used to determine the range of articular resection. During the operation, trephine was used to remove the upper 1/4 of the upper vertebral articular process and the upper vertebral articular process. If necessary, part of the lamina was removed to expand the laminar space.



(a) (b) (c) (d)

FIGURE 2: (a) Preoperative lumbar anteroposterior X-ray. (b), (c) Preoperative sagittal MRI T2-weighted images showing L_5-S_1 intervertebral disc degeneration and the lack of normal adipose tissue surrounding the left nerve root on the horizontal axis. Stenosis of the lateral crypt (arrows). (d) CT of the transverse axis of the lumbar intervertebral disc before surgery showing hyperplastic cohesion of the left facet joint and narrowing of the superior articular process (arrows).

The dilation tube was placed in the endoscopic operating system, and thickened or calcified yellow ligaments were removed, relieving the ventral and dorsal compression of the nerve root in the subarticular process. At the same time, the nerve sheath and dural sac are pulled apart using a working sleeve for complete removal of prominent or bulging disc tissue, followed by ventral nerve root decompression. Then, relaxation of the nerve roots is confirmed, hemostasis is achieved by radiofrequency coagulation, and checks are performed for thermocracking and ruptured fiber ring formation. Complete lateral crypt decompression is then verified, the catheter is removed, and the incision is sutured (Figure 3).

2.3. Postoperative Management and Rehabilitation. On the 2nd day after the operation, the waist circumference was worn to start the exercise. Do not advocate strenuous activities, 1 to 2 weeks for bed rest. Resume daily activities and normal work after 3 to 4 weeks. Avoid heavy physical labor and move, screw, lift heavy objects, etc. during work. Wear waist circumference when going out or getting up in 3 months after surgery; at the same time, the back muscle function exercise was started to avoid the disuse of the waist muscles.

2.4. Clinical and Imaging Indicators. The patients were assessed for low-back pain and leg pain at 3 days, 3 months, 6 months and 2 years after surgery. The Oswestry Disability Index (ODI) was used to evaluate daily behavior, and the modified MacNab score was used to evaluate the clinical effect.

Preoperatively, postoperatively and at 2 years after surgery, the patients were examined in terms of the orthopedics of the lumbar spine and overextended flexion. Two years after surgery, lumbar CT scans were reviewed to evaluate decompression of the lateral recess (Figure 4).

2.5. Statistical Methods. SPSS 18.0 statistical software was used for statistical processing, and the measurement data are presented as $\overline{x} \pm s$. The visual analog scale (VAS) and ODI scores were assessed repeatedly for the analysis of variance. To measure the degree of activity of the surgical segment before and after the operation, repeated measurements were performed for variance analysis. For all tests, the level of significance was in the form of alpha=0.05.

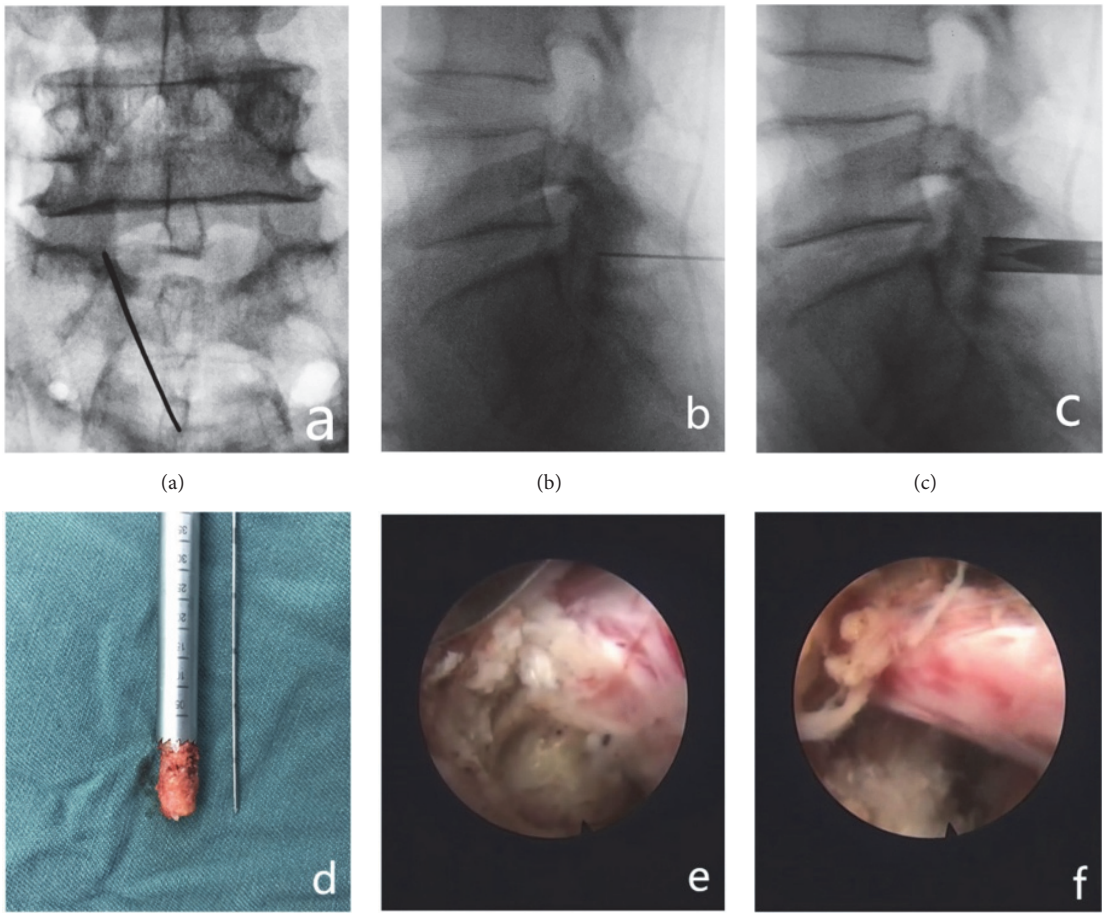
3. Results

The operation time ranged from 90 ~ 130 min, and no patient procedures were converted to open surgery. Patients with low-back pain and sciatica showed significant improvement. The VAS score for lumbago and lower-extremity pain was significantly decreased after surgery ($P<0.01$). There was no significant increase in lumbar pain in patients at the postoperative follow-up, and the postoperative ODI score was significantly improved ($P<0.01$). There were significant differences between the preoperative and all the postoperative scores. The efficacy evaluation by MacNab score showed improvement at the end of the follow-up period, with excellent in 20 cases, good in 6 cases, and fair in 1 case; the good/excellent rate was 96% (Table 1).

The patients in this group experienced no nerve injuries, dural tears, cerebrospinal fluid leakages, epidural hematomas, intervertebral space infections or other intraoperative and postoperative complications. Follow-up at two years showed no asymptomatic recurrence, lumbar instability, or other such symptoms.

4. Discussion

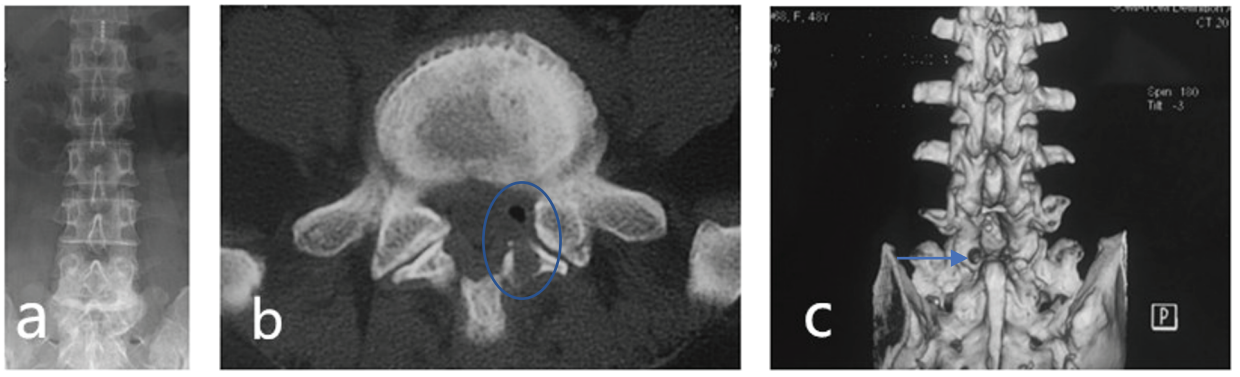
4.1. Overview of LSS and Comparison between Traditional Treatment and Total Endoscopic Techniques. Anatomically, the lumbar spinal canal is divided into two regions, the central canal and the nerve root canal. Stenosis may occur in one or both of these areas at the same time. The nerve root canal is divided into three areas: the lateral crypts, intervertebral foramen, and lateral regions of the foramen. The lateral crypts reported in this article are located in the entrance zone of the nerve root into the root canal. The lateral recess is located



(a) (b) (c)

(d) (e) (f)

Figure 3: (a), (b) Accurate positioning of lateral crypt stenosis with the following articular process in the center. (c) Part of the lower articular process is removed with a circular saw to establish a working channel. (d) Part of the lower articular process bone removed with a circular saw. (e) Herniated disc tissue is exposed outside the shoulder of the nerve root and removed. At the same time, the posterior edge of the vertebral body is removed, and the nerve root is decompressed. (f) The nerve root is dorsally, ventrally, and laterally decompressed thoroughly, allowing it to relax.



(a) (b) (c)

Figure 4: (a) Postoperative lumbar anteroposterior. (b) Posterior lumbar CT showing full left septal decompression. (c) Lumbar vertebra CT + 3D reconstruction showing the articular process sawing window decompression zone (arrows).

Table 1: VAS and ODI scores of preoperative and postoperative low-back pain and sciatica (n = 27, $\overline{x} \pm s$).

	Preoperative	3 days after surgery	3 months after surgery	6 months after surgery	2 years after surgery
Low-back pain VAS score	6.96±0.90	3.52±0.80∗	3.15±0.95∗	2.48±0.94∗	2.04±1.02∗
Lower-limb pain VAS score	7.19±0.88	3.11±0.75∗	2.52±0.75∗	2.04±0.90∗	1.93±0.92∗
ODI	(80.07±3.98) %	(58.67±3.68) %#	(38.81±4.94) %#	(34.37±3.72) %#	(29.62±4.26) %#

Note: ∗P<0.05 compared with preoperative; #P<0.05 compared with preoperative.

under the upper facet joint. The anterior wall is formed by the annulus fibrosus of the intervertebral disc. The posterior wall is formed by the facet joint and is restricted by the anterior and posterior walls. The most common pathological basis of lateral crypt stenosis is hypertrophic facet osteoarthritis, followed by bulging of the intervertebral disc annulus, hyperplasia of the vertebral posterior edge, and hypertrophic calcification of the ligamentum flavum, resulting in decreased lateral crypt height and angle. These conditions cause nerve root compression, resulting in low-back pain, lower-limb dysfunction and other clinical manifestations. Traditionally, lateral crypt LSS is mainly treated through open surgery, usually by laminectomy, laminectomy, or extensive facetectomy. Directly under the excision of the vertebral body with bone callus formation, herniated disc and posterior longitudinal ligament materials are removed to obtain annular nerve root decompression. Open surgery provides a clear view, allowing complete decompression and ideal postoperative symptom relief. However, due to structural damage to the posterior column of the spine after open surgery, some patients need lumbar fusion and internal fixation to maintain spinal stability. According to reports in the literature, the greatest problem with lumbar fusion and instrument fixation is that the incidence of adjacent segment involvement after lumbar fusion is significantly higher than that of nonfusion technique [22]. At the same time, because of the age of some patients, the risk of prolonged anesthesia and surgery cannot be ignored [23, 24]. In addition, the side effects of pulling and stripping soft tissue during the operation can lead to prolonged postoperative recovery periods. With the continuous development and improvement of minimally invasive techniques, endoscopic techniques have gradually become one of the main treatment strategies because of their advantages of reduced trauma and faster postoperative recovery. We used the posterior total endoscopic precise decompression technique to treat lateral recess LSS. Good clinical effects were obtained after the operation. The VAS and ODI scores of patients with low-back pain were significantly better after than before surgery, and their clinical symptoms were continuously relieved during one year of follow-up, with negligible low-back pain and ODI scores. Two years after the operation, the results of the MacNab evaluation indicated that the rate of excellent and good results was 96%.

4.2. The Application of Total Endoscopic Technique in Degenerative LSS. Current studies in the literature report that a transforaminal approach is used in most patients with degenerative lumbar lateral crypt stenosis. The dorsal lateral nerve root compression was relieved by removing the anterior 1/3 of the superior facet and the anterior part of the lower articular process, while removing the joint capsule and the posterior lateral nerve ligamentum of the nerve root. The endoscope can reach the predural space through the enlarged intervertebral foramen and be used to treat the prominent intervertebral disc tissue and the posterior edge osteophytes of the vertebral body to achieve ventral decompression and achieve a good clinical effect. Research shows that decompression through the transforaminal approach will not affect the structural integrity and biomechanical stability of the lumbar motion segment, with no iatrogenic lumbar segmental instability occurring after surgery. For lumbar lateral recess stenosis, both the transforaminal and translaminar approaches can effectively reduce nerve root pressure. However, some patients are affected by high iliac blockage, transverse process hypertrophy, osteophyte hyperplasia and other factors, especially in the L_5-S_1 segment, increasing the difficulty of transforaminal decompression surgery. In addition, because of the inability of the intervertebral foramen approach to treat pedicle lateral stenosis and central spinal stenosis, its range of indications is narrower. The laminar approach can be used to treat central spinal canal stenosis, using the laminar approach may be more reasonable and simpler. During the surgical procedure, we found that precision decompression technology is crucial in the treatment of lateral crypt LSS. During the percutaneous endoscopic operation, because the internal diameter of the working channel of the foramen mirror is only 6 mm, the available intraoperative space is extremely limited. To ensure the same clinical efficacy as open surgery, we must be able to accurately locate the surgical site before surgery in order to accurately target the nerve root compression site. If the position of interest cannot be accurately located, once the working channel is placed, it is difficult to change the surgical area by adjusting the working channel, and the operation becomes very difficult.

4.3. Characteristics and Advantages of the Transarticular and Translaminar Approaches. The lateral recess is also called the "Lee entrance zone." The nerve roots exit the dural sac here and extend outward under the top facet; arthritis of the facet joints is the most common cause of lateral crypt stenosis. For patients with single-stage lateral crypt LSS, which approach should be used: translaminar or transarticular? The lower margin of the vertebral plate and the articular bone were removed using a high-speed grinding drill under fully endoscopic conditions. Operation of the microscopic rongeur is relatively simple and the same as in open surgery, but it greatly reduces the efficiency of the surgery. The use of high-speed intraoperative drilling also presents certain problems. For example, debris generated

during high-speed drilling may lead to a blurred view in the microscope, more bleeding occurs when the cancellous bone is polished, the handle is longer, and the stability of the high-speed grinding bit is reduced. Another potential disadvantage is that the operator's judgment of depth requires extensive experience. Due to the special anatomical location and pathological basis of the lateral crypt, this study provides a sufficient theoretical basis for the selection of precise decompression technology for arthrodesis. In the operation, the center of the articular process is positioned with a K-wire, and the ring saw is guided through the K-wire. Under X-ray monitoring, the upper quarter of the inferior facet joint is resected with a circular saw, leaving part of the isthmus and the upper and lower facet arthrosis structures. Isopathic spondylolysis should be avoided. Resection of part of the lower articular process makes the decompression of the lateral recess simpler and more direct and improves the surgical efficiency, which are exactly the differences between the approach in this study and the total endoscopic interlaminar approach to crypt decompression. The surgeon must follow the principle of "minimum trauma" while performing surgical treatment. Intervertebral disc tissue, facet joints, and ligamentum flavum play critical roles in maintaining spinal stability. Thus, surgeons pursue minimally traumatic solutions to clinical problems. Accurate decompression is based on fully endoscopic techniques performed via the interlaminar approach to accurately decompress the area responsible for stenosis. The partial resection of the lower articular process during the operation retained the posterior structure of the spine to a maximum degree, thus maintaining the stability of the lumbar spine, reducing postoperative lumbar instability and facilitating postoperative recovery.

At the beginning of the study, the surgical indications for localized lumbar spinal stenosis were more strictly controlled, a good initial clinical effect was obtained by implementing a full endoscopic precision decompression technique. Our research should consider some potential shortcomings, the number of reported cases was small. To reaffirm the utility of this approach.it needs to be conducted on a larger number of cases. As the research progressed, our team is currently tracking more postoperative cases and comparing them with the results of open spinal decompression surgery.

5. Conclusions

From what has been discussed above, for patients with lateral crypt LSS, the total endoscopic precision decompression technique for posterior facet joint arthrodesis can effectively improve the symptoms of low-back and leg pain in patients. With the features of minimal surgical trauma, direct and safe decompression, rapid postoperative recovery, and satisfactory clinical outcomes, this approach can be used as a surgical method for the treatment of lateral crypt LSS.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

This study has been approved form the Ethics Committee of the Affiliated Hospital of Zunyi Medical College.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors of this manuscript declare that they have no conflicts of interest.

Authors' Contributions

Fujun Wu and Weijun Kong contributed equally to this work.

References

[1] P. S. Issack, M. E. Cunningham, M. Pumberger, A. P. Hughes, and F. P. Cammisa Jr., "Degenerative lumbar spinal stenosis: Evaluation and management," *Journal of the American Academy of OrthopaedicSurgeons* , vol. 20, no. 8, pp. 527–535, 2012.

[2] C. K. Lee, W. Rauschning, and W. Glenn, "Lateral lumbar spinal canal stenosis: Classification, pathologic anatomy and surgical decompression," *The Spine Journal*, vol. 13, no. 3, pp. 313–320, 1988.

[3] C. C. Arnoldi, A. E. Brodsky, J. Cauchoix et al., "Lumbar Spinal Stenosis and Nerve Root Entrapment Syndromes," *Clinical Orthopaedics and Related Research*, no. 115, pp. 4-5, 1976.

[4] W. H. Kirkaldy-Willis, J. H. Wedge, K. Yong-Hing, S. Tchang, V. D. Korompay, and R. Shannon, "Lumbar Spinal Nerve Lateral Entrapment," *Clinical Orthopaedics and Related Research*, no. 169, pp. 171–178, 1982.

[5] J. Lurie and C. Tomkins-Lane, "Management of lumbar spinal stenosis," *BMJ*, vol. 352, 2016.

[6] J. N. Weinstein, J. D. Lurie, T. D. Tosteson et al., "Surgical versus nonoperative treatment for lumbar disc herniation: four-year results for the Spine Patient Outcomes Research Trial (SPORT)," *The Spine Journal*, vol. 33, no. 25, pp. 2789–2800, 2008.

[7] M. A. Boukebir, C. D. Berlin, R. Navarro-Ramirez et al., "Ten-Step Minimally Invasive Spine Lumbar Decompression and Dural Repair Through Tubular Retractors," *Operative Neurosurgery*, p. 1, 2016.

[8] M. Alimi, C. P. Hofstetter, J. M. Torres-Campa et al., "Unilateral tubular approach for bilateral laminotomy: effect on ipsilateral and contralateral buttock and leg pain," *European Spine Journal*, vol. 26, no. 2, pp. 389–396, 2017.

[9] H. M. Mayer, J. List, A. Korge, and K. Wiechert, "Mikrochirurgie bei degenerativer lumbaler Spinalstenose," *Der Orthopäde*, vol. 32, no. 10, pp. 889–895, 2003.

[10] J. N. Katz, S. J. Lipson, M. G. Larson, J. M. McInnes, A. H. Fossel, and M. H. Liang, "The outcome of decompressive laminectomy for degenerative lumbar stenosis.," *The Journal of Bone & Joint Surgery*, vol. 73, no. 6, pp. 809–816, 1991.

[11] A. Herno, O. Airaksinen, and T. Saari, "Long-term results of surgical treatment of lumbar spinal stenosis," *The Spine Journal*, vol. 18, no. 11, pp. 1471–1474, 1993.

[12] C. J. M. Getty, J. R. Johnson, E. Kirwan O'G., and M. F. Sullivan, "Partial undercutting facetectomy for bony entrapment of the lumbar nerve root," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 63, no. 3, pp. 330–335, 1981.

[13] M. W. Fox, B. M. Onofrio, and A. D. Hanssen, "Clinical outcomes and radiological instability following decompressive lumbar laminectomy for degenerative spinal stenosis: A comparison of patients undergoing concomitant arthrodesis versus decompression alone," *Journal of Neurosurgery*, vol. 85, no. 5, pp. 793–802, 1996.

[14] A. J. Caputy and A. J. Luessenhop, "Long-term evaluation of decompressive surgery for degenerative lumbar stenosis," *Journal of Neurosurgery*, vol. 77, no. 5, pp. 669–676, 1992.

[15] A. Benini, "Lumbago and radicular complaints: not always a disc hernia or degenerative stenosis of the spinal canal. A differential diagnosis of infrequent diseases," *Der Orthopäde*, vol. 28, no. 11, pp. 916–921, 1999.

[16] J. Y. Lee, P. G. Whang, J. Y. Lee et al., "Lumbar spinal stenosis," *Instructional course lectures*, vol. 62, pp. 383–396, 2013.

[17] S.-W. Hong, K. Y. Choi, Y. Ahn et al., "A comparison of unilateral and bilateral laminotomies for decompression of L4-L5 spinal stenosis," *The Spine Journal*, vol. 36, no. 3, pp. E172–E178, 2011.

[18] A. Benditz, J. Grifka, and J. Matussek, "Lumbar spinal stenosis: From diagnosis to correct therapy," *Zeitschrift für Rheumatologie*, vol. 74, no. 3, pp. 215–225, 2015.

[19] L. T. Khoo and R. G. Fessler, "Microendoscopic decompressive laminotomy for the treatment of lumbar stenosis," *Neurosurgery*, vol. 51, no. 5, pp. 146–154, 2002.

[20] A. Y. Mogilner, "Quality and Cost-Effectiveness of Interventional Pain Procedures: Minimally Invasive Lumbar Decompression (MILD) as a Paradigm?" *Pain Medicine*, vol. 14, no. 5, pp. 613-614, 2013.

[21] D. S. Kreiner, W. O. Shaffer, J. L. Baisden et al., "An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update)," *The Spine Journal*, vol. 13, no. 7, pp. 734–743, 2013.

[22] C. Ren, Y. Song, L. Liu, and Y. Xue, "Adjacent segment degeneration and disease after lumbar fusion compared with motion-preserving procedures: a meta-analysis," *European Journal of Orthopaedic Surgery and Traumatology*, vol. 24, pp. 245–253, 2014.

[23] J. N. Weinstein, T. D. Tosteson, J. D. Lurie et al., "Surgical versus nonsurgical therapy for lumbar spinal stenosis," *The New England Journal of Medicine*, vol. 358, no. 8, pp. 794–810, 2008.

[24] Y. Smorgick, D. K. Park, K. C. Baker et al., "Single-versus multilevel fusion for single-level degenerative spondylolisthesis and multilevel lumbar stenosis: Four-year results of the spine patient outcomes research trial," *The Spine Journal*, vol. 38, no. 10, pp. 797–805, 2013.

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Review Article

The Role of Wnt Pathway in the Pathogenesis of OA and Its Potential Therapeutic Implications in the Field of Regenerative Medicine

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Introduction. Osteoarthritis (OA) is a degenerative joint disease characterized by articular cartilage degradation, subchondral damage, and bone remodelling, affecting most commonly weight-bearing joints, such as the knee and hip. The loss of cartilage leads to joint space narrowing, pain, and loss of function which could ultimately require total joint replacement. The Wnt/β catenin pathway is involved in the pathophysiology of OA and has been proposed as a therapeutic target. Endogenous and pharmacological inhibitors of this pathway were recently investigated within innovative therapies including the use of platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs). *Methods*. A review of the literature was performed on the PubMed database based on the following inclusion criteria: article written in English language in the last 20 years and dealing with (1) the role of Wnt-β catenin pathway in the pathogenesis of osteoarthritis and (2) pharmacologic or biologic strategies modulating the Wnt-β catenin pathway in the OA setting. *Results*. Evidences support that Wnt signalling pathway is likely linked to OA progression and severity. Its inhibition through natural antagonists and new synthetic or biological drugs shares the potential to improve the clinical condition of the patients by affecting the pathological activity of Wnt/β-catenin signalling. *Conclusions*. While further research is needed to better understand the mechanisms regulating the molecular interaction between OA regenerative therapies and Wnt, it seems that biologic therapies for OA exert modulation on Wnt/β catenin pathway that might be relevant in achieving the beneficial clinical effect of those therapeutic strategies.

1. Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by articular cartilage degradation, subchondral damage, and bone remodelling, affecting most commonly weight-bearing joints such as the knee and hip. Many treatment options are currently available for OA, ranging from conservative to surgical measures and regenerative medicine approaches. Despite wide research efforts on OA, there is a huge unmet need in effective therapies that ultimately change the natural history of the disease. Recently introduced autologous treatments, such as platelet-rich plasma (PRP) and mesenchymal stem cells (MSC), have been largely investigated in orthopaedic surgery and proposed as OA

treatments. The rationale for the use of these biologic products is based on their capability of modulating the joint environment by releasing a series of growth factors and immune-modulatory molecules that could play a beneficial role in reducing the local inflammation and promoting cartilage and synovium anabolism [1]. From a pathogenetic standpoint, cartilage homeostasis and bone remodelling are regulated by a complex network of metabolic pathways and, among these, the Wnt/β-catenin pathway is activated in OA and is emerging as a regulator of tissue repair and fibrosis [2]. It has been hypothesized that PRP may protect chondrocytes activated by IL-1β via inhibiting Wnt/β-catenin signalling [3]. The aim of the present review is to shed light on the current concepts concerning the role of the Wnt/β-catenin pathway in the pathogenesis of OA, and understanding the potential therapeutic implications in the field of regenerative medicine.

2. Methods

A review of the literature was performed on the PubMed database by two independent authors (CE and VND). The research string used was the following:

"((Wnt OR catenin) OR (IL 1 AND Wnt) OR (dkk1 and Wnt)) AND (osteoarthritis treatment OR PRP OR platelet rich plasma OR (MSC AND osteoarthritis))"

The inclusion criteria were in vitro articles written in English language, published in the last 20 years, and dealing with (1) the role of the Wnt-β catenin pathway in the pathogenesis of osteoarthritis and (2) pharmacologic or biologic strategies modulating the Wnt-β catenin pathway in the OA setting.

A total of 168 articles were retrieved: first, the articles were screened by title and abstract and then the full texts of the selected articles were analyzed. Reference lists from the selected papers were also screened and, at the end of the selection process, 14 papers in total were included in the present review. Relevant data were then extracted and collected in a unique database with the consensus of the two aforementioned authors.

3. Results

Of the 14 articles included in this review [3–16] (Tables 1, 2, and 3), ten focused on the molecular mechanism in which OA, Wnt, and endogenous inhibitors are associated [5–14], two on PRP and its potential to modulate the Wnt pathway, and two on new potential pharmacological inhibitors [4, 16]. Most of the studies reported how the Wnt inhibition can be a potential new target for OA treatment and explored how this can improve the clinical outcome of patients. Early investigations of the Wnt/β-catenin pathway modulation with biologicals and regenerative therapies demonstrate promise. However, in the absence of any long-term clinical data in a substantial number of clinical subjects, further study is required to elucidate proof of concept, safety, and efficacy. What emerged from the present review of the literature is an increasing interest in therapeutic approaches to influence this signalling way, especially with PRP, but also with other biologics, and new experimental inhibitors.

3.1. Wnt Canonical and Noncanonical Signalling Pathways: A Comprehensive Synthesis. The Wnt family of proteins includes morphogens associated with embryonic formation, tissue repair, fibrosis, and homeostasis of the bone and joint tissues, among others [4, 17].

Wnt regulates multiple signalling cascades, including one β-catenin–dependent (canonical) and two β-catenin–independent pathways [18]. The Wnt/β-catenin canonical signalling pathway is initiated by the binding of the Wnt proteins to their 7-pass transmembrane Frizzled (Fz) receptors and results in the activation of the central player of the pathway, downstream β-catenin. To activate the canonical signalling pathway, Wnt ligands must bind to both Fz receptors and the coreceptor low-density lipoprotein receptor-related protein (LRP) 5/6. This binding further enables the release of β-catenin from its intracellular binding complex [composed of glycogen synthase kinase-3β (GSK3β), caseine kinase 1-α (CK1α), adenomatous polyposis coli (APC), and Axin2], which in the Wnt-off state phosphorylates and ubiquitinates β-catenin, leading to its degradation in proteasomes [19, 20]. Alternatively, in the Wnt-on state, or when a Wnt ligand is available, Fz receptors and LRP 5/6 are activated upon ligand binding. The receptor occupancy leads to the phosphorylation of LRP 5/6 by Gsk3β and Ck1α in its cytoplasmic region, followed by the recruitment of the dishevelled (DVL)1–3 andaxin [20], which inhibits the destruction of the complex and the stabilization of β-catenin in the cytoplasm. The activated β-catenin translocates into the nucleus where it binds the transcription factors of T cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors, converting them from repressors to activators causing the transcription of targeted genes [21, 22]. The two noncanonical pathways include a Ca^{2+} dependent (transmitted via calmodulin kinase II and protein kinase C) and a planar cell polarity pathway (transmitted via small GTPases) and both contribute to the regulation of cytoskeletal organisation, cell differentiation, and communication [22–24]. Members of the Wnt ligand family, currently including 19 members, activate either the canonical or the noncanonical pathway, according to the receptor they bind to as mentioned above [25]. Ultimately, both β-catenin dependent and independent cascades are demonstrated in the joint where the noncanonical pathways appear to counterregulate the canonical Wnt pathway [26].

The Wnt signalling pathways also undergo strict regulation by different inhibitors, including the family of secreted frizzled related proteins (SFRP) 1-4 and Wnt inhibitor factor (WIF) which act as a soluble scavenger of Wnt ligands [27]; other molecules, such as members of Dickkopf (DKK) family and sclerostin, bind to LRP 5/6 and interfere with the Wnt downstream activation cascade disabling their ability to interact with Wnt-Fz [17, 28], among other inhibitors [28].

The dysregulation of the Wnt canonical pathway is believed to be central to the pathogenesis of cancer, chronic inflammation, and degenerative diseases, and natural inhibitors are thus under investigation for therapeutic purpose. The mechanisms by which the Wnt pathway is influenced by inflammation remain unclear, but its involvement is well established in new bone formation through osteoblast differentiation and function, in the role of TNFα as a major

Table 1: In vitro animal studies included.

Reference	Author	Subjects	Pathway involved	Results
[3]	*J. Wu et al. (2018)*	New Zealand white rabbit chondrocytes	PRP and Wnt/β-catenin	A lower expression level of *WNT1* and *β-catenin* than in another group treated with IL-1β was observed
[4]	*C.Lietman et al. (2018)*	OA-induced murine model synovial fibroblasts and chondrocytes	XAV-939	After it was injected inside the joint, a reduction of the cartilage degradation and synovial inflammation was observed
[6]	*L. Lodewyckx et al. (2012)*	Cell culture (ATDC5) and mouse ribcage and tibial plateau chondrocytes from $Frzb^{-/-}$ and wild type mices	Wnt/β-catenin	Overexpression of *FRZB* coupled with an up-regulation of *aggrecan* and *Col2a1* and down-regulation of *Col3a1* and *Col5a1. FRZB is in strict relationship to Wnt pathway*
[7]	*T. Yuasa et al. (2008)*	New Zealand rabbit articular chondrocytes and guinea pig knee chondrocytes	Wnt/β-catenin	Wnt/beta-catenin signalling is a powerful stimulator of chondrocyte matrix catabolic action and may be part of mechanisms leading to excessive remodelling and degradation of cartilage matrix in age-associated joint pathologies
[8]	*M. Zhu et al. (2009)*	Adult *Col2a1-CreER*^{T2} transgenic mice chondrocytes	β-catenin	Activation of beta-catenin signalling in articular chondrocytes in adult mice leads to the premature chondrocyte differentiation and the development of an OA-like phenotype.
[10]	*Y. Tamamura et al. (2005)*	transgenic mice expressing a fusion mutant protein of β-catenin and LEF (CA-LEF) in nascent chondrocytes	δ-β-Catenin	Increase of proteins involved in cartilage matrix degradation (*MMP-13*, *ADAMTS-4*, *ADAMTS-5* and *RUNX-2*)
[11]	*Shi et al. (2016)*	Sprague-Dawley rats (n=24) articular chondrocytes	WNT5A	Silencing *WNT5A* mRNA prevented degradation of *COL2*
[15]	*Wang D. et al (2018)*	100 BALB/c transgenic mice osteoclasts	PRP/RANKL/Wnt	The study indicated that PRP inhibits osteoclast differentiation through activation of the Wnt pathway and inhibiting RANKL

driver of bone destruction in arthritis, and upregulating the Wnt antagonist Dkk-1 and inhibiting new bone formation. In particular, a prolonged mechanical stress can induce TNF-α but also IL-1 expression in chondrocytes [29], thus suggesting a possible role for both cytokines in OA.

3.2. Role of the Wnt Pathway in OA Development. The pathological processes involved in OA have been widely investigated during the last decades and can be summarized in articular cartilage degradation, subchondral bone remodeling, and synovitis regulated by a complex network of different molecular pathways, including the Wnt/β-catenin signaling network in the homeostasis of bone and cartilage [30–32]. WNTs, a large family of 19 secreted glycoproteins, bind their frizzled (FZD) receptors preventing β-catenin to be phosphorylated and disposed, leading to its accumulation and subsequent migration to the nucleus, where it activates the transcription of different target genes [33].

In OA, this pathway is enhanced in both human and animal models [6–9, 34]. There is an increase in the expression

Table 2: In vitro human studies included.

Reference	Author	Subjects	Pathway involved	Results
[5]	*J. Wu et al. (2017)*	Human chondrocytes from OA (n=57) and healthy subjects (n=6) knees	SOST/Wnt	*SOST* may not have beneficial effects on chondrocytes affected by OA
[9]	*F. Dell'Accio et al. (2008)*	human articular chondrocytes (explants 24 hours after mechanical injury) from 8 patients	Wnt family	A systematic analysis of the Wnt signalling pathway revealed up-regulation of Wnt-16, down-regulation of FRZB, up-regulation of Wnt target genes, and nuclear localization of beta-catenin in injured cartilage
[13]	*S.-G. Gao et al. (2016)*	40 patients with various stages of primary OA cartilage and subchondral bone from tibial plateau	WIF-1	Patients with disease had significantly decreased *WIF-1* levels. Thus, *WIF-1* levels were negatively correlated with the severity of the disease

Table 3: In vitro both human and animal studies included.

Reference	Author	Subjects	Pathway involved	Results
[12]	*L. Chen et al. (2016)*	C57BL/6 transgenic mice and OA human (n=10) articular chondrocytes	EZH2	*EZH2* level was found significantly increased. Pharmacological inhibition of *EZH2* silenced β-catenin signalling pathway and delayed OA progression in mice
[14]	*H. Oh et al. (2012)*	Human and mouse OA model chondrocytes	DKK-1/Wnt	Overexpressing *Dkk-1* by intra-articular injection significantly reduced progression of OA in mice induced with DMM thanks to the inhibition of Wnt-mediated expression of catabolic factors
[16]	*Deshmukh V. et al. (2018)*	Cell culture of bone-marrow-derived human mesenchymal stem cells (hMSCs) and in vivo studies in a rodent acute cruciate ligament tear and partial medial meniscectomy (ACLT + pMMx) OA model	SM04690	SM04690 induced hMSC differentiation into mature, functional chondrocytes and decreased cartilage catabolic marker levels compared to vehicle. A single SM04690 intra-articular (IA) injection was effective in a rodent OA model

levels of different proteins involved in OA and facilitating cartilage matrix degradation, including MMP-13, ADAMTS-4, ADAMTS-5, and RUNX-2C [10]. One of the initial steps of OA physiopathology is the destruction of collagen type II (COL2) and this phenomenon is activated by the upregulation of WNT5A in rat model of OA-chondrocytes. Silencing WNT5A mRNA through delivering small interfering RNA by a lentiviral vector prevented degradation of COL2 [11]. The WNT/β-catenin pathway can also be activated by the induction of the histone methyltransferase enhancer of zeste homologue 2 (EZH2) [12]. EZH2 level was found significantly increased in chondrocytes of OA patients compared to healthy humans, along with high-level expression of MMP-13, ADAMTS-5, and COLX. Pharmacological inhibition of EZH2 silenced β-catenin signaling pathway and delayed OA progression in mice. Evidence from in vivo and in vitro studies indicates that synoviocytes, chondrocytes, and cells from other joint tissues produce cytokines in response to mechanical or oxidative stress or degradation products [35]. The in vitro mechanical loading data support the hypothesis that static compression stimulates the depletion of proteoglycans and damage to the collagen network and decreases the synthesis of cartilage matrix proteins, through the action of reactive oxygen species (ROS) and TNF-α [36], whereas dynamic cyclic compression increases matrix synthetic activity inhibiting IL-1-induced cartilage matrix degradation [37]. IL-1β is a key proinflammatory cytokine that drives OA progression by inducing the expression of cartilage degrading enzymes, such as matrix metalloproteinases (MMPs) [38] and nitric oxide (NO) expression involved in joint damage. NO is highly expressed by OA chondrocytes and cartilage and inhibits both the synthesis of proteoglycan and collagen, activates MMPs, mediates chondrocyte apoptosis, and promotes inflammatory responses, ultimately resulting in a

major catabolic effect. A recent study on human chondrocytes reported that IL-1β decreases the expression of DKK1 and FRZB through the upregulation of nitric oxide synthase, and the activation of Wnt target gene transcription [39].

3.3. Genetic Variability of the Wnt Pathway. The key role of Wnt in joint homeostasis, OA development, and treatment is demonstrated by several studies, which provide evidence of the association between single nucleotide polymorphisms (SNPs) in different genes encoding for proteins of the pathway associated to disease. Variants of the gene of WNT inhibitor sFRP-3/FRZB were associated with OA, reducing its capacity to antagonizing β-catenin [40]. A SNP in the frizzled coreceptor LRP5 prevents the Wnt signaling antagonists SOST and Dkk-1 from binding, inducing spinal OA [41]. More recently, a SNP in WNT1 inducible signaling pathway protein 1 (WISP1), a Wnt-induced protein, has been related to spine OA [42]. Another important consideration about the Wnt/β-catenin pathway comes from a genome-wide analysis of gene expression in knee cartilage affected by OA [43]. Network analysis of RNA-sequencing identified the presence of two different major pathogenetic pathways: one with higher expression of chondrogenic genes and altered expression of chemokine signaling, inflammasome, and innate immune response and the other with a more osteogenic phenotype and altered WNT signaling and mechanoreceptors. This observation may well represent a new starting point for the stratification of patients with OA, based on the phenotype of the disease: i.e., inflammatory and load-related, thus allowing more specific and individualized targeted treatments.

3.4. Endogenous Inhibitors of Wnt. The Wnt pathway is controlled by endogenous antagonists and the expression levels of some of these inhibitors may decrease in parallel with OA progression, thus supporting a link between Wnt pathway and OA pathogenesis.

3.4.1. Sclerostin. Bone tissue cells are actively involved in the development of OA by synthesizing molecules that regulate the joint homeostasis. In particular, osteocytes produce sclerostin, an endogenous Wnt/β-catenin inhibitor that plays an important role in maintaining cartilage integrity, as demonstrated in a study on a murine model of OA [5]. Healthy and OA chondrocytes were incubated with 250 ng/ml sclerostin for 48h and as a result decreased mRNA expression levels of β-catenin have been obtained in both groups. Treatment with sclerostin also inhibited the expression levels of downstream catabolic effector genes RUNX-2, MMP-13, ADAMTS-4, and ADAMTS-5 in healthy chondrocytes. Anabolic factor COL2A1 expression increased with sclerostin challenge and these effects have not been observed in OA chondrocytes compared with the control group, indicating that sclerostin may not have beneficial effects on OA chondrocytes. Chondrocytes were also incubated with 10 ng/l IL-1α for 48h, resulting in increased mRNA expression levels of β-catenin. Therefore IL-1α may control cartilage degradation via overactivation of the WNT/β-catenin pathway.

The protective role of sclerostin through the inhibition of Wnt was also suggested in another study [44]. Sclerostin-knockout mice with DMM had a high OA score, increased expression of aggrecanases and type X collagen, and cartilage damage with inhibition of both WNT canonical and noncanonical pathways.

3.4.2. Wnt-Inhibitor Factor-1. The WNT-inhibitory factor 1 (WIF-1) is a potent extracellular WNT antagonist whose role has been investigated in many trials. Looking at its implications in articular degenerative pathology, it was found that patients with OA had significantly decreased WIF-1 levels compared to control, and WIF-1 levels also negatively correlated with the severity of the disease, as described by Gao et al. who analyzed specimens obtained from 40 patients with various stages of knee OA [13].

3.4.3. Dickkopf. Dkk-1 is also a Wnt antagonist and is activated in osteocytes of the subchondral bone as well as in osteophytes and synovium after 4-6 weeks, as shown in a group of Topgal mice (transgenic mice that express Beta-galactosidase in the presence of the lymphoid enhancer binding factor 1/transcription factor 3 (LEF/TCF) and activated Beta-catenin) with OA induced by meniscectomy. The Dkk-1 expression is also elevated in chondrocytes of control mice but decreased greatly in knees of mice that underwent meniscectomy, starting from week 4 [45]. In a 2012 study, Dkk-1 overexpression by intra-articular injection significantly reduced progression of OA in mice induced with surgical destabilization of the medial meniscus. This was linked to Dkk-1 capacity to inhibit Wnt-mediated expression of catabolic factors, such as MMP-13, showing how Dkk-1 may exert a protective role in OA [14]. But data are conflicting. In 2010 Weng et al. demonstrated that elevated Dkk-1 levels were associated with a high Mankin score and high serum levels of cartilage degradation markers in murine models. Dkk-1 knockdown increased β-catenin but attenuated the expression of inflammatory factors (TLR-4, TLR-9, IL-1β, and TNF-α), the apoptosis regulator Bax, MMP-3, and RANK-L and these data suggest that Dkk-1 knockout produced less cartilage destruction and less subchondral damage in OA knee [46]. Dickkopf-3 (Dkk-3) is also a member of the Dkk family of WNT antagonists and elevated concentrations inhibited the loss of proteoglycan and collagen from cartilage in a model of OA obtained with IL-1β and oncostatin-M [47].

3.4.4. Pharmacological Inhibitors of Wnt. Recently, new potential drugs which selectively inhibit the Wnt pathway have been investigated and in a phase 1 study, the inhibition of Wnt/β-catenin pathway in mice led to a less severe OA. The small-molecule "XAV-939", a tankyrase inhibitor that promotes the phosphorylation of β-catenin leading to its destruction, was intra-articularly injected in a murine model of traumatic OA, obtained by a surgical destabilization of the medial meniscus and a reduced cartilage degradation and synovial inflammation was observed. XAV-939, along with the small-molecule inhibitor Cl13, was also tested in vitro on human synovial fibroblasts and OA-derived chondrocytes and led to an attenuated proliferation and type I collagen synthesis in synovial fibroblasts while in chondrocytes, although there was no affection in proliferation. In further

detail, the Wnt inhibition led to an increased transcription of COL2A1 and PRG4, two genes which are downregulated in the cartilage affected by OA [4]. Another preclinical study evaluated the effectiveness of SM04690, a small-molecule Wnt pathway inhibitor, both in cultured human mesenchymal stem cells (hMSC) and in rodent OA model. The new potential drug induced hMSC differentiation into mature, functional chondrocytes and decreased cartilage catabolic marker levels compared to vehicle. A single SM04690 intra-articular (IA) injection was effective in a rodent OA model, with increased cartilage thickness, evidence for cartilage regeneration, and protection from cartilage catabolism [16].

3.4.5. Biological Therapies and Wnt. PRP is an autologous blood derivate widely used for treating several musculoskeletal diseases and, despite limited evidence, its use has demonstrated promising results also in OA. The effects on OA progression and clinical outcome can be related to the growth factors contained in it. The effects of PRP on the WNT/β-catenin pathway were studied in New Zealand white rabbit chondrocytes. These chondrocytes were cultured, and a group was treated with PRP, whereas another group was treated by IL-1b: concentrations of cartilage degradation proteins CTX-II and COMP were lower in PRP group and less ultrastructural abnormalities and enhanced chondrocyte proliferation were also observed by electron microscopy [3]. Wang et al. reported that PRP inhibits bone degradation via downregulation of osteoclast-associated genes induced by RANKL. A gene expression profile chip analysis revealed the overexpression of WNT/β-catenin pathway genes and an important downregulation of Dkk1, which was demonstrated to enhance osteoclast genesis [48], thus proving conflicting data [15]. Similar to PRP, intra-articular MSC, both derived from the adipose tissue and bone marrow, have been used for the treatment of OA. The therapeutic mechanism involves Wnt pathway and MMP-13, TNF-α, and IL-1β expression [49], even though until now there is a lack of clinical efficacy evidence. As shown by Cassano et al, the growth factors concentrations of whole blood, PRP, and bone marrow concentrate differ significantly [50], and the higher presence of factor such as IL 1β capable of influencing Wnt pathway can potentially change the clinical outcome of OA patients and should be investigated. We strongly encourage further clinical studies associated with a quantitative analysis of the different autologous therapies used in relationship with the WNT/β-catenin pathway.

4. Discussion

In recent years, there has been a growing interest in trying to identify molecular patterns to target as a therapeutic strategy for OA, which represents the most common diseases of musculoskeletal system, involving millions of patients worldwide [51]. In line with the progress made in other fields of medicine, identifying novel pathways has led to the understanding that OA treatment should be multimodal in order to maximize the clinical outcome.

In the present review, we described one of the molecular pathways that has recently come into light for its role in OA development: the Wnt pathway. Wnt family of proteins plays a central role in several signalling cascades that are ultimately involved in increasing the inflammation in the articular environment and stimulating the release of catabolic molecules such as metalloproteinases, which are responsible for cartilage degradation, thus feeding a vicious circle between inflammation and progressive degeneration, which involves all the articular tissues [5, 6, 30, 47]. Interesting in vitro findings have shown that the Wnt pathway is significantly involved in type II collagen degradation and chondrocyte apoptosis, thus justifying the interest in deepening our knowledge of this family of proteins [33–35]. The involvement of Wnt pathway in the pathogenesis of OA has been investigated and described in many animal models, as shown by the present review: it may be argued that species-specific patterns exist that could limit the generalization of results and their application in the human setting but, despite this limitation, the search for strategies to modulate this pathway seems justified and the principal aim is to develop new pharmacological strategies that could stop OA progression at a molecular level. The most common conservative management of OA is by intra-articular injection: in recent times, traditional products such as corticosteroids and hyaluronic acid have been flanked by novel therapies based on immunomodulatory molecules and also on "autologous" derivatives such as PRP and MSCs that have the potential advantage of minimizing side effects due to their autologous nature [52]. Although limited evidence suggests that these biologic products could exert a modulation on the Wnt pathway [3, 45, 46, 53], further studies are needed to understand which mechanisms are involved in Wnt-pathway modulation and how to take full advantage of PRP and MSCs concentrate in the control of OA progression. These powerful biologic products can be regarded as a reservoir of many bioactive molecules: understanding their role and the pathways they can influence will open the possibility of manipulating these products to obtain "autologous" drugs with specific biologic actions within the joint.

There is also the opportunity for new synthetic "on-the-shelf" drugs to be developed, to influence and modulate these specific pathways. In the present review, we described some endogenous inhibitors of Wnt-pathway that could be exploited to this purpose in the near future.

Beyond the aspects related to OA therapy, the awareness on the different molecular pathways involved in OA onset and progression could stimulate further effort in the field of "early diagnosis" and "stratification" of patients affected by OA. At present, clinicians lack any reliable biomarker to identify OA in its early stages and even the definition of OA is too generic, since under this name we include very different pathological entities, ranging from posttraumatic conditions to overload-based OA (i.e., following meniscectomy) to inflammatory-based disease [54]. Each of these entities has peculiar pathogenetic features and, therefore, should be addressed differently. Therefore, the present review shows that molecular targets are among the frontiers of future therapeutic strategies in the treatment of OA: deeper insights into this field will hopefully lead to developing products, as both "intelligent" drugs and autologous derivatives, that could better modulate

specific signalling pathways responsible for the progression of OA. Beyond this, better knowledge of the many molecular cascades involved in inflammatory OA will help in the future basic researchers and clinicians to stratify patients according to the molecular features of their OA, thus offering the possibility of selecting a "personalized" therapeutic approach to their disease [55].

Data Availability

All the data will be available upon motivated request to the corresponding author of the present paper.

Conflicts of Interest

All the authors of the present paper declare no conflicts of interest and nothing to disclose.

Authors' Contributions

Maria De Santis and **Berardo Di Matteo** equally contributed to the present paper and should be considered as first authors.

References

[1] W. Lim, S. H. Park, B. Kim, S. W. Kang, J. W. Lee, and Y. L. Moon, "Relationship of cytokine levels and clinical effect on platelet-rich plasma-treated lateral epicondylitis," *Journal of Orthopaedic Research*.

[2] A. B. Blom, P. L. Van Lent, P. M. Van Der Kraan, and W. B. Van Den Berg, "To seek shelter from the Wnt in osteoarthritis? Wnt-signaling as a target for osteoarthritis therapy," *Current Drug Targets*, vol. 11, no. 5, pp. 620–629, 2010.

[3] J. Wu, J. Huang, X. Qin et al., "Platelet-rich plasma inhibits Wnt/β-catenin signaling in rabbit cartilage cells activated by IL-1β," *International Immunopharmacology*, vol. 55, pp. 282–289, 2018.

[4] C. Lietman, B. Wu, S. Lechner et al., "Inhibition of Wnt/β-catenin signaling ameliorates osteoarthritis in a murine model of experimental osteoarthritis," *JCI Insight*, vol. 3, no. 3, 2018.

[5] J. Wu, L. Ma, L. Wu, and Q. Jin, "Wnt-β-catenin signaling pathway inhibition by sclerostin may protect against degradation in healthy but not osteoarthritic cartilage," *Molecular Medicine Reports*, vol. 15, no. 5, pp. 2423–2432, 2017.

[6] L. Lodewyckx, F. Cailotto, S. Thysen, F. P. Luyten, and R. J. Lories, "Tight regulation of wingless-type signaling in the articular cartilage—subchondral bone biomechanical unit: transcriptomics in Frzb-knockout mice," *Arthritis Research & Therapy*, vol. 14, article R16, 2012.

[7] T. Yuasa, T. Otani, T. Koike, M. Iwamoto, and M. Enomoto-Iwamoto, "Wnt/β-catenin signaling stimulates matrix catabolic genes and activity in articular chondrocytes: Its possible role in joint degeneration (Laboratory Investigation (2008) 88, (264-274) DOI: 10.1038/labinvest.3700747)," *Laboratory Investigation*, vol. 88, no. 4, p. 451, 2008.

[8] M. Zhu, D. Tang, Q. Wu et al., "Activation of β-catenin signaling in articular chondrocytes leads to osteoarthritis-like phenotype in adult β-catenin conditional activation mice," *Journal of Bone and Mineral Research*, vol. 24, no. 1, pp. 12–21, 2009.

[9] F. Dell'Accio, C. De Bari, N. M. Eltawil, P. Vanhummelen, and C. Pitzalis, "Identification of the molecular response of articular cartilage to injury, by microarray screening: Wnt-16 expression and signaling after injury and in osteoarthritis," *Arthritis & Rheumatology*, vol. 58, no. 5, pp. 1410–1421, 2008.

[10] Y. Tamamura, T. Otani, N. Kanatani et al., "Developmental Regulation of Wnt/β-Catenin Signals Is Required for Growth Plate Assembly, Cartilage Integrity, and Endochondral Ossification," *The Journal of Biological Chemistry*, vol. 280, no. 19, pp. 19185–19195, 2005.

[11] S. Shi, Z. Man, W. Li, S. Sun, and W. Zhang, "Silencing of Wnt5a prevents interleukin-1β-induced collagen type II degradation in rat chondrocytes," *Experimental and Therapeutic Medicine*, vol. 12, no. 5, pp. 3161–3166, 2016.

[12] L. Chen, Y. Wu, Y. Wu, Y. Wang, L. Sun, and F. Li, "The inhibition of EZH2 ameliorates osteoarthritis development through the Wnt/β-catenin pathway," *Scientific Reports*, vol. 6, no. 1, 2016.

[13] S.-G. Gao, C. Zeng, J.-J. Liu et al., "Association between Wnt inhibitory factor-1 expression levels in articular cartilage and the disease severity of patients with osteoarthritis of the knee," *Experimental and Therapeutic Medicine*, vol. 11, no. 4, pp. 1405–1409, 2016.

[14] H. Oh, C.-H. Chun, and J.-S. Chun, "Dkk-1 expression in chondrocytes inhibits experimental osteoarthritic cartilage destruction in mice," *Arthritis & Rheumatology*, vol. 64, no. 8, pp. 2568–2578, 2012.

[15] D. Wang, Y. Weng, S. Guo et al., "Platelet-rich plasma inhibits RANKL-induced osteoclast differentiation through activation of Wnt pathway during bone remodeling," *International Journal of Molecular Medicine*, 2017.

[16] V. Deshmukh, H. Hu, C. Barroga et al., "A small-molecule inhibitor of the Wnt pathway (SM04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee," *Osteoarthritis and Cartilage*, vol. 26, no. 1, pp. 18–27, 2018.

[17] H. Clevers and R. Nusse, "Wnt/β-catenin signaling and disease," *Cell*, vol. 149, no. 6, pp. 1192–1205, 2012.

[18] Y. Komiya and R. Habas, "Wnt signal transduction pathways," *Organogenesis*, vol. 4, no. 2, pp. 68–75, 2008.

[19] M. H. van den Bosch, T. A. Gleissl, A. B. Blom, W. B. van den Berg, P. L. van Lent, and P. M. van der Kraan, "Wnts talking with the TGF-β superfamily: WISPers about modulation of osteoarthritis," *Rheumatology*, vol. 55, no. 9, pp. 1536–1547, 2016.

[20] T. P. Rao and M. Kühl, "An updated overview on wnt signaling pathways: a prelude for more," *Circulation Research*, vol. 106, no. 12, pp. 1798–1806, 2010.

[21] J. Yu and D. Virshup, "Updating the Wnt pathways," *Bioscience Reports*, vol. 34, no. 5, pp. 593–607, 2014.

[22] N. Bengoa-Vergniory and R. M. Kypta, "Canonical and non-canonical Wnt signaling in neural stem/progenitor cells," *Cellular and Molecular Life Sciences*, vol. 72, no. 21, pp. 4157–4172, 2015.

[23] R. Sugimura and L. Li, "Noncanonical Wnt signaling in vertebrate development, stem cells, and diseases," *Birth Defects Research Part C: Embryo Today Reviews*, vol. 90, no. 4, pp. 243–256, 2010.

[24] J. B. Wallingford and B. Mitchell, "Strange as it may seem: the many links between Wnt signaling, planar cell polarity, and cilia," *Genes & Development*, vol. 25, no. 3, pp. 201–213, 2011.

[25] M. Majidinia, J. Aghazadeh, R. Jahanban-Esfahlani, and B. Yousefi, "The roles of Wnt/β-catenin pathway in tissue development and regenerative medicine," *Journal of Cellular Physiology*, vol. 233, no. 8, pp. 5598–5612, 2018.

[26] R. Cheng, B. Sun, Z. Liu et al., "Wnt5a suppresses colon cancer by inhibiting cell proliferation and epithelial-mesenchymal transition," *Journal of Cellular Physiology*, vol. 229, no. 12, pp. 1908–1917, 2014.

[27] Q. Tang, H. Zhao, B. Yang et al., *Oncology letters. [Spandidos Publications]*, 2017, https://www.spandidos-publications.com/10.3892/ol.2017.5566.

[28] A Voronkov and S. Krauss, "Wnt/beta-Catenin Signaling and Small Molecule Inhibitors," *Current Pharmaceutical Design*, vol. 19, no. 4, pp. 634–664, 2012.

[29] Q. Liu, X. Zhang, X. Hu et al., "Emerging Roles of circRNA Related to the Mechanical Stress in Human Cartilage Degradation of Osteoarthritis," *Molecular Therapy - Nucleic Acids*, vol. 7, pp. 223–230, 2017.

[30] R. Meliconi, L. Pulsatelli, O. Addimanda, V. Brusi, and B. Pavloska, "New findings in osteoarthritis pathogenesis: Therapeutic implications," *Therapeutic Advances in Chronic Disease*, vol. 4, no. 1, pp. 23–43, 2013.

[31] J. Chun, H. Oh, S. Yang, and M. Park, "Wnt signaling in cartilage development and degeneration," *BMB Reports*, vol. 41, no. 7, pp. 485–494, 2008.

[32] T. F. Day, X. Guo, L. Garrett-Beal, and Y. Yang, "Wnt/β-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis," *Developmental Cell*, vol. 8, no. 5, pp. 739–750, 2005.

[33] D. G. Monroe, M. E. McGee-Lawrence, M. J. Oursler, and J. J. Westendorf, "Update on Wnt signaling in bone cell biology and bone disease," *Gene*, vol. 492, no. 1, pp. 1–18, 2012.

[34] M. Corr, "Wnt-β-catenin signaling in the pathogenesis of osteoarthritis," *Nature Clinical Practice Rheumatology*, vol. 4, no. 10, pp. 550–556, 2008.

[35] M. B. Goldring and M. Otero, "Inflammation in osteoarthritis," *Current Opinion in Rheumatology*, vol. 23, no. 5, pp. 471–478, 2011.

[36] L. Ding, E. Heying, N. Nicholson et al., "Mechanical impact induces cartilage degradation via mitogen activated protein kinases," *Osteoarthritis and Cartilage*, vol. 18, no. 11, pp. 1509–1517, 2010.

[37] P. A. Torzilli, M. Bhargava, S. Park, and C. T. C. Chen, "Mechanical load inhibits IL-1 induced matrix degradation in articular cartilage," *Osteoarthritis and Cartilage*, vol. 18, no. 1, pp. 97–105, 2010.

[38] M. Kobayashi, G. R. Squires, A. Mousa et al., "Role of interleukin-1 and tumor necrosis factor α in matrix degradation of human osteoarthritic cartilage," *Arthritis & Rheumatology*, vol. 52, no. 1, pp. 128–135, 2005.

[39] L. Zhong, S. Schivo, X. Huang, J. Leijten, M. Karperien, and J. Post, "Nitric Oxide Mediates Crosstalk between Interleukin 1β and WNT Signaling in Primary Human Chondrocytes by Reducing DKK1 and FRZB Expression," *International Journal of Molecular Sciences*, vol. 18, no. 11, p. 2491, 2017.

[40] J. Loughlin, B. Dowling, K. Chapman et al., "Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females," *Proceedings of the National Acadamy of Sciences of the United States of America*, vol. 101, no. 26, pp. 9757–9762, 2004.

[41] T. Urano, M. Shiraki, K. Narusawa et al., "Q89R polymorphism in the LDL receptor-related protein 5 gene is associated with spinal osteoarthritis in postmenopausal Japanese women," *The Spine Journal*, vol. 32, no. 1, pp. 25–29, 2007.

[42] T. Urano, K. Narusawa, M. Shiraki et al., "Association of a single nucleotide polymorphism in the WISP1 gene with spinal osteoarthritis in postmenopausal Japanese women," *Journal of Bone and Mineral Metabolism*, vol. 25, no. 4, pp. 253–258, 2007.

[43] J. Soul, S. L. Dunn, S. Anand et al., "Stratification of knee osteoarthritis: two major patient subgroups identified by genome-wide expression analysis of articular cartilage," *Annals of the Rheumatic Diseases*, vol. 77, no. 3, pp. 423-423, 2018.

[44] W. Bouaziz, T. Funck-Brentano, H. Lin et al., "Loss of sclerostin promotes osteoarthritis in mice via β-catenin-dependent and -independent Wnt pathways," *Arthritis Research & Therapy*, vol. 17, no. 1, p. 24, 2015.

[45] T. Funck-Brentano, W. Bouaziz, C. Marty, V. Geoffroy, E. Hay, and M. Cohen-Solal, "Dkk-1-mediated inhibition of Wnt signaling in bone ameliorates osteoarthritis in mice," *Arthritis & Rheumatology*, vol. 66, no. 11, pp. 3028–3039, 2014.

[46] L.-H. Weng, C.-J. Wang, J.-Y. Ko, Y.-C. Sun, and F.-S. Wang, "Control of Dkk-1 ameliorates chondrocyte apoptosis, cartilage destruction, and subchondral bone deterioration in osteoarthritic knees," *Arthritis & Rheumatology*, vol. 62, no. 5, pp. 1393–1402, 2010.

[47] S. J. B. Snelling, R. K. Davidson, T. E. Swingler et al., "Dickkopf-3 is upregulated in osteoarthritis and has a chondroprotective role," *Osteoarthritis and Cartilage*, vol. 24, no. 5, pp. 883–891, 2016.

[48] T. D. Rachner, A. Göbel, P. Benad-Mehner, L. C. Hofbauer, and M. Rauner, "Dickkopf-1 as a mediator and novel target in malignant bone disease," *Cancer Letters*, vol. 346, no. 2, pp. 172–177, 2014.

[49] W. Wang and W. Cao, "Treatment of osteoarthritis with mesenchymal stem cells," *SCIENCE CHINA Life Sciences*, vol. 57, no. 6, pp. 586–595, 2014.

[50] J. M. Cassano, J. G. Kennedy, K. A. Ross, E. J. Fraser, M. B. Goodale, and L. A. Fortier, "Bone marrow concentrate and platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration," *Knee Surgery, Sports Traumatology, Arthroscopy*, 2016.

[51] M. Cross, E. Smith, D. Hoy et al., "The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study," *Annals of the Rheumatic Diseases*, vol. 73, no. 7, pp. 1323–1330, 2014.

[52] E. Kon, G. Filardo, B. Di Matteo, and M. Marcacci, "PRP for the treatment of cartilage pathology," *The Open Orthopaedics Journal* , vol. 7, pp. 120–128, 2013.

[53] P. Tornero-Esteban, A. Peralta-Sastre, E. Herranz et al., "Altered Expression of Wnt Signaling Pathway Components in Osteogenesis of Mesenchymal Stem Cells in Osteoarthritis Patients," *PLoS ONE*, vol. 10, no. 9, p. e0137170, 2015.

[54] L. A. Deveza and R. F. Loeser, "Is osteoarthritis one disease or a collection of many?" *Rheumatology*, vol. 57, no. suppl_4, pp. iv34–iv42, 2018.

[55] S. S. Adkar, J. M. Brunger, V. P. Willard, C.-L. Wu, C. A. Gersbach, and F. Guilak, "Genome Engineering for Personalized Arthritis Therapeutics," *Trends in Molecular Medicine*, vol. 23, no. 10, pp. 917–931, 2017.

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Research Article

Comparison of Synovial Fluid and Serum Procalcitonin for Diagnosis of Periprosthetic Joint Infection: A Pilot Study in 32 Patients

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Background. Periprosthetic joint infection (PJI) remains challenging since a "gold standard" for diagnosis has not yet been established. This study aimed to evaluate the accuracy of synovial fluid procalcitonin (SF-PCT) and serum procalcitonin as a diagnostic biomarker for PJI and to compare its accuracy against standard methods. *Methods*. A prospective cohort study was conducted during 2015–2017 in 32 patients with painful hip or knee arthroplasty who have underwent revision surgery. Relevant clinical and laboratory data were collected. PJI was diagnosed based on the 2013 international consensus criteria. Preoperative blood sample and intraoperatively acquired joint fluid were taken for PCT measurement with a standard assay. Diagnostic accuracy was analyzed by the receiver-operating characteristic curve and the area under the curve (AUC). *Results*. Twenty patients (62.5%) were classified as the PJI group, and 12 (37.5%) were classified as the aseptic loosening group. The median age was 68 years (range 38–87 years). The median values of SF-PCT and serum PCT in the PJI group were both significantly higher than those in the aseptic loosening group: the median serum PCT levels (interquartile range: IQR) were 0.33 ng/mL (0.08-2.79 ng/mL) in the PJI group compared with 0.04 ng/mL (0.03-0.06 ng/mL), and the median SF-PCT levels (IQR) were 0.16 ng/mL (0.12-0.26 ng/mL) in PJI group compared with 0.00 (0.00-0.00 ng/mL) ($p < 0.001$, both). SF-PCT, with a cut-off level of 0.08 ng/mL, had an AUC of 0.87, a sensitivity of 90.0%, a specificity of 83.3%, and a negative likelihood ratio (LR-) of 0.12. Serum PCT, with a standard cut-off level of 0.5 ng/mL, had an AUC of 0.70, a sensitivity of 40.0%, a specificity of 100.0%, and a LR- of 0.60. *Conclusion*. SF-PCT appears to be a reliable test and could be useful as an alternative indicator or in combination with standard methods for diagnosing PJI.

1. Introduction

Periprosthetic joint infection (PJI) is a serious complication after total joint arthroplasty resulting in devastating consequences, such as revision surgery, limb loss, or death [1–3]. However, the diagnosis of this condition is difficult and often delayed, especially with chronic or low-grade infections, due to the lack of "gold standard" examinations and limited accuracy with current diagnostic methods. Therefore, a combination of preoperative and intraoperative markers—including synovial fluid cell count/differential, serum inflammatory markers, cultures, clinical signs, and tissue pathology—are required for PJI diagnosis. Recent studies regarding the new diagnostic techniques demonstrated that some biomarkers—such as procalcitonin (PCT), interleukin-6 (IL-6), and α-defensin—are helpful and a better marker for PJI [4–6]. Moreover, several studies also showed that the synovial fluid biomarkers obtained directly from the infected joint are more reliable and accurate for diagnosing PJI compared to serum biomarkers and other existing tests [7, 8].

PCT, the precursor of calcitonin, is a 116-amino-acid protein produced by the neuroendocrine and the parafollicular cells of the thyroid. Serum PCT level is generally very low (< 0.05 ng/mL) in healthy subjects [9], but specifically elevates in bacterial and fungal infections [10]. It is also unresponsive or only mildly reactive to aseptic inflammation and viral infection [11]. Therefore, numerous studies have

Table 1: Definition for periprosthetic joint infection by International Consensus Group.

Periprosthetic joint infection (PJI) is present when one major criterion exists or when three of five minor criteria exist	
Major criteria	(1) Two positive periprosthetic cultures with phenotypically identical organisms
	(2) A sinus tract communicating with the joint
Minor criteria	(1) Elevated serum C-reactive protein AND erythrocyte sedimentation rate
	(2) Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip
	(3) Elevated synovial fluid polymorphonuclear neutrophil percentage
	(4) Positive histological analysis of periprosthetic tissue
	(5) A single positive culture

Table 2: The threshold for the minor diagnostic criteria according to the International Consensus Group.

Criterion	Acute PJI (<90 days)	Chronic PJI (>90 days)
Erythrocyte sedimentation rate (mm/hr)	Not helpful; no threshold was determined	30
C-reactive protein (mg/L)	100	10
Synovia white blood cell count (cells/μL)	10,000	3,000
Synovial polymorphonuclear percentage (%)	90	80
Leukocyte esterase	+ or ++	Same as acute
Histological analysis of tissue	>5 neutrophils/HPF in 5 HPFs (x400)	Same as acute

PJI: periprosthetic joint infection; HPF: high power field.

shown its ability for differentiating septic arthritis from the aseptic condition [12–14]. Regarding the accuracy with PJI diagnosis, a recent meta-analysis showed that serum PCT had a pooled sensitivity and a pooled specificity for detecting PJI as 53% and 92%, respectively [15]. However, to the best of our knowledge, while serum PCT seems reliable [4, 15, 16], only a few studies addressed the efficacy of synovial fluid PCT (SF-PCT) for PJI diagnosis [13], and its diagnostic utility has not been clearly established. The aim of this study was to assess synovial fluid and serum levels of PCT as a diagnostic tool for PJI and to evaluate their diagnostic accuracy compared with the standard tests.

2. Patients and Methods

2.1. Study Design, Inclusion, and Exclusion Criteria. This study design was a single-centered prospective cohort study in a medical university hospital, and the study was approved by the institutional board review committee (Faculty of Medicine Ramathibodi Hospital, Mahidol University: Protocol number ID 05-58-01). All patients signed informed consent forms prior to being enrolled. The study was conducted in accordance with the declaration of Helsinki. Between 2015 and 2017, patients undergoing revision hip or knee arthroplasty were recruited into this prospective study. The patient-inclusion criteria were (1) pain at the site of total hip or total knee arthroplasty that prompted a clinical evaluation for infection or possible revision hip or knee arthroplasty, (2) no history of previous septic arthritis treatment or previous septic revision surgery, (3) sufficient synovial fluid for the study methods, and (4) sufficient clinical and laboratory data for PJI classification according to the criteria of the International Consensus Meeting on Periprosthetic Joint Infection 2013 [17] (Tables 1 and 2). Patients were excluded if they received any antibiotics or joint puncture treatments prior to enrollment in the current study.

All patients underwent standard diagnostic evaluation for PJI diagnosis. Preoperative blood samples were taken for complete blood count (CBC) erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and PCT. Joint aspiration was done intraoperatively before opening the joint capsule, and then synovial fluid was sent for cell differentiation, cell count, gram stain, aerobic culture, and PCT. Intraoperative frozen section was performed. Periprosthetic tissue from five different areas (joint capsule, synovial lining, intramedullary material, granulation tissue, and bone fragments) was delivered for microbiology and histology.

2.2. Determination of the Levels of Serum and Synovial Fluid PCT. PCT levels were quantified using a standard quantitative PCT enzyme immunoassay kit, according to the manufacturers' instructions (Elecsys® BRAHMS PCT test, Roche Diagnostics Ltd., Switzerland), on the Roche Cobas e601 analyzer. The lower limit of detection was 0.02 ng/mL. The specimens, either blood or synovial fluid, were collected and kept at room temperature (10°C–25°C) and were measured within 2 hours. When synovial fluid cannot be measured within 2 hours, the specimen must be kept at approximately 2°C–8°C and must be measured within 24 hours. Due to the high viscosity of synovial fluid, the specimen was diluted at a ratio of 1:4 (100 μL of synovial fluid sample with 300 μL normal saline). Therefore, the synovial PCT level was then calculated from the measured PCT value multiplied by 4, such as 0.08, 0.12, and 0.16 ng/mL.

2.3. Statistical Analysis. Statistical analysis was carried out with MedCalc Statistical Software version 15.8 (MedCalc Software bvbv, Ostend, Belgium). Normally distributed continuous data were shown as mean ± standard deviation (SD) and

Table 3: Patient characteristics data.

	Total (n=32)	PJI (n=20)	Aseptic loosening (n=12)	p value
Age, year◆	68 (65–74)	70 (66–76)	67 ± 5	0.098
Female gender ◎	25 (78%)	13 (65%)	12 (100%)	0.029*
BMI, kg/m^2△	26.9 ± 4.0	26.3 ± 4.5	28.1 ± 3.0	0.229
Hip : Knee❖	5 : 27	0 : 20	5 : 7	0.004*
Left : Right❖	14 : 18	10 : 10	4 : 8	0.471
CCI◆	3 (2-4)	3 (3-4)	2.5 ± 1.0	0.083
Systemic inflammatory disease◎	2 (6%)	1 (5%)	1 (8%)	1.000
Receiving immunomodulating drugs◎	2 (6%)	1 (5%)	1 (8%)	1.000
Body temperature (°C)◆	36.8 (36.5–37.3)	37.4 ± 0.9	36.6 ± 0.2	0.010*
WBC count (cell/mm^3)◆	6,620 (5,755–10,250)	9,170 (1,700–28,100)	6106 ± 1433	0.021*

PJI: periprosthetic joint infection, BMI: body mass index, CCI: Charlson comorbidity index, and WBC: white blood cell; ◆: value presented as mean ± SD or mean (IQR) and calculated with Mann–Whitney U test; ◎: value presented as number of cases (percentage) and calculated with Fisher exact test or Chi-square test as appropriate; △: value presented with mean ± standard deviation and calculated with unpaired t-test; ❖: value presented as the proportion of cases with that condition and calculated with Fisher exact test; * significant p value with $p < 0.05$.

compared using student's *t*-test. Non-normally distributed continuous data were shown as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. The categorical variables were presented as number of cases with proportion and compared with Chi-square or Fisher's exact test. A p value < 0.05 was considered statistically significant. Diagnostic accuracy of serum PCT and SF-PCT was assessed with receiver-operating characteristic (ROC) curves between the PJI and aseptic loosening groups. Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), area under the ROC curve (AUC), and their 95% confidence interval (CI) for any cut-off level were calculated.

3. Results

A total of 32 patients (5 revision hip arthroplasties and 27 revision knee arthroplasties) were recruited into our prospective study between 2015 and 2017. Regarding the International Consensus Criteria on PJI [17], 20 patients (20 revision knee arthroplasties) were classified in the PJI group and 12 patients (5 revision hip arthroplasties and 7 revision knee arthroplasties) were classified in the aseptic group. The patient characteristics data are presented in Table 3. There were 7 males (22%) and 25 females (78%). The median patient age was 68 years (range 38–87 years). The mean BMI was 26.9 ± 4.0 kg/m^2, and the median CCI was 3 (range 0–9). Of these, 2 patients had preexisting rheumatoid arthritis (1 patient in each group) and were receiving immunomodulating drugs. No significant difference existed in age, BMI, operated side, CCI, presence of systemic inflammatory disease, and concomitant immunomodulation drugs between both groups. However, the PJI group was significantly higher for male gender, revision knee arthroplasties, body temperature, and serum WBC count than the aseptic group ($p < 0.05$ all).

Tables 4 and 5 demonstrate the relevant clinical and laboratory findings according to the PJI definition [17] in both groups and the microbiological findings in our study. Of the 20 patients with PJI, 13 (65%) had positive synovial fluid culture and 14 (70%) had positive tissue culture. The most common microorganism from cultures-positive PJI was *Streptococci* (n = 7, 50%). The PJI group demonstrated significantly greater values in serum and synovial fluid markers related to infection than the aseptic loosening group ($p < 0.001$, all). The median serum PCT level (interquartile range: IQR) in the PJI and aseptic groups was 0.33 (0.08 to 2.79) and 0.04 (0.03 to 0.06), respectively ($p < 0.001$). The median SF-PCT (IQR) in the PJI and aseptic groups was 0.16 (0.12 to 0.26) and 0.00 (0.00 to 0.00), respectively ($p < 0.001$). Regarding the aseptic loosening group, the median serum PCT and SF-PCT values from revision hip arthroplasties (0.04 and 0.00 ng/mL) did not significantly differ compared to those from revision knee arthroplasties (0.04 and 0.00 ng/mL) ($p = 0.400$ and 0.287, respectively).

Table 6 and Figure 1 show the diagnostic accuracy of PJI diagnosis by using serum PCT or SF-PCT in each cut-off

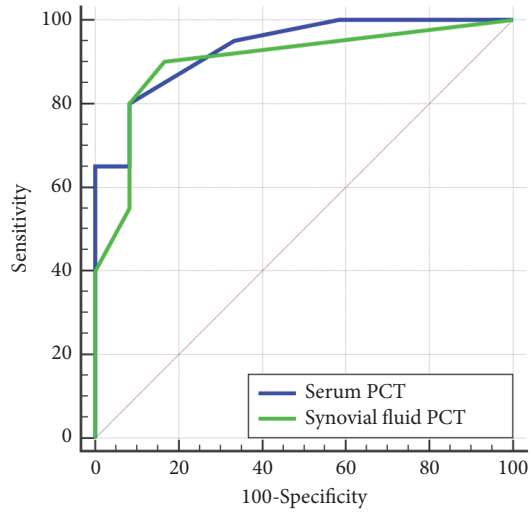

Figure 1: Receiver-operating characteristic (ROC) curves comparing ability between serum and synovial fluid PCT to detect periprosthetic joint infection (PJI) before revision arthroplasty.

Table 4: Relevant clinical and laboratory findings for PJI definition.

	PJI (n=20)	Aseptic loosening (n=12)	p value
Sinus tract presence◎	0 (0%)	0 (0%)	1.00
Synovial fluid culture◎	13 (65%)	0 (0%)	<0.001
Tissue culture◎	14 (70%)	0 (0%)	<0.001
Serum markers			
ESR, mm/hour △▽	81 ± 27	18.5 (12.5–36.5)	<0.001
CRP, mg/dL △	149 ± 98	2.9 ± 2.5	<0.001
Serum PCT, ng/mL ▽	0.33 (0.08–2.79)	0.04 (0.03–0.06)	<0.001
Hip	n/a	0.04 (0.02–0.06)	n/a
Knee	0.33 (0.08–2.79)	0.04 ± 0.04	0.001
Synovial fluid markers			
Synovial fluid WBC, cell/mm^3▽△	78,920 (3,420–335,400)	1350 ± 827	<0.001
%Neutrophil △	90.8 ± 6.2	54.9 ± 17.2	<0.001
SF-PCT, ng/mL▽	0.16 (0.12–0.26)	0.00 (0.00–0.00)	<0.001
Hip	n/a	0.00 0.00	n/a
Knee	0.16 (0.12–0.26)	0.00 (0.00–0.06)	0.004

◎: value presented as number of cases (percentage), △: value presented as mean ± standard deviation, ▽: value presented as median (interquartile range), and n/a: not available.

Table 5: Microbiological findings of culture-diagnosed PJI among 14 episodes.

Micro-organisms	No. (%)
Gram positive	
Staphylococcus aureus	1 (7%)
CNS	1 (7%)
Streptococci	7 (50)
Gram positive	
Escherichia coli	3 (21%)
Proteus mirabilis	1 (7%)
Other[a]	1 (7%)

CNS: *coagulative negative staphylococcus*; [a]: *Propionibacterium* spp.

value and ROC curve comparison between serum PCT and SF-PCT. The cut-off references of serum PCT were set as 0.1, 0.3, and 0.5 ng/mL, whereas those of SF-PCT were set as 0.08, 0.12, and 0.16 ng/mL. Regarding the accuracy of the serum PCT test with the standard cut-off reference level as 0.5 ng/mL, the sensitivity, specificity, LR+, and LR- were 40.0%, 100.0%, not available, and 0.60, respectively. However, with the lower cut-off level as 0.1 ng/mL, the serum PCT test showed sensitivity, specificity, LR+, and LR- as 65.0%, 91.7%, 7.80, and 0.38, respectively. The AUC of 0.5 and 0.1 ng/mL cut-off levels was 0.70 and 0.78, respectively.

Regarding the accuracy of the SF-PCT test for PJI diagnosis, the cut-off value as 0.08 ng/mL resulted in sensitivity of 90.0%, specificity of 83.3%, LR+ of 5.40, and LR- of 0.12. Conversely, the higher cut-off level as 0.12 ng/mL showed sensitivity of 80.0%, specificity of 91.7%, LR+ of 9.40, and LR- of 0.22. The AUC of 0.08 and 0.12 ng/mL cut-off levels was 0.87 and 0.86, respectively (Table 6).

4. Discussion

Periprosthetic joint infection (PJI) is one of the most severe and costly complications following total joint arthroplasty. Although there is an international consensus for the definition of PJI, no single "gold standard" test currently exists for diagnosing PJI. Recently, many studies have reported the usefulness of synovial fluid cytokines—such as interleukin-6, c-reactive protein, and alpha-defensin—as alternative and better diagnostic markers for PJI compared to the standard technique [7, 8, 18–21]. The overall sensitivity and specificity of these markers were more than 80% and 90%, respectively [7]. However, to our knowledge, although some biomarkers have demonstrated excellent diagnostic performance for PJI, the comparison of diagnostic accuracy between these biomarkers did not achieve statistical significance [8]. Moreover, according to the current evidence on these new biomarkers, serum PCT is a promising and reliable test, but the utility of synovial fluid PCT for detecting PJI has not been clearly demonstrated.

The results of this study show that both serum PCT and SF-PCT could be used as diagnostic biomarkers to support clinicians in differentiating PJI from aseptic loosening. The PJI group had significantly higher serum PCT and SF-PCT values, the same as serum ESR and CRP ($p < 0.001$ all), compared with the aseptic loosening group (Table 4). Using ROC curve analysis, the present study demonstrates that serum PCT, with the standard cut-off level as 0.5 ng/mL (a sensitivity of 40%, a specificity of 100%, and AUC of 0.70), is comparable to PCT from the previous meta-analysis (pooled sensitivity of 53%, pooled specificity of 92%, and AUC of 0.76) [15]. Additionally, this study also reveals that, with the lower serum PCT cut-off level as 0.1 ng/mL, the diagnostic accuracy of serum PCT could be further improved to sensitivity of 65%, persistently good specificity (92%), and AUC of 0.78

Table 6: Diagnostic accuracy of PJI diagnosis using serum or synovial fluid procalcitonin.

	Sensitivity	Specificity	AUC	LR+	LR-
Serum PCT (ng/mL)					
0.1	65.0 (40.8–84.6)	91.7 (61.5–99.8)	0.78 (0.60–0.91)	7.80 (1.16–52.35)	0.38 (0.21–0.71)
0.3	50.0 (27.2–72.8)	100.0 (73.5–100.0)	0.75 (0.57–0.89)	n/a	0.47 (0.29–0.76)
0.5	40.0 (19.1–64.0)	100.0 (73.5–100.0)	0.70 (0.51–0.85)	n/a	0.60 (0.42–0.86)
Synovial fluid PCT (ng/mL)					
0.08	90.0 (68.3–98.8)	83.3 (51.6–97.9)	0.87 (0.70–0.96)	5.40 (1.51–19.30)	0.12 (0.03–0.46)
0.12	80.0 (56.3–94.3)	91.7 (61.5–99.8)	0.86 (0.69–0.96)	9.60 (1.45–63.50)	0.22 (0.09–0.53)
0.16	55.0 (31.5–76.9)	91.7 (61.5–99.8)	0.73 (0.55–0.87)	6.60 (0.97–44.93)	0.49 (0.29–0.82)

AUC: area under curve, LR+: positive likelihood ratio, LR-: negative likelihood ratio, and PCT: procalcitonin.

(Table 5). However, serum PCT with a lower cut-off level should be used with caution and may need future larger studies to ensure an effective strategy implementation.

Regarding ROC curve analysis, SF-PCT showed an ability to be a more valuable biomarker for identifying PJI from aseptic loosening than serum PCT. With a cut-off level as 0.08 ng/mL, SF-PCT showed the greatest accuracy with sensitivity of 90%, specificity of 83%, LR+ of 5.40, LR- of 0.12, and AUC of 0.87 (Table 5). These high sensitivity, high LR+, and very low LR- characteristics are all good indicators for ruling in and out the diagnosis of PJI [22], especially for preoperative and intraoperative settings. This is because the PCT test would take only 30 minutes to perform in the laboratory and may have the potential to become a point-of-care test in the patients who obtain the synovial fluid. Additionally, this study also found that, according to the PJI group, the concentration of PCT in blood (median value 0.33 ng/mL, interquartile range 0.08 ng/mL–2.79 ng/mL) seemed to be greater (about two times) than those in joint fluid (median value 0.16 ng/mL, interquartile range 0.12 ng/mL–0.26 ng/mL). However, the difference did not reach statistical significance ($p = 0.20$) (Table 4). This could imply that the cut-off reference for SF-PCT should be different from those for serum PCT, the same as the other synovial fluid biomarker [21].

Concerning the comparison of the diagnostic performance between synovial fluid biomarkers for PJI diagnosis, although this study demonstrated a good accuracy of SF-PCT for PJI diagnosis with an AUC of 0.87, this diagnostic accuracy appeared to be slightly inferior to biomarkers from previous studies—such as CRP, IL-6, and alpha-defensin—with AUC between 0.90 and 0.99 [18, 20, 23, 24]. However, due to the previously noted potential of the PCT test, we still recommend using SF-PCT as a complementary tool with the standard technique for diagnosing PJI.

This study also had some limitations. Firstly, due to the prospective cohort nature in only one university hospital center, our sample size was relatively small and included both knee and hip patients. Therefore, future longitudinal studies with a larger sample size and a specific analytic approach for revision knee or hip arthroplasties would require determining the usefulness of SF-PCT for detecting PJI. Secondly, this study did not include patients with prior antibiotics therapy or with concomitant disease that might affect SF-PCT, such as crystal-induced arthritis or malignancy [13]. Lastly, a diagnostic accuracy comparison between SF-PCT and other biomarkers was not performed. However, the information related to other biomarkers is already published.

5. Conclusion

The accuracy of SF-PCT was significantly higher than that of serum PCT. Therefore, SF-PCT may be used as an alternative indicator in the differential diagnosis of PJI from aseptic loosening in cases where patients are undergoing revision hip or knee arthroplasty. However, further prospective studies with a larger sample size are required to validate the usefulness of SF-PCT.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

All of the authors declare that they have no conflicts of interest.

Authors' Contributions

Paphon Sa-ngasoongsong and Siwadol Wongsak were main researchers who designed and performed this study and prepared the manuscript. Chavarat Jarungvittayakon, Kawee Limsamutpetch, and Thanaphot Channoom were orthopaedic trauma surgeons who assisted in data collection and manuscript preparation. Viroj Kawinwonggowit was senior orthopaedic consultant who assisted in research process.

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References

[1] K. J. Bozic, S. M. Kurtz, E. Lau et al., "The epidemiology of revision total knee arthroplasty in the united states," *Clinical Orthopaedics and Related Research*, vol. 468, no. 1, pp. 45–51, 2010.

[2] K. J. Bozic, S. M. Kurtz, E. Lau, K. Ong, D. T. P. Vail, and D. J. Berry, "The epidemiology of revision total hip arthroplasty in the united states," *The Journal of Bone & Joint Surgery*, vol. 91, no. 1, pp. 128–133, 2009.

[3] J. S. Coste, S. Reig, C. Trojani, M. Berg, G. Walch, and P. Boileau, "The management of infection in arthroplasty of the shoulder," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 86-B, no. 1, pp. 65–69, 2004.

[4] K. Yuan, W.-D. Li, Y. Qiang, and Z.-M. Cui, "Comparison of procalcitonin and C-reactive protein for the diagnosis of periprosthetic joint infection before revision total hip arthroplasty," *Surgical Infections*, vol. 16, no. 2, pp. 146–150, 2015.

[5] C. Deirmengian, K. Kardos, P. Kilmartin et al., "The Alpha-defensin Test for Periprosthetic Joint Infection Outperforms the Leukocyte Esterase Test Strip," *Clinical Orthopaedics and Related Research*, vol. 473, no. 1, pp. 198–203, 2015.

[6] A. Elgeidi, A. E. Elganainy, N. Abou Elkhier, and S. Rakha, "Interleukin-6 and other inflammatory markers in diagnosis of periprosthetic joint infection," *International Orthopaedics*, vol. 38, no. 12, pp. 2591–2595, 2014.

[7] Y. S. Lee, K. Koo, H. J. Kim et al., "Synovial Fluid Biomarkers for the Diagnosis of Periprosthetic Joint Infection," *The Journal of Bone & Joint Surgery*, vol. 99, no. 24, pp. 2077–2084, 2017.

[8] A. Saleh, D. Ramanathan, M. B. P. Siqueira, A. K. Klika, W. K. Barsoum, and C. A. H. Rueda, "The diagnostic utility of synovial fluid markers in periprosthetic joint infection: A systematic review and meta-analysis," *Journal of the American Academy of OrthopaedicSurgeons* , vol. 25, no. 11, pp. 763–772, 2017.

[9] N. G. Morgenthaler, J. Struck, C. Fischer-Schulz, E. Seidel-Mueller, W. Beier, and A. Bergmann, "Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA," *Clinical Laboratory*, vol. 48, no. 5-6, pp. 263–270, 2002.

[10] F. Ferriere, "Procalcitonin, a new marker for bacterial infections," *Annales de Biologie Clinique*, vol. 58, no. 1, pp. 49–59, 2000.

[11] A. Abd El-Azim, M. Sultan, U. Alkholi, and N. Abd Al-monem, "Serum procalcitonin in viral and bacterial meningitis," *Journal of Global Infectious Diseases*, vol. 3, no. 1, pp. 14–18, 2011.

[12] K. Maharajan, D. K. Patro, J. Menon et al., "Serum Procalcitonin is a sensitive and specific marker in the diagnosis of septic arthritis and acute osteomyelitis," *Journal of Orthopaedic Surgery and Research*, vol. 8, no. 1, article no. 19, 2013.

[13] K. Saeed, M. Dryden, A. Sitjar, and G. White, "Measuring synovial fluid procalcitonin levels in distinguishing cases of septic arthritis, including prosthetic joints, from other causes of arthritis and aseptic loosening," *Infection*, vol. 41, no. 4, pp. 845–849, 2013.

[14] C. Wang, D. Zhong, Q. Liao, L. Kong, A. Liu, and H. Xiao, "Procalcitonin levels in fresh serum and fresh synovial fluid for the differential diagnosis of knee septic arthritis from rheumatoid arthritis, osteoarthritis and gouty arthritis," *Experimental and Therapeutic Medicine*, vol. 8, no. 4, pp. 1075–1080, 2014.

[15] K. Xie, X. Qu, and M. Yan, "Procalcitonin and α-Defensin for Diagnosis of Periprosthetic Joint Infections," *The Journal of Arthroplasty*, vol. 32, no. 4, pp. 1387–1394, 2017.

[16] S. Ali, A. Christie, and A. Chapel, "The pattern of procalcitonin in primary total hip and knee arthroplasty and its implication in periprosthetic infection," *Journal of Clinical Medicine Research*, vol. 1, no. 2, pp. 90–94, 2009.

[17] J. Parvizi and T. Gehrke, "Definition of periprosthetic joint infection," *The Journal of Arthroplasty*, vol. 29, no. 7, p. 1331, 2014.

[18] K. Xie, K. Dai, X. Qu, and M. Yan, "Serum and Synovial Fluid Interleukin-6 for the Diagnosis of Periprosthetic Joint Infection," *Scientific Reports*, vol. 7, no. 1, 2017.

[19] J. Pupaibool, E. J. Fulnecky, R. L. Swords, W. W. Sistrunk, and A. D. Haddow, "Alpha-defensin—novel synovial fluid biomarker for the diagnosis of periprosthetic joint infection," *International Orthopaedics*, vol. 40, no. 12, pp. 2447–2452, 2016.

[20] M. W. Tetreault, N. G. Wetters, M. Moric, C. E. Gross, and C. J. Della Valle, "Is Synovial C-reactive Protein a Useful Marker for Periprosthetic Joint Infection?" *Clinical Orthopaedics and Related Research*, vol. 472, no. 12, pp. 3997–4003, 2014.

[21] T. M. Randau, M. J. Friedrich, B. Wimmer et al., "Interleukin-6 in serum and in synovial fluid enhances the differentiation between periprosthetic joint infection and aseptic loosening," *PLoS ONE*, vol. 9, no. 2, Article ID e89045, 2014.

[22] A. M. Simundic, "Measures of Diagnostic Accuracy: Basic Definitions," *EJIFCC*, vol. 19, no. 4, pp. 203–211, 2009.

[23] T. Bonanzinga, A. Zahar, M. Dütsch, C. Lausmann, D. Kendoff, and T. Gehrke, "How Reliable Is the Alpha-defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study," *Clinical Orthopaedics and Related Research*, vol. 475, no. 2, pp. 408–415, 2017.

[24] M. Wyatt, A. Beswick, S. Kunutsor, M. Wilson, M. Whitehouse, and A. Blom, "The Alpha-Defensin Immunoassay and Leukocyte Esterase Colorimetric Strip Test for the Diagnosis of Periprosthetic Infection," *The Journal of Bone & Joint Surgery*, vol. 98, no. 12, pp. 992–1000, 2016.

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Research Article

In Vivo Evaluation of Different Collagen Scaffolds in an Achilles Tendon Defect Model

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In the present study, a newly introduced bovine cross-linked collagen scaffold (test material) was investigated in vivo in an Achilles tendon defect model and compared to a commercially available porcine collagen scaffold (control material). In total, 28 male Sprague Dawley rats (about 400 g) were examined. The defined Achilles tendon defect of 5 mm of the right hind limb was replaced by one of the scaffold materials. After euthanasia, the hind limbs were transected for testing. Biomechanical evaluation was carried out via tensile testing (n = 8 each group, observation time: 28 days). Nonoperated tendons from the bilateral side were used as a control (native tendon, n = 4). For the histological evaluation, 12 animals were sacrificed at 14 and 28 days postoperatively (n = 3 each group and time point). Stained slices (Hematoxylin & Eosin) were evaluated qualitatively in terms of presence of cells and cell migration into scaffolds as well as structure and degradation of the scaffold. All transected hind limbs were additionally analyzed using MRI before testing to verify if the tendon repair using a collagen scaffold was still intact after the observation period. The maximum failure loads of both scaffold materials (test material: 54.5 ± 16.4 N, control: 63.1 ± 19.5 N) were in the range of native tendon (76.6 ± 11.6 N, $p \geq 0.07$). The stiffness of native tendons was twofold higher ($p \leq 0.01$) and the tear strength was approximately fivefold higher ($p \leq 0.01$) compared to the repaired tendons with both scaffolds. Histological findings indicated that neither the test nor the control material induced inflammation, but the test material underwent a slower remodeling process. An overall repair failure rate of 48% was observed via MRI. The experimental data of the newly developed test material showed similar outcomes compared to the commercially available control material. The high repair failure rate indicated that MRI is recommended as an auxiliary measurement tool to validate experimental data.

1. Introduction

Tendon regeneration, e.g., after rotator cuff tears, is known to be a complex and slow process, and the healing of tendon repair still remains a clinical challenge. Depending on individual factors (e.g., patient's age, tendon quality, and tear size) high rerupture rates can be observed [1–3]. Therefore, scaffold devices for tendon augmentation, whether biologic or synthetic, have been introduced to increase healing rates [4–6]. It is important to note that the absence of approval from the health authorities limits the clinical use of some graft materials in many countries. For example, in Germany, allografts are subjected to regulations based on transplantation law. In Japan, the use of allografts is also not approved and therefore the use of autografts is common [7].

The biomechanical behavior of graft materials in vitro was characterized by means of uniaxial mechanical tests [8, 9]. The results can be adjusted by varying the sample characteristics of the material tested such as thickness [10] or the processing method of the material [11], independently from graft source. Therefore, clinically relevant scaffold constructs should be performed to produce qualitative evidence. In recent years, several clinical trials have evaluated the functional outcome of the augmented rotator cuff repair (RCR) with the use of different scaffold devices. Most of these trials were quite limited as they were often retrospective case series with small patient populations, without control groups, and produced controversial results [12, 13]. Based on the recent literature, allografts made of acellular human dermis are thought to provide the most beneficial clinical outcome

with low rerupture rates compared to other scaffolds [14–16]. In the current literature, the clinical outcome of xenografts is discussed controversially [7, 17, 18]. Thus, the source of the graft plays an important role [4, 12]. In particular, collagen-based grafts made from porcine small intestine submucosa (SIS) are known to end up in suboptimal results and may promote postoperative inflammatory reactions. Therefore, the use of porcine SIS xenografts (Restore, DePuy) for augmentation in RCR is not recommended [12, 19]. Ciampi et al. [20] reported that RCR using bovine pericardium-derived patches (Tutopatch, RTI Surgical, Inc. Alachua, FL, USA) showed significantly lower healing rates compared to synthetic grafts (Repol Angimesh, Angiologica BMSrl, Pavia, Italy). However, the healing rate was not significantly lower than RCR without a graft. Further clinical data showed that xenografts, based on dermal collagen, led to more promising results [5, 21–23]. However, it is not known if there are differences in clinical outcome with respect to the dermal graft source (porcine versus bovine).

Currently, there are two graft materials based on bovine dermis available for clinical use (TissueMend, Stryker Corp., Mahwah, NJ, USA, and Bio-Blanket, Kensey Nash Corp., PA, USA), but only few results have been published on clinical outcomes. Sears et al. [24] compared the clinical outcome of an allograft (GraftJacket, Wright Medical Arlington, TN, USA), a porcine dermal extracellular matrix (ECM) (Conexa, Tornier Inc., Bloomington, MN, USA), and a bovine dermal ECM (TissueMend, Stryker Corp.) in a retrospective case study. Significant differences in clinical outcome were not found between the different patches. However, the study was strongly limited by the small sample size.

The inconsistent clinical outcomes using scaffolds for tendon augmentation underline that there is still a need for new scaffold materials. Therefore, we have developed a new scaffold material, based on bovine collagen and a chemical cross-linking process. The material has been already tested in vitro and showed favorable biomechanical, biochemical, and cell biological properties [25]. In the present pilot animal study, the newly introduced bovine collagen scaffold was investigated with regard to functional outcomes and remodeling using an Achilles tendon defect model in rats.

2. Materials and Methods

2.1. Scaffolds. Two collagen scaffold materials were evaluated. As the test material, a newly developed scaffold based on bovine collagen was used, as described previously [25]. Briefly, for scaffold preparation, bovine dermal collagen was treated chemically with NaOH, H_2O_2, and HCl in order to remove noncollagenous proteins, fatty acids, and cells and to inactivate viruses. The purified dermal collagen was processed into a matrix with longitudinally orientated fibrils consisting mainly of collagens type I, type III, and type V. This predefined matrix structure was first stabilized by freeze-drying within a temperature range of 55 to 65°C and further by chemical cross-linking. Then, the freeze-dried matrix was subjected to an aqueous epoxide solution with a concentration of 0.19% (w/w). Before further use, the cross-linked collagen matrix was successively washed with reverse osmosis (RO) water to remove any free epoxide. For the control group, DX Reinforcement scaffolds (Arthrex, Inc., Naples, FL, USA) based on porcine dermal extracellular matrix with no cross-linking were used.

Before testing, the test material was hydrated in saline solution (NaCl, 0.9%) for at least 30 min (thickness after rehydration: 0.89 ± 0.04 mm). The control material was delivered hydrated (thickness: 1.43 ± 0.16 mm). Test samples for *in vitro* and *in vivo* evaluation were obtained from two patches of one charge for the test material and from two patches of two charges for the control material.

2.2. Biomechanical Testing of Scaffold Materials In Vitro. As we used samples from new charges, we repeated the initial biomechanical testing [25] according to Barber and Aziz-Jacobo [8]. Before animal testing, additionally a suture retention test was performed according to Barber and Aziz-Jacobo [8]. Samples were bisected and one vertical stitch with No. 2 FiberWire (Arthrex, Inc., Naples, FL, USA) was passed to the distal end of the scaffold with a distance of 5 mm from the tissue edge. The scaffold was mounted on the upper grip with roughened chuck jaws in the testing machine; the suture was fixed with a sample grip with corrugated chuck jaws. The start length was 3 cm and the predetermined tearing location was centered. The destructive test was conducted again with a distraction rate of 12.5 mm/s.

For all biomechanical evaluations of the test material, care was taken that the load was applied longitudinally to the orientation of collagen fibers (according to native in vivo situation). Six samples of the test material were tested. Only four samples of the control material were tested due to the limited quantity of the material. The orientation of the control material during testing was not required, since this graft has no directional fiber alignment.

2.3. Animal Testing. For in vivo testing of both scaffold materials, a total of 28 male Sprague-Dawley rats (Janvier Labs, Le Genest-Saint-Isle, France) weighing 404 ± 20 g were used. The study was approved by the local animal research committee (LALLF MV, reference number 7221.3-1-036/15). Rats were kept in an animal facility, where temperature and light/dark cycle (12:12 hours) were controlled, and access to standard food and water was provided ad libitum. Animals were randomly divided into two groups: the test material group, where the Achilles tendon defect was replaced by the bovine collagen scaffold, and the control group, where the DX Reinforcement graft material was used as the scaffold. For functional and biomechanical evaluations, the postoperative observation time was 28 days (n = 8 each group). To determine the optimal number of animals, an a priori analysis was performed for the mean of two independent samples using G∗Power (version 3.1.9.2). For the histological evaluation, in total 12 animals were sacrificed 14 and 28 days postoperatively (n = 3 each group and each time point). The allocation of the rats is shown in Figure 1.

Surgery was performed by an experienced orthopedic surgeon (TT), who underwent additionally a training

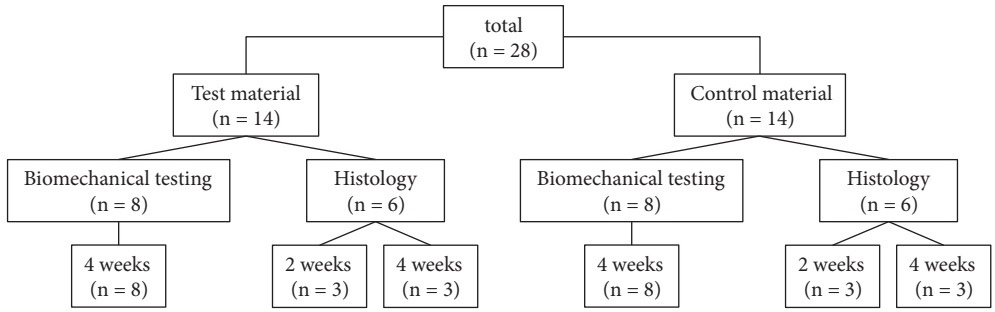

Figure 1: Overview of the allocation of rats and experiments used in present study.

on cadaveric rats before. For surgery, the animals were anesthetized with medetomidine (150 μg/kg), midazolam (2 mg/kg), and fentanyl (5 μg/kg) due to an intraperitoneal injection. The right Achilles tendon was dissected and freed from soft tissue and the M. plantaris tendon was removed. Each rat underwent a transection of 5 mm of the Achilles tendon. Due to differences of sizes of the animals, the transection was set individually in the middle part of the tendon. A 5 mm scaffold of either the new bovine material (n = 14) or the porcine control material (n = 14) was replaced in the defect and the remaining ends were refixed with two single stitches (Vicryl® 4-0, Ethicon, Somerville, NJ, USA) (Figure 2). Collagen fibers of the test material scaffold device were aligned longitudinally to the orientation of the Achilles tendon.

Finally, anesthesia was antagonized by a subcutaneous (s.c.) dose of atipamezole (750 μg/kg), flumazenil (200 μg/kg), and naloxone (120 μg/kg). Postoperative analgesia was provided through an intramuscular injection of 0.5 ml metamizol (0.5 g/ml) immediately after surgery, as well as orally via the drinking water (30 drops 500 mg/ml metamizol per 0.5 l) for three days. Animals were allowed to move freely in their cages after surgery. In the first postoperative week, they were kept individually per cage to prevent adverse events like fighting or mutually gnawing on surgical sites. At the end of the observation period, the animals were euthanized by an intracardiac injection with an overdose of pentobarbital sodium (80 mg/kg) under anesthesia.

2.4. Imaging Analysis. After scarification of the animals, hind limbs were transected proximal to the knee joint, and magnetic resonance imaging (MRI) scans were acquired using 7.0 Tesla scanner (BioSpec 70/30, Bruker, Ettlingen, Germany). T_2-weighted TurboRARE sequences in axial, coronal, and sagittal plane were recorded (TE/TR: 28/4400 ms, spatial in-plane resolution: 0.12 mm, slice thickness: 0.7 mm, matrix size (sagittal/frontal/transversal): 338 × 304 / 320 × 166 / 280 × 196, FoV (sagittal/frontal/transversal): 40.5 mm x 36.5 mm / 38.3 mm × 20 mm / 33.5 mm x 23.5 mm, RARE factor: 8, averages: 5). Afterwards, specimens for biomechanical testing were wrapped in gauze soaked with NaCl solution (0.9%) and stored at −20°C. Specimens for histomorphometric analyses were fixed in buffered formalin (4%).

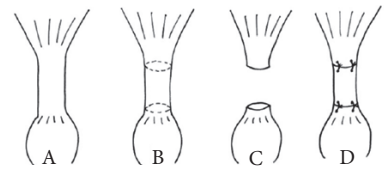

Figure 2: Schematic illustration of implantation procedure. A: preparation of the Achilles tendon, B: marking defined defect length of the Achilles tendon, C: setting the defined defect, D: implantation of the scaffold material, suturing with two single stitches at each end.

For analysis, the software Amira 5.4.1 (Thermo Fisher Scientific, USA) was used. The distance between the distal edge of the scaffold and the tendon insertion on the calcaneus was measured. Three measurements per view were executed, and mean value was calculated for each sample, as shown in Figure 3. Additionally, the junction between the scaffold and the native tendon was evaluated. It was determined whether the reconstruction was still intact or if it had failed during the observation time. Failure was defined if either the position of the scaffold was obviously slipped into the proximal direction (distance to calcaneus > 10 mm) and/or the musculotendinous junction was elongated.

2.5. Functional Evaluation. A gait analysis was performed for the animals planned for biomechanical testing. A modified method for the Achilles Functional Index (AFI) described by Murrel et al. [26], according to Kurtz et al. [27], was used. Therefore, the hind paws of the rats were colored by dipping a sponge soaked with nontoxic food dye. Animals were then allowed to walk a confined walkway prepared with white paper on the floor of the corridor, leaving paw prints on the paper. Gait was recorded preoperatively, at day 4 and day 7, and then at weekly intervals up to day 28. The papers were scanned and measurements of from paw prints were performed with GIMP 2.8.20 (GIMP, the GIMP Team). Measurements included print length (PL), total spreading (TS, distance between first and fifth toes), and intermediary spreading (IT, distance between second and fourth toes). Three left and three right paw prints were

evaluated and averaged each time point to calculate the corresponding factors (PLF, TSF, and ITF) according to [21]. Murrel's formula was used for determination of AFI:

$$\text{AFI} = 74\,(\text{PLF}) + 161\,(\text{TSF}) + 48\,(\text{ITF}) - 5 \quad (1)$$

[26].

2.6. Biomechanical Testing In Vivo. Prior to testing, the fresh-frozen animal specimens were thawed in a bath of NaCl overnight at 4°C and stored at room temperature for at least 4 hours before preparation. The Achilles tendon-calcaneus-foot complex was dissected from the hind limb. The gastrocnemius-soleus muscle was removed with the blunt end of a scalpel, as described in literature [28]. The proximal end of the tendon was spread out of some paper. The paper was then folded two times and fixed with tape. The foot was mounted with a cyanoacrylate adhesive (LOCTITE® 4902™, Henkel, Düsseldorf, Germany) at 45° to the surface of a custom-made aluminum block and additionally fixed due to a clamping unit via screws. The specimens were mounted on a custom-made test setup in a materials testing machine (Z1.0, Zwick, Ulm, Germany) for tensile testing (Figure 4). All tendons were preloaded with 1 N, and width and thickness were measured with a caliper at three measuring points. Cross-sectional area was calculated from the averaged values under the assumption that the area is oval. Subsequently, the tendons were stretched at a rate of 1 mm/s until complete rupture was observed. Care was taken that the specimens were kept moist with NaCl throughout the procedure. Non-operated tendons from the bilateral side (left leg) were used as a control (n = 4). Load-displacement curves were recorded and evaluated.

2.7. Histological Analysis. The specimens were dehydrated in a graded series of alcohol and embedded in polymethylmethacrylate. Slices in the longitudinal direction of the implant were cut with a laser microtome (TissueSurgeon, LLS ROWIAK GmbH, Hannover, Germany) and stained with Hematoxylin & Eosin (HE). Slice thickness was 10 μm. Scanning and digitalizing for evaluation were performed using a digital microscope (VHX-6000, Keyence, Osaka, Japan) at 500x (objective VH-Z250T) magnification. Samples were evaluated qualitatively in terms of structure and degradation of the scaffold (preserved fiber structure), reaction of surrounding tissue (cell infiltration), and cell migration into scaffolds.

2.8. Data Analysis. Statistical analysis was performed using IBM SPSS Statistics 22 software (IBM, Ehningen, Germany). The statistical significance of differences was calculated by Mann–Whitney test within two independent groups. The level of significance was set to $p < 0.05$.

3. Results

3.1. Biomechanical Testing of Scaffolds In Vitro. Biomechanical data of the new charges of scaffolds used in this study are displayed in Table 1. The test material shows initial higher mean maximum failure load (Fmax) compared to the control material, but the difference is not significant ($p < 0.05$). There is also no significant difference of stiffness. Mean tear strength (tensile load normalized to cross section) and elastic modulus of the test material were significantly higher compared to the control material ($p < 0.05$).

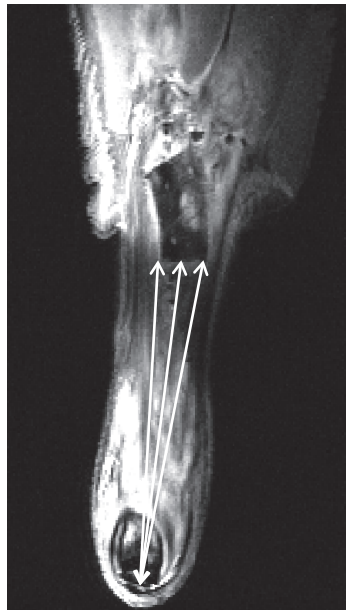

Figure 3: T_2-weighted MR image of an experimental hind limb repaired with a collagen scaffold (dorsal view). Arrows indicate measurement of the distance between the distal edge of the scaffold and tendon insertion into the calcaneus.

The retention strength of single vertical stitches in both scaffold materials (maximum failure load) is demonstrated in Figure 5. The test material showed a lower maximum failure load (41.5 ± 2.2 N) compared to the control material with 77.0 ± 21.0 N. Differences were significant ($p < 0.05$).

3.2. Analysis of MRI Data. All animals tolerated the surgical procedure. No dropouts or adverse events occurred during the observation period. MR images showed that the location of the scaffolds relative to the tendon insertion on the calcaneus differed considerably in some cases. Some of the scaffolds were located in the proximal part of the lower leg, which was an indication that the reconstruction might have failed distally. Total distances ranged from 3.2 mm to 18 mm (Figure 6).

An overall failure rate of refixation of 48% (13/27) was observed. In one case in the test material group, failure could not be determined due to MR image artifacts. MR analysis indicated that all failures were caused due to suture tear-out. No material defects of scaffolds themselves were visible, independent of the scaffold material. An overview of the location of scaffolds and failures are displayed in Table 2.

3.3. AFI. Achilles Functional Index values are shown in Figure 7. Differences between the Achilles tendon repairs

Table 1: Biomechanical data (mean ± standard deviation) of the two collagen scaffold materials. Fmax: maximal failure load, Rm: tear strength, S: stiffness, EM: elastic modulus. ∗ $p < 0.05$.

Scaffold	Fmax (N)	Rm (N/mm^2)	S (N/mm)	EM (MPa)
Test Material	395.6 ± 70.5	22.7 ± 4.9∗	75.0 ± 10.1	90.4 ± 12.1∗
Control Material	309.8 ± 193.9	10.4 ± 5.5	79.4 ± 30.6	61.7 ± 13.5

Table 2: MRI analysis: location of the scaffolds and failure rates of the samples (n.d.: nondescript).

Material	position in vivo	n	n (failure)	n (no failure)	n (n.d.)
Test Material	proximal	6	5	-	1
	distal	8	2	6	-
Control Material	proximal	3	3	-	-
	distal	11	3	8	-

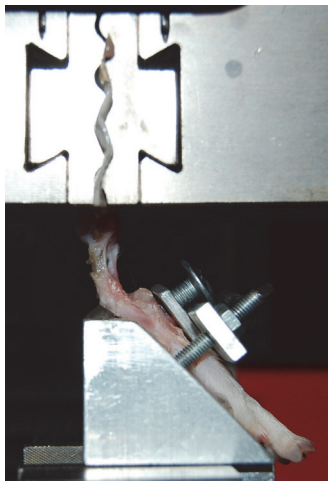

Figure 4: Custom-made setup for tensile testing with mounted Achilles tendon-calcaneus-foot complex.

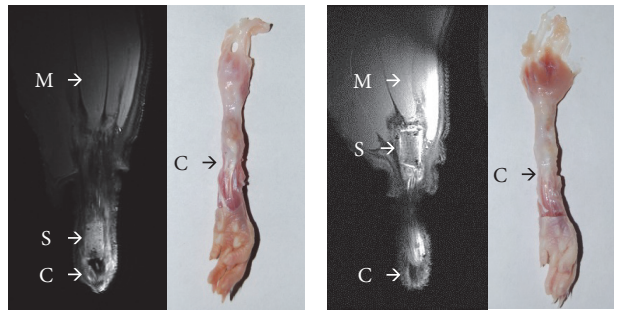

Figure 6: T_2-weighted MR images and photographs (dorsal view) of experimental hind limbs repaired with collagen scaffolds after 28 days of implantation. Left MRI: scaffold is located distally as implanted and expected. Right MRI: scaffold is located proximally in the gastrocnemius muscle. Both prepared samples (for biomechanical testing) with analogues scaffold position gave no evidence about this position macroscopically. Arrows mark the position of calcaneus (C), scaffold (S), and gastrocnemius muscle (M).

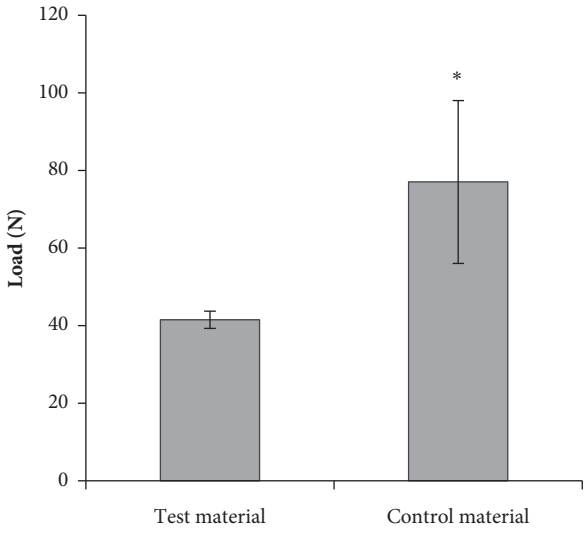

Figure 5: Suture retention strength (maximum failure load, mean ± standard deviation) using a single vertical stitch. ∗ $p < 0.05$.

with the two different scaffold materials were not significant for all time points ($p > 0.05$).

The results of both groups showed typical curves, as the AFI is neutral preoperatively, decreased significantly ($p < 0.01$) in the first days after surgery, and recovers over time. The lowest AFI over time was seen on day 4 for the test material group and on day 7 for the control group, respectively. Postoperatively, the increase in AFI of the total sample at two consecutive time points was significant from day 14 to 21 and from day 21 to 28 for the test material ($p \leq 0.05$) and from day 14 to 21 for the control material ($p < 0.05$). The AFI on day 28 was significantly higher compared to all other postoperative days ($p \leq 0.05$) for the test material group, and for the control material group AFI on day 28 was higher compared to day 4 up to day 14 ($p \leq 0.01$). The AFI on day 28 of both groups was still decreased compared to the preoperative AFI ($p < 0.01$).

When the failed samples (detected within MRI) were excluded from the analysis retrospectively, both groups still showed a significant difference between preoperative evaluation and day 28 postoperatively, but the difference between the materials was also still not significant ($p \geq 0.126$). Only

Table 3: Cross section area (mean ± standard deviation) of explanted Achilles tendons treated with both collagen scaffold materials compared to contralateral native Achilles tendon. ∗∗ $p < 0.01$.

	Test Material	Control Material	Native Tendon
Cross section (mm^2)	22.93 ± 4.71	22.75 ± 4.69	6.76 ± 3.01∗∗

Table 4: Biomechanical data (mean ± standard deviation) of the Achilles tendon defects treated with collagen scaffolds after 28 days postoperatively compared to native tendons. Sample sizes: native) n = 4; Test Material) total: n = 7, not failed: n = 4, failed: n = 3; Control Material) total: n = 8, not failed: n = 6, failed: n = 2. ∗∗ $p < 0.01$.

	Test Material	Control Material	Native Tendon
Failure load (N)			
total	54.5 ± 16.4	63.1 ± 19.5	
not failed	55,7 ± 18.7	67.7 ± 20.2	76.6 ± 11.6
failed	52.9 ± 16.7	49.2 ± 10.3	
Stiffness (N/mm)			
total	9.0 ± 2.8	10.7 ± 2.7	
not failed	8.6 ± 1.8	11.1 ± 2.5	20.2 ± 6.6∗∗
failed	9.6 ± 4.3	9.4 ± 4.0	
Tear strength (N/mm^2)			
total	2.5 ± 0.8	2.8 ± 1.0	
not failed	2.2 ± 0.9	2.9 ± 1.2	13.3 ± 5.9∗∗
failed	2.8 ± 06	2.6 ± 0.5	

a slight tendency of improved AFI for the test material was found.

3.4. Biomechanical Testing. Preparation of samples revealed higher cross section areas of repaired tendons compared to contralateral native tendons ($p < 0.01$; see Table 3). The surrounding connective tissue could not be distinguished from the scaffold material (Figure 6).

During tensile testing, one sample of the test material group was not correctly mounted in the test setup, so slipping occurred. The sample was excluded from evaluation. In total, healed tendon defects replaced with the test material (n = 7) and the control material (n = 8) showed almost similar maximum tensile loads. The respective native tendons showed only slightly higher tensile loads. Data did not differ significantly between the three groups ($p \geq 0.07$). The stiffness of the samples showed no significant differences between the two scaffold materials ($p > 0.23$). The stiffness of native group was significantly higher ($p < 0.01$). Tear strength was also significantly reduced in the tendons treated with collagen scaffolds compared to the respective native tendons ($p \leq 0.01$). There was no significant difference between the test and control material ($p > 0.69$). In total, there were only slight differences in the biomechanical data between failed and successful repairs (according to MRI). No significant difference was detected ($p > 0.40$; see Table 4).

3.5. Histology. At two weeks postoperatively, the fiber structure of both scaffold materials was clearly visible. Low cell reaction could be observed overall, although the cell reaction on the ventral side was higher compared to the dorsal side. There was only slight to no visible cell migration into both scaffold materials. Furthermore, bridging between the native tendon and scaffold materials with tendon tissues could not be found (Figure 8, first row).

One sample of the test material implanted for four weeks could not be analyzed as the histological preparation failed. One of the remaining two scaffolds was located in the distal part of the lower limb and looked similar compared to the two-week samples. Scaffold structure was well preserved and little cell reaction was observed. Only at the outside margins of the scaffold, some cell migration could be detected. The other sample moved in the proximal part of the limb after failure and showed an obvious rebuilding process. Scaffold fibers were visible at only a few locations. Overall, cell migration into the scaffold was seen (Figure 8, second row).

At two weeks postoperatively, samples of the control material showed a higher surrounding cell reaction, compared to the test material. The scaffolds were in rebuilding process, as there were only few structures visible. Cell migration into the scaffolds was mainly visible at the outer margin (Figure 8, third row).

Within the four-week samples of the control material, there was one failed scaffold located next to the calcaneus. The remodeling process was visible and some ossification occurred on the distal side of the scaffold. The two successful samples showed less remodeling. The fiber structure of the scaffolds was visible and cell migration was seen in deeper scaffold regions (Figure 8, fourth row).

4. Discussion

In the present study, a newly introduced scaffold material for tendon augmentation based on bovine cross-linked collagen

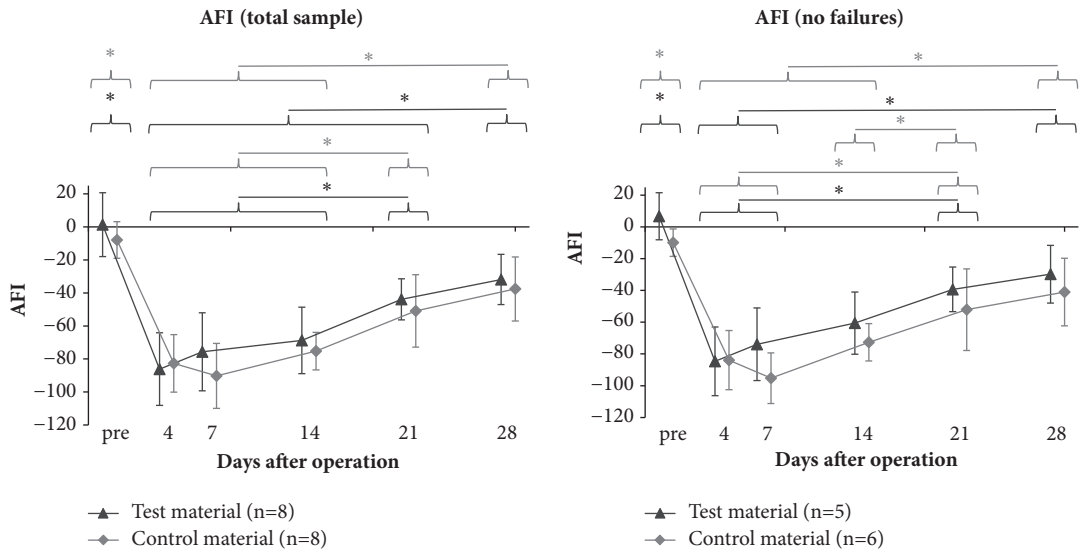

Figure 7: Achilles Functional Index (AFI) at different postoperative observation times after Achilles tendon repair with collagen scaffolds. Symbols represent mean ± standard deviation. ∗ $p \leq 0.05$.

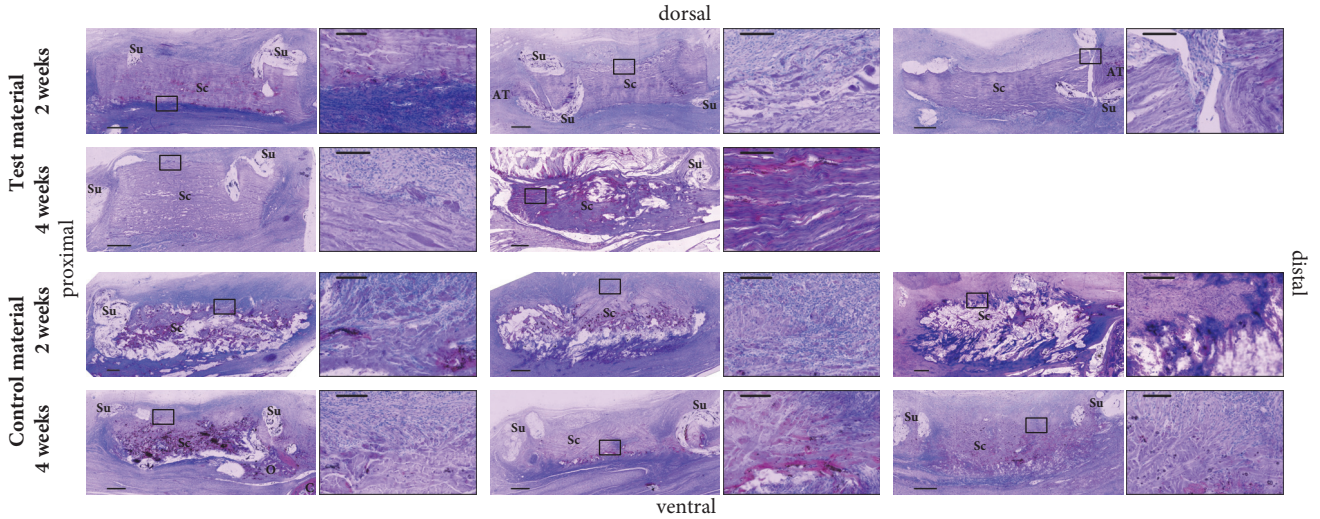

Figure 8: Histological specimens of test material (first two rows) and control material (bottom two rows) obtained two and four weeks after surgery, respectively (HE-staining, original magnification 500x); bar in survey views: 500 μm; bar in detailed views: 100 μm. Sc: scaffold; Su: suture; AT: Achilles tendon; C: calcaneus, O: ossification.

was tested and compared to a control material based on porcine collagen (DX Reinforcement).

Before animal testing, the scaffold material was tested in vitro, showing promising biomechanical and cell biological properties [25]. The biomechanical data of the test material used in the present study were superior to the DX Reinforcement Matrix material and were in the range of the GraftJacket allograft [8]. In the present study, we used two patches of the control material which differed in their mechanical properties, resulting in high standard deviations in vitro. Also the means of stiffness and tensile modulus were about three times higher compared to the control material [25]. Due to high costs and long delivery times of the commercial control material, the patches were used for both in vitro and in vivo trials to save time and material. The retention strength of single stiches was significantly lower for the used test material compared to the control material. It should be noted that results of the suture retention test [10] are influenced by sample characteristics of the material tested such as thickness; the control material was 1.5 times thicker than the test material. However, in clinical use, single stitch sutures are not commonly used to augment RCR [29]. Therefore, future studies should be carried out with clinically more relevant suture techniques.

MRI allowed a qualitative evaluation of the Achilles tendon repair before the samples were prepared for further testing. In the present study, an overall failure rate of 48% was observed. Most of these failures were not visible during

sample preparation (Figure 6), as all animals showed rebuilt tendon and new connective tissue (e.g., scar tissue). By means of MR imaging conducted postmortem at the transected hind limb, elongation of the native tendon was detected, causing dislocation of the scaffolds. The implanted scaffolds themselves remained intact. It was assumed that failures were caused due to suture tear-out. While the evaluation of the distal failure was quite obvious (big distance to calcaneus), the classification of proximal failure was more difficult, because the elongation of the musculotendinous junction was subjected a higher variability. Although the problem of suture failure rates in tendon repair in humans is known [10, 30, 31], this issue is rarely discussed with respect to the outcome of tendon repair in animal models. Therefore, MRI may be a suitable auxiliary tool to validate functional, biomechanical, and histological outcomes. Another enhancement, such as contrast-agent enhanced MRI as described by Cutlip et al. [32], could be suitable for in vivo experiments.

The AFI was shown to be valuable for quantifying the functional performance of the repair over time in the rat model [26]. We used a simple setup using white paper on the floor of the walkway and food dye to color the hind paws. Even after conditioning trials, the rats often stopped and walked backwards to explore the corridor. Therefore, they were sent over the walkway up to three times each time point to obtain at least three left and right printed hind paws for the evaluation. Compared to other studies [28, 33–35], we observed similar functional outcomes with a sharp decrease in AFI in the first postoperative days with improvement over time. In the literature the time to improvement varied from 15 days [28, 33] to 40 days [34], depending on factors like defect size or scaffold material. Return to complete function was nowhere to be found. In our study, AFI also did not achieve initial preoperative values after 28 postoperative days of healing. However, differences in Achilles tendon repair with both different scaffold materials could not be observed. Murrell et al. [26] showed that AFI is sensitive for different groups such as sham-op, repair, and defect. AFI seems to be not sensitive enough to differentiate treatment groups, which differ only in the scaffold material used. Liang et al. [35] therefore introduced a video-based gait analysis with higher sensitivity. Nevertheless, the results coincide with our biomechanical data.

The biomechanical data of the newly developed test material showed similar outcomes compared to the control material. The maximum failure loads of both scaffold materials were in the range of native tendon. This is in agreement with the results of Best el al. [28] who investigated a simple repair of a division of the Achilles tendon in rats. However, in a study by Webb et al. [34], the maximum failure loads of the repaired tendons at 40 days postoperatively using several synthetic scaffolds in an Achilles tendon defect model were significantly decreased compared to the native control.

In our study, the tear strength and stiffness of native tendons were significantly higher compared to the repaired tendons. In this context, our animal study was limited by missing a negative control group. Aspenberg and Virchenko [36] showed in their investigation that a 3 mm defect without repair achieved 70% of the force at failure of unoperated tendons after 28 days postoperatively. For further investigations, negative control groups (i.e., tendon repair without a scaffold) should be attempted to determine the biomechanical properties of the native scar and connective tissue.

Our histological findings are limited due to a small sample size and high failure rates. We assume that cell infiltration, remodeling, and tissue organization of newly formed ECM are highly dependent on whether the Achilles tendon repair using scaffolds was intact over time, particularly at the junction with native tendon tissue, and whether it transferred tensile load. The histological evaluation of the in vivo host response to several collagen scaffold materials was performed in a defect in the musculotendinous tissue of the abdominal wall by Valentin et al. [37], but this model lacked tensile and strain loads applied to the grafts, like in tendons [38]. Although our results with respect to the remodeling and degradation process were inconsistent in some cases, the test material seemed to undergo a slower remodeling process, which was expected due to the processing of the test material by means of cross-linking. ECM material that is further processed to minimize its degradation rate, e.g., through cross-linking, is associated with fibrous encapsulation and chronic inflammation [39]. Therefore, removal of potential free epoxide was carried out by successive washing. However, neither the test material nor the control material showed any signs of inflammation. For further histological investigations not only a higher sample size, but also a preparation with additional staining (e.g., Picrosirius red) is recommended, which allows a more detailed analysis, like quantitative analysis of cell migration and evaluation of new versus old collagen.

The relatively high implant failure rate observed in our study was caused by the limitations of the animal model. The scaffolds were applied as an interposition in a large tendon defect. For tendon repair of the Achilles tendon in rats, defect sizes range from 3 mm [36] to 5 mm [34]. The defect size of 5 mm was considered suitable as we used comparatively big rats (mean weight operation about 400 g). Thus, healthy tissue, which is important for secure anchoring of the sutures, was resected. Furthermore, the M. plantaris tendon was removed to prevent any negative impact as splints [26]. As the space in small animals is limited, we used only a simple stitch suture technique as described in [34, 40]. Suture techniques using more stiches preventing suture tear-out are recommended [41]. Our animals were allowed to move free in their cages postoperatively. Some animal models examine if postoperative immobilization may improve the outcome of tendon regeneration [38, 42], but in rodent studies, immobilization due to several casting methods resulted in skin irritation, weight loss, slipping out of the cast, or muscle trophy due to the resting position of the limbs [43]. In addition, we used anesthesia that could be directly antagonized after the surgical procedure. Thus, the animals spent less time under anesthesia after the operation, which incurred fewer perioperative risks like hypothermia. Since the animals were supplied with analgesics, this allowed them to stress their operated leg immediately postoperatively and may have promoted rupture of the sutures. In a subsequent investigation we tested the primary fixation

stability of different suture techniques for the described animal model [44]. The results support the findings that almost all samples failed due to suture tear-out of the tendon and simple sutures performed poorly against techniques with more suture strands. Therefore, it is important to use a secure suture technique to decrease the risk and prevent suture tear-out or other defects in vivo. In our defect model we did not consider the normal anatomy of the native Achilles tendon of the rat, which consist of three subtendons. It was reported that they cause nonuniform behavior (relative displacement and differential strains) within the tendon [45]. Further investigation may include influence of the subtendon organization and properties on tendon defect models. For further investigations, large animal models should also be considered to assess the application of scaffolds for tendon repair in a situation closer to that of humans.

5. Conclusion

We analyzed a newly introduced bovine collagen scaffold material for tendon repair in an Achilles tendon defect model in rats. The experimental data revealed that the bovine scaffold material had comparable biomechanical and biological properties in vitro and in vivo compared to a commercially available porcine scaffold material. In order to detect possible failure of the replaced tendon and therefore to validate the functional, biomechanical, and histological outcomes, MRI as an auxiliary measurement tool is recommended. Further in vivo investigations should be carried out to assess the degradation and remodeling process of the scaffolds in detail.

Data Availability

The data used to support the findings of this study are included within the article.

Disclosure

The results were presented in part at the annual meeting of the Orthopaedic Research Society in 2017 (ORS 2017, March 19-22, 2017, San Diego, California).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] R. R. Clark, B. D. Dierckman, M. S. Bahk, N. S. Ghodadra, S. J. Snyder, and J. P. Burns, "Patch augmentation for rotator cuff repair: indications, techniques, and outcomes," *Operative Techniques in Sports Medicine*, vol. 20, no. 3, pp. 224–232, 2012.

[2] S. Choi, M. K. Kim, G. M. Kim, Y.-H. Roh, I. K. Hwang, and H. Kang, "Factors associated with clinical and structural outcomes after arthroscopic rotator cuff repair with a suture bridge technique in medium, large, and massive tears," *Journal of Shoulder and Elbow Surgery*, vol. 23, no. 11, pp. 1675–1681, 2014.

[3] A. M. Müller, M. Flury, H. N. Alsayed, and L. Audigé, "Influence of patient and diagnostic parameters on reported retear rates after arthroscopic rotator cuff repair," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 25, no. 7, pp. 2089–2099, 2017.

[4] Y. Ono, D. A. Dávalos Herrera, J. M. Woodmass, R. S. Boorman, G. M. Thornton, and I. K. Lo, "Can grafts provide superior tendon healing and clinical outcomes after rotator cuff repairs?" *Orthopaedic Journal of Sports Medicine*, vol. 4, no. 12, p. 232596711667419, 2016.

[5] J. H. James Choi, E. Alentorn-Geli, J. J. Stuart, G. E. Garrigues, and A. P. Toth, "Rotator cuff reconstruction and augmentation using polymer, allograft, and xenograft constructs," *Techniques in Orthopaedics*, vol. 31, no. 2, pp. 102–107, 2016.

[6] C. Jung, G. Spreiter, L. Audigé, S. J. Ferguson, and M. Flury, "Patch-augmented rotator cuff repair: influence of the patch fixation technique on primary biomechanical stability," *Archives of Orthopaedic and Trauma Surgery*, vol. 136, no. 5, pp. 609–616, 2016.

[7] Y. Ono, D. A. Dávalos Herrera, J. M. Woodmass, R. S. Boorman, G. M. Thornton, and I. K. Lo, "Healing rate and clinical outcomes of xenografts appear to be inferior when compared to other graft material in rotator cuff repair: a meta-analysis," *Journal of ISAKOS: Joint Disorders & Orthopaedic Sports Medicine*, vol. 1, no. 6, pp. 321–328, 2016.

[8] F. A. Barber and J. Aziz-Jacobo, "Biomechanical testing of commercially available soft-tissue augmentation materials," *Arthroscopy: The Journal of Arthroscopic and Related Surgery*, vol. 25, no. 11, pp. 1233–1239, 2009.

[9] K. A. Derwin, A. R. Baker, R. K. Spragg, D. R. Leigh, and J. P. Iannotti, "Commercial extracellular matrix scaffolds for rotator cuff tendon repair: biomechanical, biochemical, and cellular properties," *The Journal of Bone & Joint Surgery*, vol. 88, no. 12, pp. 2665–2672, 2006.

[10] E. T. Ricchetti, A. Aurora, J. P. Iannotti, and K. A. Derwin, "Scaffold devices for rotator cuff repair," *Journal of Shoulder and Elbow Surgery*, vol. 21, no. 2, pp. 251–265, 2012.

[11] J. E. Reing, L. Zhang, J. Myers-Irvin et al., "Degradation products of extracellular matrix affect cell migration and proliferation," *Tissue Engineering Part A*, vol. 15, no. 3, pp. 605–614, 2009.

[12] M. H. Amini, E. T. Ricchetti, J. P. Iannotti, and K. A. Derwin, "An update on scaffold devices for rotator cuff repair," *Techniques in Shoulder & Elbow Surgery*, vol. 18, no. 3, pp. 101–112, 2017.

[13] T. Thangarajah, C. J. Pendegrass, S. Shahbazi, S. Lambert, S. Alexander, and G. W. Blunn, "Augmentation of rotator cuff repair with soft tissue scaffolds," *Orthopaedic Journal of Sports Medicine*, vol. 3, no. 6, 2015.

[14] F. A. Barber, J. P. Burns, A. Deutsch, M. R. Labbé, and R. B. Litchfield, "A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair," *Arthroscopy: The Journal of Arthroscopic and Related Surgery*, vol. 28, no. 1, pp. 8–15, 2012.

[15] G. J. Gilot, A. M. Alvarez-Pinzon, L. Barcksdale, D. Westerdahl, M. Krill, and E. Peck, "Outcome of large to massive rotator cuff tears repaired with and without extracellular matrix augmentation: a prospective comparative study," *Arthroscopy—Journal of Arthroscopic and Related Surgery*, vol. 31, no. 8, pp. 1459–1465, 2015.

[16] J. P. Yoon, S. W. Chung, J. Y. Kim et al., "Outcomes of combined bone marrow stimulation and patch augmentation for massive rotator cuff tears," *The American Journal of Sports Medicine*, vol. 44, no. 4, pp. 963–971, 2015.

[17] M. E. Steinhaus, E. C. Makhni, B. J. Cole, A. A. Romeo, and N. N. Verma, "Outcomes after patch use in rotator cuff repair," *Arthroscopy—Journal of Arthroscopic and Related Surgery*, vol. 32, no. 8, pp. 1676–1690, 2016.

[18] M. Flury, D. Rickenbacher, C. Jung, M. M. Schneider, D. Endell, and L. Audigé, "Porcine dermis patch augmentation of supraspinatus tendon repairs: a pilot study assessing tendon integrity and shoulder function 2 years after arthroscopic repair in patients aged 60 years or older," *Arthroscopy—Journal of Arthroscopic and Related Surgery*, vol. 34, no. 1, pp. 24–37, 2018.

[19] C. G. Ziegler, C. Edgar, M. Cote, and A. D. Mazzocca, "Biological augmentation in repair and reconstruction of the rotator cuff," *Operative Techniques in Sports Medicine*, vol. 23, no. 1, pp. 2–10, 2015.

[20] P. Ciampi, C. Scotti, A. Nonis et al., "The benefit of synthetic versus biological patch augmentation in the repair of posterosuperior massive rotator cuff tears: a 3-year follow-up study," *The American Journal of Sports Medicine*, vol. 42, no. 5, pp. 1169–1175, 2014.

[21] J. A. Neumann, M. H. Zgonis, K. D. Rickert et al., "Interposition dermal matrix xenografts: a successful alternative to traditional treatment of massive rotator cuff tears," *The American Journal of Sports Medicine*, vol. 45, no. 6, pp. 1261–1268, 2017.

[22] S. P. Badhe, T. M. Lawrence, F. D. Smith, and P. G. Lunn, "An assessment of porcine dermal xenograft as an augmentation graft in the treatment of extensive rotator cuff tears," *Journal of Shoulder and Elbow Surgery*, vol. 17, no. 1, pp. S35–S39, 2008.

[23] E. S. Lederman, A. P. Toth, G. P. Nicholson et al., "A prospective, multicenter study to evaluate clinical and radiographic outcomes in primary rotator cuff repair reinforced with a xenograft dermal matrix," *Journal of Shoulder and Elbow Surgery*, vol. 25, no. 12, pp. 1961–1970, 2016.

[24] B. W. Sears, A. Choo, A. Yu, A. Greis, and M. Lazarus, "Clinical outcomes in patients undergoing revision rotator cuff repair with Extracellular matrix augmentation," *Orthopedics*, vol. 38, no. 4, pp. e292–e296, 2015.

[25] C. Gabler, J. Spohn, T. Tischer, and R. Bader, "Biomechanical, biochemical, and cell biological evaluation of different collagen scaffolds for tendon augmentation," *BioMed Research International*, vol. 2018, Article ID 7246716, 11 pages, 2018.

[26] G. A. C. Murrell, E. G. Lilly, H. Davies, T. M. Best, R. D. Goldner, and A. V. Seaber, "The achilles functional index," *Journal of Orthopaedic Research*, vol. 10, no. 3, pp. 398–404, 1992.

[27] C. A. Kurtz, T. G. Loebig, D. D. Anderson, P. J. DeMeo, and P. G. Campbell, "Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model," *The American Journal of Sports Medicine*, vol. 27, no. 3, pp. 363–369, 1999.

[28] T. M. Best, A. Collins, E. G. Lilly, A. V. Seaber, R. Goldner, and G. A. C. Murrell, "Achilles tendon healing: a correlation between functional and mechanical performance in the rat," *Journal of Orthopaedic Research*, vol. 11, no. 6, pp. 897–906, 1993.

[29] A. Aurora, J. A. McCarron, A. J. van den Bogert, J. E. Gatica, J. P. Iannotti, and K. A. Derwin, "The biomechanical role of scaffolds in augmented rotator cuff tendon repairs," *Journal of Shoulder and Elbow Surgery*, vol. 21, no. 8, pp. 1064–1071, 2012.

[30] M. T. Rodrigues, R. L. Reis, and M. E. Gomes, "Engineering tendon and ligament tissues: Present developments towards successful clinical products," *Journal of Tissue Engineering and Regenerative Medicine*, vol. 7, no. 9, pp. 673–686, 2013.

[31] G. Walden, X. Liao, S. Donell, M. J. Raxworthy, G. P. Riley, and A. Saeed, "A clinical, biological, and biomaterials perspective into tendon injuries and regeneration," *Tissue Engineering—Part B: Reviews*, vol. 23, no. 1, pp. 44–58, 2017.

[32] R. G. Cutlip, M. S. Hollander, G. A. Johnson, B. W. Johnson, S. A. Friend, and B. A. Baker, "Magnetic resonance imaging of graded skeletal muscle injury in live rats," *Environmental Health Insights*, vol. 8, supplement 1, pp. 31–39, 2014.

[33] G. A. C. Murrell, E. G. Lilly, R. D. Goldner, A. V. Seaber, and T. M. Best, "Effects of immobilization on achilles tendon healing in a rat model," *Journal of Orthopaedic Research*, vol. 12, no. 4, pp. 582–591, 1994.

[34] W. R. Webb, T. P. Dale, A. J. Lomas et al., "The application of poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) scaffolds for tendon repair in the rat model," *Biomaterials*, vol. 34, no. 28, pp. 6683–6694, 2013.

[35] J. Liang, M. Chen, T. Hsieh et al., "Video-based gait analysis for functional evaluation of healing achilles tendon in rats," *Annals of Biomedical Engineering*, vol. 40, no. 12, pp. 2532–2540, 2012.

[36] P. Aspenberg and O. Virchenko, "Platelet concentrate injection improves Achilles tendon repair in rats," *Acta Orthopaedica*, vol. 75, no. 1, pp. 93–99, 2004.

[37] J. E. Valentin, J. S. Badylak, G. P. McCabe, and S. F. Badylak, "Extracellular matrix bioscaffolds for orthopaedic applications: a comparative histologic study," *Journal of Bone and Joint Surgery—Series A*, vol. 88, no. 12, pp. 2673–2686, 2006.

[38] T. W. Lin, L. Cardenas, and L. J. Soslowsky, "Biomechanics of tendon injury and repair," *Journal of Biomechanics*, vol. 37, no. 6, pp. 865–877, 2004.

[39] L. M. Delgado, Y. Bayon, A. Pandit, and D. I. Zeugolis, "To cross-link or not to cross-link? cross-linking associated foreign body response of collagen-based devices," *Tissue Engineering—Part B: Reviews*, vol. 21, no. 3, pp. 298–313, 2015.

[40] T. Zantop, T. W. Gilbert, M. C. Yoder, and S. F. Badylak, "Extracellular matrix scaffolds are repopulated by bone marrow-derived cells in a mouse model of Achilles tendon reconstruction," *Journal of Orthopaedic Research*, vol. 24, no. 6, pp. 1299–1309, 2006.

[41] R. Y. Ikemoto, J. Murachovsky, L. G. P. Nascimento, R. S. Bueno, L. H. Almeida, and E. Strose, "Study on the resistance of the supraspinous tendon using simple, matress and mason allen stitches," *Acta Ortopédica Brasileira*, vol. 18, no. 2, pp. 100–103, 2010.

[42] C. Güngörmüş, M. A. Çetinkaya, and A. Demirutku, "A new model for partial immobilization of rat hind limb after Achilles

tendon excision/reinterposition," *Turkish Journal of Veterinary & Animal Sciences*, vol. 37, pp. 546–552, 2013.

[43] E. L. Coutinho, A. R. S. Gomes, C. N. Fança, and T. F. Salvini, "A new model for the immobilization of the rat hind limb," *Brazilian Journal of Medical and Biological Research*, vol. 35, no. 11, pp. 1329–1332, 2002.

[44] C. Gabler, S. Gierschner, T. Tischer, and R. Bader, "Comparison of different suture techniques for Achilles tendon repair in rat model using collagen scaffolds," *Acta of Bioengineering and Biomechanics*, vol. 20, no. 2, pp. 73–77, 2018.

[45] T. Finni, M. Bernabei, G. C. Baan, W. Noort, C. Tijs, and H. Maas, "Non-uniform displacement and strain between the soleus and gastrocnemius subtendons of rat Achilles tendon," *Scandinavian Journal of Medicine & Science in Sports*, vol. 28, no. 3, pp. 1009–1017, 2018.

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Research Article

Partial Anterior Cruciate Ligament Ruptures: Advantages by Intraligament Autologous Conditioned Plasma Injection and Healing Response Technique—Midterm Outcome Evaluation

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The historical treatment options for partial anterior cruciate ligament (ACL) ruptures were conservative therapy or ACL reconstruction by injured bundle or entire ACL replacement. In awareness of the regenerative potential of biologic agents such as mesenchymal stem cells or platelet rich plasma (PRP), the healing response technique was developed to preserve the injured ACL with better outcomes than the conservative therapy. Further improvement of this technique seems to be obtained by the additional application of PRP products. Thus, the aim of this study was to evaluate the midterm outcome after intraligament autologous conditioned plasma (ACP) by a clinical, scoring, and functional performance assessment. 42 patients were evaluated in this study. The failure rate was 9.5%. Outcome evaluation showed good to excellent results. The scores were IKDC subjective 83.2 (SD 14.5), Lysholm 85.5 (SD 15.5), Tegner 4.7 (SD 1.7), and Cincinnati 85.4 (SD 15.5) after a mean follow-up of 33 months. Clinical examination showed stable Lachman test, negative pivot shift phenomenon, and a significant reduction in AP-laxity compared to preoperative status (rolimeter preoperative: 1.9 (SD1.4); postoperative 0.6 (SD1.8), p=0.001) in all patients. Functional performance testing showed no significant differences between the injured and healthy side. Return to sport was achieved after a mean of 5.8 months (SD 3.6) in 71.1% of the included patients. In summary, this new treatment option revealed in midterm follow-up promising results to treat partial ACL lesions with a reduced need for conversion to ACL reconstruction and with a high percentage of return to preinjury sport activity.

1. Introduction

Partial anterior cruciate ligament (ACL) ruptures are a challenging condition for orthopaedic surgeons. The prevalence ranges up to 28% [1–3]. Diagnosis and management of this type of ACL lesions are still under discussion [3, 4]. A reliable assessment of the extension of injury of partial ACL tears usually requires multiple findings by clinical examination, MRI examination, and almost confirming arthroscopically examination [3]. The therapeutic options for the treatment of partial ACL tears historically range from conservative treatment up to partial reconstruction in terms of a bundle augmentation or complete ACL reconstruction according to the injured bundles [1, 3]. The choice of therapy depends on the physical demands of the patients, clinical proven instability, location, and amount of tear as well as concomitant injuries [1]. However, there are many limitations for these therapeutic options. Conservative therapy of partial ACL tears is associated with a high failure rate and often consecutive complete ACL rupture, followed by ACL reconstruction. Initial ACL reconstruction is reported to be potentially associated with diminished proprioception, postoperative muscular weakness, no fully restoration of normal kinematics, donor site morbidity, and possible premature osteoarthritis [4]. Thus, ACL preserving techniques have to be favoured.

Table 1: Grading system of partial ACL ruptures.

Grade	Definition
1	intact ACL sheet with haemorrhage of the synovial ACL sheet
2	ruptured synovial ACL sheet without extrusion of ACL tissue
3	ruptured synovial ACL sheet with extrusion of ACL tissue
4	partial rupture of one ACL bundle with 25-50% remaining ACL structure cave: in case of a two bundle partial ACL rupture, the percentage of the more injured bundle is used for classification
5	partial rupture of one ACL bundle with 10-25% remaining ACL structure cave: in case of a two bundle partial ACL rupture, the percentage of the more injured bundle is used for classification

Regarding the awareness on the role of biologic agents, such as growth factors and stem cells, in promoting tissue healing further therapeutic options for the therapy of partial ACL tears were developed. In the most known "healing response technique" introduced by Steadman et al. bone marrow stimulation by microfracturing of the lateral fossa intercondylaris of the femur is performed to obtain a clot formation near to the femoral insertion of the torn ACL [4–7]. However, the clinical results are still under discussion. While Steadman et al. showed promising results [5, 6], Wasmaier et al. stated contrary results with no beneficial effects in comparison to the conservative approaches regarding clinical scores, rate of revision surgery, or joint laxity [4, 8].

However, the "healing response technique" can auspiciously be upgraded by the additional application of platelet rich plasma (PRP) [1, 9]. PRP products are already in clinical practice for many orthopaedic disorders, such as osteoarthritis, tendinopathies, or ligament injuries [1, 10–12]. Preclinical studies demonstrated the qualities of PRP in the regulation of the articular environment, exerting a positive metabolic modulation on all joint tissues and promoting tissue healing. Furthermore, PRP was associated with beneficial effects in stimulating fibroblasts proliferation, collagen fibres deposition, and reducing catabolic distress, when applied to ACL-derived tenocytes [13, 14]. Also in vivo studies emphasise the beneficial effect of PRP augmentation, which provide better histological appearance and superior biomechanical properties [15, 16]. So, according to Andriolo et al. there is a strong rationale for the use of PRP to improve ACL healing [1, 17].

Thus, the aim of this study was to evaluate the midterm outcome of patients having partial ACL tears treated by intraligament injection of autologous conditioned plasma (ACP) (Arthrex) and healing response technique according to both, functional, and clinical criteria.

2. Material and Methods

The study was approved by the University Hospital Ethic Committee and Scientific Board, and written consent was collected for each patient.

2.1. Patient Selection. Patients had been elucidated concerning intraoperative assessment of the ACL rupture and intraoperative decision concerning the treatment (ACL reconstruction versus healing response technique and intraligament ACP injection) in detail before. During regular arthroscopy, patients were screened for partial ACL rupture, while partial ACL rupture was defined as "a partial rupture of the anteromedial or posterolateral or partial rupture of both ACL bundles" and the presence of exclusion criteria. The degree of partial ACL rupture was classified according to a previously introduced ACL grading system [1], which describes the amount of injured ACL tissue in five increasing steps (see Table 1).

In case of a confirmed diagnosis intraligament ACP injection and healing response technique were performed as previously described by Koch et al. [1] (see Figure 1).

Inclusion criteria were defined as patients aged > 18 years and affected by partial ACL rupture according to the definition above.

Exclusion criteria were defined as previously described [1]:

(1) complete tear of at least one bundle of the ACL;

(2) previous or concurrent major cartilage procedures and meniscus replacement;

(3) previous or concurrent ligament reconstruction in the index knee joint;

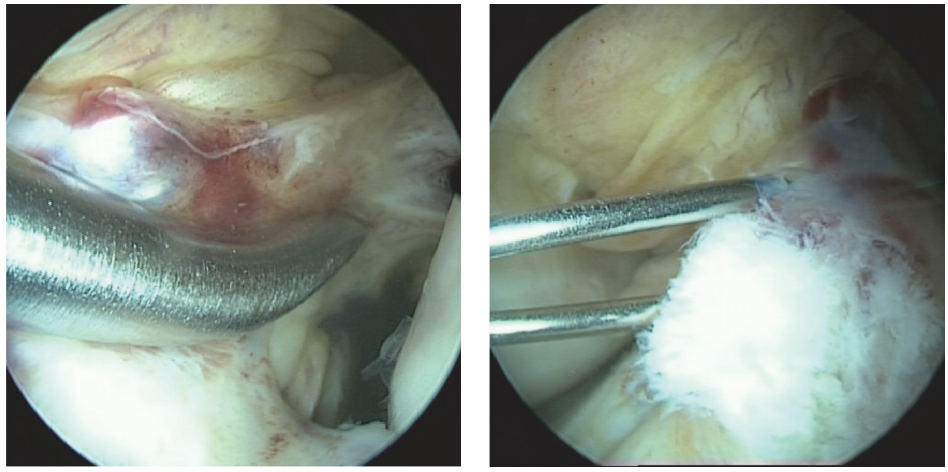
(4) presence of rheumatic diseases or chronic inflammatory arthropathy;

(5) therapeutic anticoagulation;

(6) further other surgical procedure in the index knee joint within 12 months from the present treatment.

2.2. Surgical Procedure and Rehabilitation. Partial ACL rupture was confirmed during diagnostic arthroscopy as described above. Intraligament ACP application into the distal ACL stump and healing response technique at the lateral femoral fossa intercondylaris as well as postoperative care were performed as previously described by Koch et al. [1].

After removal of the arthroscopic fluid both procedures were realised as the last procedure during surgery. No drains were inserted. For postoperative rehabilitation the index knee was immobilized in a 20° flexed splint and partial load bearing (10 kg body weight) was followed for 1-2 weeks. During this period passive range of motion with 0-20-60° trained by the physiotherapist was allowed. Full extension had to be avoided to reduce tension on the ACL during the initial healing period. Full weight bearing started in the third week. For additional external stabilization an ACL brace with a limited range of motion (lack of 10° extension to 90° flexion)



(a) (b)

Figure 1: (a) Healing response technique and (b) intraligament ACP injection in a partial ACL rupture grade 3.

during the day and a 20° flexed immobilizing splint overnight were applied. Propriozeption was trained by physiotherapy. After 6 weeks training intensity increased to active assisted and active muscle strengthening.

2.3. Patient Evaluation and Follow-Up. For retrospective midterm outcome evaluation at follow-up, all patients were screened for the presence of exclusion and failure criteria. Outcome was assessed using the following items:

(1) patients' history:

patient satisfaction, time to return to sport (RTS), and postoperative complications;

(2) clinical scores:

IKDC subjective/objective, Lysholm, Tegner, Cincinnati Scores, and the Marx Activity Scale;

(3) clinical examination:

rolimeter assessment and clinical stability testing (Lachman test, pivot shift test);

(4) functional performance tests:

drop-jump test, side-hop test, one- and two-leg stability test, and quick-feet test.

Failure was defined as

(1) persisting knee instability with general indication for ACL reconstruction;

(2) side to side difference > 4 mm in rolimeter analysis of the knee joint;

(3) persisting positive pivot shift test or no firm endpoint in Lachman-testing in the follow-up evaluation.

2.4. Statistical Analysis. Statistical analysis was performed using the SPSS software version 23.0 (SPSS, Chicago, IL, USA) to determine relationships between the different variables. To determine whether data followed a Gaussian distribution a Kolmogorov-Smirnov-test was performed. Due to nonnormal distributed data Wilcoxon signed-rank test was used for quantitative data analysis. The significance level was set at $p \leq 0.05$.

3. Results

In total 42 patients after intraligament ACP application and healing response in partial ACL ruptures were reviewed in this retrospective study. Four patients had to be excluded due to the exclusion criteria. One patient of those had an Achilles tendon rupture during follow-up period, so no usable follow-up assessment was available. One patient developed a symptomatic progressing cartilage defect and received a reoperation during the follow-up period. Two patients had a complete rupture in the index knee after ACP treatment that required ACL reconstruction. At the end, n = 38 patients aged between 18 and 70 years with a mean age of 42.8 years (SD 13.5 years) were included. The mean follow-up after index surgery was 33.0 months (SD 17.4 months). Concerning the gender distribution, 17 (44.7%) male and 21 (55.3%) female patients were treated in context of this study. Overall, in n = 25 cases (65.8%) the right knee and in n = 13 cases (34.2%) the left knee were injured. In n = 30 (78.9%) of the affected patients the dominant side was concerned. Concomitant injuries of the knee joint, such as meniscus lesions or injury of the collateral ligaments, were registered in 55.3% (see Table 2).

In 84.2% of the cases, patients injured themselves by a sport associated trauma (62.5% ski; 15.6% football; 6.25% volleyball; 3.1% mountain biking; 3.1% kung-fu). However, just the minority of the patients (2.6%) performed professional sport (see Table 2).

After index surgery, patients returned to sport after a mean period of 5.8 months (SD 3.6 months). Full sportive activity level was regained by 71.1% of the included patients during the follow-up period. Overall, all patients subjectively

Table 2: Epidemiological data and injury pattern.

	all included patients n = 38	Grade I / II n = 9	Grade III n = 23	Grade IV / V n = 6	failure n = 4
follow-up [months, mean (SD)]	**33.0 (17.4)**	38.7 (18.3)	30.5 (18.6)	34.0 (9.6)	-
age [years, mean (SD)]	**42.8 (13.5)**	39.1 (14.6)	43.7 (14.0)	45.2 (10.8)	26.8 (8.6)
gender [%; male/ female]	**44.7/55.3**	44.4/55.6	47.8/52.2	33.3/66.6	50/50
index side [%; right/ left]	**65.8/34.2**	88.9/11.1	60.9/39.1	50.0/50.0	50/50
dominant side [%; right/ left]	**78.9/21.1**	77.8/22.2	60.9/39.1	100/0	75/25
concomitant injury [%]	**55.3**	33.3	60.9	66.7	75.0
meniscus [%]	**80.9**	66.7	47.8	66.7	75.0
collateral ligament [%]	**47.6**	33.3	39.1	0	0
sports associated injury	**84.2**	88.9	65.2	100	100
football [%]	**15.6**	12.5	20.0	16.7	25
ski [%]	**62.5**	62.5	73.3	66.7	50
mountain biking [%]	**3.1**	12.5	0	0	0
volleyball [%]	**6.25**	12.51	6.7	0	25
kung-fu [%]	**3.1**	0	0	16.7	0
pre-injury sport level					
recreational [%]	**55.3**	55.6	52.2	66.7	25
amateur [%]	**42.1**	33.3	47.8	33.3	75
professional [%]	**2.6**	11.1	0	0	0

Table 3: Return to sport data.

	all included patients	Grade I / II	Grade III	Grade IV / V
return to ...	**mean (SD)**	mean (SD)	mean (SD)	mean (SD)
training [weeks]	**12.8 (7.2)**	9.8 (4.8)	14.4 (7.6)	12.3 (8.3)
sports [months]	**5.8 (3.6)**	4.9 (3.4)	6.0 (2.2)	6.8 (5.8)
pre-injury sport level [%]	**71.1**	88.9	43.5	100
subjective regain of sport level [%]	**85.8 (19.0)**	86.9 (18.5)	82.8 (21.3)	94.2 (8.0)

regained in mean 85.8% (SD 19.0%) of their preinjury sportive activity level (see Table 3).

Concerning the clinical outcome evaluation, a firm endpoint in the ACL stability testing and no positive pivot shift glide test was documented for all assessed patients. Femorotibial translation was quantitatively analysed by rolimeter testing and significant reduction (preoperative: 1.9 mm (SD 1.4 mm) versus postoperative at the latest FU: 0.6 mm (SD 1.8 mm)) was registered after combined intraligament ACP application and healing response technique ($p = 0.001$) (see Table 4).

Activity scores, such as IKDC subjective score, Lysholm score, Tegner activity score, Cincinnati score, Marx scale, and IKDC objective score, revealed almost full recovery of the functional activity level at the latest follow-up (see Table 5).

For objective outcome evaluation established functional performance tests, like the drop-jump test, side-hop test, and one- and two-leg stability test as well as quick-feet test, were performed. The comparison of the index versus the healthy side in the drop jump as well as the one-leg-stability test showed no significant differences. Overall, good to excellent results were achieved (see Table 6).

4. Discussion

The current study showed for the first time midterm outcome results of patients after an ACL preserving procedure in terms of intraligament ACP application and healing response in partial ACL ruptures evaluated by functional performance tests. Additionally it presents a big cohort of patients after partial ACL rupture treated with intraligament ACP application and healing response assessed by clinical tests and clinical scores with the longest follow-up currently available. In total, 42 patients with a mean follow-up of 33 months (SD 17.4 months) were initially reviewed in this study. However, 4 out of 42 (9.5%) patients had to be excluded as a failure; whereas one had an Achilles tendon injury during follow-up, so the follow-up assessment could not be completed. One patient received an operative cartilage therapy during the follow-up period because of a symptomatic progressing cartilage lesion. A consecutive complete ACL rupture was diagnosed and treated with entire ACL replacement in two patients during follow-up period. Previous studies evaluating the effect of PRP products in partial ACL therapy are limited to a mean follow-up of at least up to 25.1 months (SD 10.0 months)

Table 4: Clinical outcome data.

	all included patients	Grade I / II	Grade III	Grade IV / V
ROM deficit [%]	**10.5**	0	13.0	16.7
LM test				
negative [%]	**100**	100	100	100
positive [%]	**0**	0	0	0
pivot shift				
negative [%]	**100**	100	100	100
positive [%]	**0**	0	0	0
rolimeter test				
pre-operative [mm]	**1.9 (SD 1.4)**	1.7 (SD 1.5)	1.7 (SD 1.4)	3.2 (SD 1.0)
post-operative [mm]	**0.6 (SD 1.8)**	0.6 (SD 1.7)	1.2 (SD 1.8)	0.2 (SD 1.2)
p-value	**0.001∗**	0.01∗	0.4	0.0007∗

[∗] = sign for significance; significance level < 0.05.

Table 5: Postoperative outcome scoring.

score	**all included patients**	Grade I / II	Grade III	Grade IV / V
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
IKDC subjective	**83.2 (14.5)**	85.6 (18.4)	80.1 (13.8)	89.7 (8.1)
Lysholm	**85.5 (15.5)**	83.2 (26.6)	85.4 (10.3)	89.3 (8.5)
Tegner	**4.7 (1.7)**	5.1 (2.1)	4.6 (1.6)	4.6 (1.9)
Cincinnati	**85.4 (15.5)**	81.6 (23.5)	86.4 (11.7)	90.0 (8.9)
Marx	**4.8 (4.4)**	7.0 (4.4)	3.5 (3.8)	1.7 (0.8)
IKDC objective	**[%]**	[%]	[%]	[%]
A	**59.4**	62.5	61.1	50.0
B	**28.1**	25.0	27.8	33.3
C	**12.5**	12.5	11.1	16.7
D	**0**	0	0	0

Table 6: Functional performance tests.

functional performance test	**all included patients**	Grade I / II	Grade III	Grade IV / V
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
drop jump test				
index side [points]	**7.4 (1.2)**	7.9 (1.0)	7.3 (1.3)	6.8 (1.1)
healthy side [points]	**7.5 (1.3)**	7.5 (1.1)	7.7 (1.3)	6.8 (1.6)
p-value	**n.s.**	n.s.	n.s.	n.s.
side-hop-test				
(1) trial [sec]	**0.2 (1.9)**	0.7 (0.9)	0.6 (1.8)	-1.8 (1.3)
(2) trial [sec]	**0.6 (1.6)**	0.4 (1.0)	0.7 (1.8)	0.9 (1.8)
two-leg-stability test				
(1) trial [sec]	**3.5 (0.8)**	3.2 (0.6)	3.5 (0.8)	3.8 (0.7)
(2) trial [sec]	**3.1 (0.8)**	3.0 (0.3)	3.1 (1.0)	3.5 (0.8)
one-leg-stability test				
index side				
(1) trial [sec]	**2.9 (0.9)**	2.8 (0.9)	2.9 (1.0)	3.1 (0.6)
(2) trial [sec]	**2.9 (0.7)**	2.6 (0.5)	2.9 (0.8)	3.2 (0.9)
healthy side				
(1) trial [sec]	**3.0 (0.8)**	2.9 (0.8)	3.0 (0.8)	3.3 (0.9)
(2) trial [sec]	**2.8 (0.8)**	2.7 (0.5)	2.8 (0.9)	3.1 (0.7)
p-value (index vs healthy side)	**n.s.**	n.s.	n.s.	n.s.
quick-feet-test				
[sec]	**12.0 (3.4)**	10.7 (1.6)	12.6 (3.9)	11.8 (2.7)

n.s. = not significant according the level of significance > 0.05.

[1, 18]. Overall, a satisfactory outcome after intraligament ACP application and healing response was detected with a low failure rate of 9.5% and a high percentage of return to sport activity (85.8%, SD 19%) as measured by the preinjury sport level.

The therapy of partial ACL ruptures is still challenging. Historically, the treatment options ranged from conservative therapy of partial ACL tears to reconstruction of the entire ACL. The conservative treatment was used to be associated with a high failure rate because of the low endogenous regeneration potential of the ACL, based on the weak blood supply, and high rate of consecutive complete ACL ruptures based on the persistent joint instability [4]. Due to this fact, in the past there was a trend to reconstruct the entire ACL. However, regarding the comorbidities, such as donor site morbidity, loose of natural anatomy, physiology, intrinsic cell population, or proprioception after entire ACL reconstruction [4, 19], entire ACL replacement was found to be an overtreatment for partial ACL lesions. ACL "augmentation" in terms of a selective replacement of the injured ACL bundle was propagandised to preserve healthy parts of the ACL [1, 2, 4].

Based on the purpose to preserve healthy ACL tissue and regarding the increasing knowledge about stimulation of endogenous regenerative potential by the use of biologic agents, such as growths factors and stem cells, Steadman et al. developed the healing response technique to promote ACL tissue healing [5, 6]. By trephination of the fossa intercondylaris of the lateral femoral condyle next to the ACL insertion there was an inflow of growths factors and mesenchymal stem cells out of the femoral condyle into the ACL defect site stimulating tissue regeneration and scarring [1, 4–7]. Steadman et al. showed promising clinical results after performing this healing response technique in proximal ACL tears of skeletally immature athletes and older active patients [5, 6]. Overall, it was concluded that this technique is a promising tool for the treatment of very proximal ACL ruptures in young and middle aged patients [1, 5–7]. However, Wasmaier et al., reviewing clinical and radiological long-term results, were not able to comprehend the promising effect of the healing response technique in 30 young patients in comparison to a conservative treatment of proximal ACL tears [1, 4, 7, 8]. ACL insufficiency required subsequent ACL reconstruction in 36% of the evaluated patients compared to 56% of the conservative treated patients after ACL rupture [1, 8]. Also, the remaining patients (64%) showed no better outcome results than the conservative treated patients [1, 8].

However, in the awareness of the regenerative potential of platelet rich plasma (PRP) products, in the present study the healing response technique according to Steadman et al. was improved by the additional application of a commercially available PRP product, ACP.

PRP products are obtained by concentration from peripheral blood and have already been successfully applied in the treatment of many orthopaedic disorders, such as osteoarthritis, tendinopathies, or ligament injuries [1, 10–12]. As such a biologic agent, the PRP product ACP is able to mediate the tissue regeneration by influencing the inflammatory and remodelling process [4, 20]. This tissue healing enhancing effect is also based on the involvement of the platelets in the joint homeostasis, aggregation, and clot formation steps by the release of several growths factors [4, 21]. In this context, some in vitro studies showed beneficial effects of PRP on the stimulation of fibroblast proliferation, collagen fibre deposition, and reduction of catabolic distress, when applied to ACL-derived tenocytes [1, 13, 14]. Consequently, there are also some in vivo and clinical studies promoting the use of PRP products for enhancing ACL healing [1, 7, 9, 15, 16, 18, 22, 23]. Thus, there is a strong rationale to combine the beneficial effect of ACP with the regenerative effect of the healing response technique. Regarding the current literature most ACL tears are located in the midsubstance area of the ACL especially in younger patients [24]. Assuming a decreasing effect of the healing response technique dependent on an increasing distance from the femoral ACL insertion to the lesion site in midsubstance lesions, an increasing impact of the ACP application for ACL regeneration has to be postulated. So, by application into the distal ACL stump a local depot of PRP can be placed next to the lesion site to focus the regenerative effect on the target area and to provide a longer release of growth factors by reducing a wash out phenomenon, which needs to be considered after intra-articular application.

Overall, there are just few clinical studies currently available, evaluating the effect of PRP on the ACL healing in partial ACL tears. Seijas et al. showed positive results in football players after application of a PRP product into the proximal and distal ACL stump without healing response after partial ACL rupture [18]. These findings confirm results of our own cohort, which were previously published [1, 9]. However, there is no additional information about the degree of partial ACL tears available and overall just limited literature exists regarding the definition and classification of partial ACL tears [4].

Furthermore, all currently available studies concerning the use of PRP products to enhance ACL healing in partial ACL ruptures are characterized by a small cohort of patients and are limited to clinical and scoring results. Objective functional outcome measurements, such as functional performance tests, have not been published in context of outcome evaluation after partial ACL tears up to now; although, they are known to enable the physician to objectively assess the patients' knee function and ability to tolerate the daily physical demands in work and sport [25, 26]. The functional performance test mainly consists of two components, the quantity of movement and the quality of movement [27]. Both components are important factors for the assessment of rehabilitation quality as well as preventing ACL recurrent injury or treatment failure [27]. In this study the quantity and quality of movement were evaluated using a test battery including drop jump, side-hop, and quick feet as well as one- and two-leg stability tests. All of these tests showed promising results in all included patients. Also, regarding the different grades of partial ACL rupture an outcome depending on injury severity was documented in the drop jump, side-hop as well as one- and two-leg stability tests. Overall, particularly in the drop-jump test as well as in the side-hop test a clear benefit in comparison to the ACL

reconstruction was detected [28, 29]. Bell et al. performed the drop-jump test in 29 patients after ACL reconstruction and 27 healthy patients. Overall, the results after intraligament ACP application and healing response technique almost conform to the results of the healthy group [28]. Similar results were shown for the side-hop test evaluated by Itoh et al. [29]. Comparing chronic ACL deficient patients with a healthy control group, the healthy control group achieved good results like the intraligament ACP/healing response technique cohort, whereas in the ACL deficient group inferior results were detected [29]. Hildebrandt et al. evaluated the one- and two-leg stability as well as the quick-feet tests in a healthy control group as a reference group [30]. In the one-leg stability test no significant differences were detected after ACP application and healing response technique as also seen in the reference group tested by Hildebrandt et al. [30]. Overall, in the one- and two-leg stability test as well as quick-feet test the intraligament ACP/healing response technique group was inferior to the healthy control group of Hildebrandt et al. These differences might be explained by the obvious younger and healthy study population assessed by Hildebrandt et al. However, further studies also determined prolonged stabilizing deficits in patients after ACL reconstruction, for example, in comparison to a healthy control even 2.5 years after surgery [31–35].

The clinical follow-up examination as well as postoperative scoring results are in accordance with results of the functional performance tests. In the included patients good anteroposterior knee stability with a firm endpoint in the Lachman test and no positive pivot shift phenomenon were detected. Rolimeter testing showed a significant improvement of the antero-postero translation of the knee joint after intraligament application of ACP and healing response in comparison to the preinjury status in all included patients ($p = 0.001$). Likewise, the functional scores correlate with the good results of the clinical examination and functional performance tests. They are comparable with previous data of the use of PRP products in partial ACL rupture as well as after ACL bundle reconstruction technique [1, 5, 6, 36].

Overall, the described technique for the treatment of partial ACL tears enables the patients to return to sport already after a short rehabilitation period. Training started after a mean of 12.8 weeks (SD 7.2 weeks) and the preinjury level of sport activity was achieved after a mean of 5.8 months (SD 3.6 months) in 71.1% of the reviewed patients. Regarding all included patients 85.8% (SD 19.0%) of the initial sportive capacity could be restored after intraligament ACP application and healing response technique. Here, especially in case of partial ACL tears grade 1 and 2 return to training (9.8 weeks, SD 4.8 weeks) and particularly to sport (4.9 months, SD 3.4 months) was accelerated and the return to preinjury sport level (88.9%) increased. These results correlate with the promising results previously published after the use of PRP products [1, 9, 18] and showed a clear advantage for this technique over both conservative ACL therapy [18, 36–38] as well as ACL reconstruction in recreational athletes as also reviewed in this study [39, 40].

Nevertheless, there are few limitations in this study, which have to be addressed in further studies. Due to the retrospective study design, no preoperative functional performance and scoring results are available. This study also lacks a comparative control group with serial MRI analysis. Furthermore, studies with higher numbers of participating patients are required to detect significant differences in the different degrees of injury severity and to other treatment options.

Thus, it can be concluded that the intraligament application of ACP in combination with the healing response technique is a promising treatment option for the therapy of partial ACL ruptures. Good functional performance results and concurrent good subjective clinical outcome results can be achieved by this technique at a midterm follow-up of averaged almost 3 years. Overall, the procedure is associated with a low failure rate and a high percentage of full recovery concerning the preinjury sport level. However, further high quality comparative and matched studies are needed to verify the qualities of the intraligament ACP application in combination with the healing response technique in comparison to the ACL reconstruction and to detect significant differences in the outcome of patients classified according to the grading system to develop a reliable treatment algorithm.

Data Availability

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they received support from Arthrex for this study.

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References

[1] M. Koch, B. D. Matteo, J. Eichhorn et al., "Intra-ligamentary autologous conditioned plasma and healing response to treat partial ACL ruptures," *Archives of Orthopaedic and Trauma Surgery*, vol. 138, no. 5, pp. 675–683, 2018.

[2] B. Sonnery-Cottet and P. Colombet, "Partial tears of the anterior cruciate ligament," *Orthopaedics & traumatology, surgery & research : OTSR*, vol. 102, no. 1, pp. S59–S67, 2016.

[3] E. F. Temponi, L. H. de Carvalho Júnior, B. Sonnery-Cottet, and P. Chambat, "Partial tearing of the anterior cruciate ligament: diagnosis and treatment," *Revista Brasileira de Ortopedia (English Edition)*, vol. 50, no. 1, pp. 9–15, 2015.

[4] I. Dallo, J. Chahla, J. J. Mitchell, C. Pascual-Garrido, J. A. Feagin, and R. F. LaPrade, "Biologic approaches for the treatment of partial tears of the anterior cruciate ligament: a current concepts review," *Orthopaedic Journal of Sports Medicine*, vol. 5, no. 1, 2017.

[5] M. L. Cameron-Donaldson, K. K. B. Cameron-Donaldson, W. G. Rodkey, and J. R. Steadman, "A minimally invasive technique ("Healing Response") to treat proximal ACL injuries in

skeletally immature athletes," *Journal of Knee Surgery*, vol. 19, no. 1, pp. 8–13, 2006.

[6] J. Steadman, L. Matheny, K. Briggs, W. Rodkey, and D. Carreira, "Outcomes following healing response in older, active patients: a primary anterior cruciate ligament repair technique," *Journal of Knee Surgery*, vol. 25, no. 03, pp. 255–260, 2012.

[7] A. M. Kiapour and M. M. Murray, "Basic science of anterior cruciate ligament injury and repair," *Bone & Joint Research*, vol. 3, no. 2, pp. 20–31, 2014.

[8] J. Wasmaier, K. Eid, R. Kubik-Huch, C. Bieg, C. Pfirrmann, and H. Grehn, "Proximal anterior cruciate ligament tears: the healing response technique versus conservative treatment," *Journal of Knee Surgery*, vol. 26, no. 4, pp. 263–272, 2012.

[9] J. Eichhorn, "Einsatz von ACP bei der Healing response, -Technik zur Behandlung von Knieverletzungen," *JATROS Unfallchirurgie Sporttraumatologie*, vol. 10, pp. 10–12, 2015.

[10] E. Kon, G. Filardo, B. Di Matteo, and M. Marcacci, "PRP for the treatment of cartilage pathology," *The Open Orthopaedics Journal*, vol. 7, pp. 120–128, 2013.

[11] B. Di Matteo, G. Filardo, E. Kon, and M. Marcacci, "Platelet-rich plasma: evidence for the treatment of patellar and Achilles tendinopathy—a systematic review," *Musculoskeletal Surgery*, vol. 99, no. 1, pp. 1–9, 2015.

[12] L. Podesta, S. A. Crow, D. Volkmer, T. Bert, and L. A. Yocum, "Treatment of partial ulnar collateral ligament tears in the elbow with platelet-rich plasma," *The American Journal of Sports Medicine*, vol. 41, no. 7, pp. 1689–1694, 2013.

[13] R. Yoshida, M. Cheng, and M. M. Murray, "Increasing platelet concentration in platelet-rich plasma inhibits anterior cruciate ligament cell function in three-dimensional culture," *Journal of Orthopaedic Research*, vol. 32, no. 2, pp. 291–295, 2014.

[14] L. Fallouh, K. Nakagawa, T. Sasho et al., "Effects of autologous platelet-rich plasma on cell viability and collagen synthesis in injured human anterior cruciate ligament," *The Journal of Bone & Joint Surgery*, vol. 92, no. 18, pp. 2909–2916, 2010.

[15] S. M. Joshi, A. N. Mastrangelo, E. M. Magarian, B. C. Fleming, and M. M. Murray, "Collagen-platelet composite enhances biomechanical and histologic healing of the porcine anterior cruciate ligament," *The American Journal of Sports Medicine*, vol. 37, no. 12, pp. 2401–2410, 2009.

[16] A. N. Mastrangelo, P. Vavken, B. C. Fleming, S. L. Harrison, and M. M. Murray, "Reduced platelet concentration does not harm PRP effectiveness for ACL repair in a porcine in vivo model," *Journal of Orthopaedic Research*, vol. 29, no. 7, pp. 1002–1007, 2011.

[17] L. Andriolo, B. Di Matteo, E. Kon, G. Filardo, G. Venieri, and M. Marcacci, "PRP augmentation for ACL reconstruction," *BioMed Research International*, vol. 2015, Article ID 371746, 15 pages, 2015.

[18] R. Seijas, O. Ares, X. Cuscó, P. Álvarez, G. Steinbacher, and R. Cugat, "Partial anterior cruciate ligament tears treated with intraligamentary plasma rich in growth factors," *World Journal of Orthopedics*, vol. 5, no. 3, pp. 373–378, 2014.

[19] B. L. Proffen, J. T. Sieker, and M. M. Murray, "Bio-enhanced repair of the anterior cruciate ligament," *Arthroscopy—Journal of Arthroscopic and Related Surgery*, vol. 31, no. 5, pp. 990–997, 2015.

[20] B. J. Cole, S. T. Seroyer, G. Filardo, S. Bajaj, and L. A. Fortier, "Platelet-rich plasma: where are we now and where are we going?" *Sports Health*, vol. 2, no. 3, pp. 203–210, 2010.

[21] A. Mishra, J. Woodall Jr., and A. Vieira, "Treatment of tendon and muscle using platelet-rich plasma," *Clinics in Sports Medicine*, vol. 28, no. 1, pp. 113–125, 2009.

[22] M. Sánchez, D. Delgado, and P. Sánchez, "Platelet rich plasma and knee surgery," *BioMed Research International*, vol. 2014, Article ID 890630, 10 pages, 2014.

[23] P. Vavken, P. Sadoghi, and M. M. Murray, "The effect of platelet concentrates on graft maturation and graft-bone interface healing in anterior cruciate ligament reconstruction in human patients: a systematic review of controlled trials," *Arthroscopy: The Journal of Arthroscopic and Related Surgery*, vol. 27, no. 11, pp. 1573–1583, 2011.

[24] J. P. van der List, D. N. Mintz, and G. S. DiFelice, "The location of anterior cruciate ligament tears: a prevalence study using magnetic resonance imaging," *Orthopaedic Journal of Sports Medicine*, vol. 5, no. 6, 2017.

[25] E. Narducci, "The clinical utility of functional performance tests within one-year post-acl reconstruction: a systematic review," *International Journal of Sports Physical Therapy*, vol. 6, no. 4, pp. 333-42, 2011.

[26] N. C. Clark, "Functional performance testing following knee ligament injury," *Physical Therapy in Sport*, vol. 2, no. 2, pp. 91–105, 2001.

[27] A. Almangoush and L. Herrington, "Functional performance testing and patient reported outcomes following ACL reconstruction: a systematic scoping review," *International Scholarly Research Notices*, vol. 2014, pp. 1–14, 2014.

[28] D. R. Bell, M. D. Smith, A. P. Pennuto, M. R. Stiffler, and M. E. Olson, "Jump-landing mechanics after anterior cruciate ligament reconstruction: a landing error scoring system study," *Journal of Athletic Training*, vol. 49, no. 4, pp. 435–441, 2014.

[29] H. Itoh, M. Kurosaka, S. Yoshiya, N. Ichihashi, and K. Mizuno, "Evaluation of functional deficits determined by four different hop tests in patients with anterior cruciate ligament deficiency," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 6, no. 4, pp. 241–245, 1998.

[30] C. Hildebrandt, L. Müller, B. Zisch, R. Huber, C. Fink, and C. Raschner, "Functional assessments for decision-making regarding return to sports following ACL reconstruction. Part I: development of a new test battery," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 23, no. 5, pp. 1273–1282, 2015.

[31] E. Herbst, C. Hoser, C. Hildebrandt et al., "Functional assessments for decision-making regarding return to sports following ACL reconstruction. Part II: clinical application of a new test battery," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 23, no. 5, pp. 1283–1291, 2015.

[32] R. A. Clark, B. Howells, Y.-H. Pua, J. Feller, T. Whitehead, and K. E. Webster, "Assessment of standing balance deficits in people who have undergone anterior cruciate ligament reconstruction using traditional and modern analysis methods," *Journal of Biomechanics*, vol. 47, no. 5, pp. 1134–1137, 2014.

[33] B. E. Howells, C. L. Ardern, and K. E. Webster, "Is postural control restored following anterior cruciate ligament reconstruction? A systematic review," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 19, no. 7, pp. 1168–1177, 2011.

[34] H. Negahban, P. Ahmadi, R. Salehi, M. Mehravar, and S. Goharpey, "Attentional demands of postural control during single leg stance in patients with anterior cruciate ligament reconstruction," *Neuroscience Letters*, vol. 556, pp. 118–123, 2013.

[35] K. A. Webster and P. A. Gribble, "Time to stabilization of anterior cruciate ligament-reconstructed versus healthy knees in

nationalcollegiate athletic association division I female athletes," *Journal of Athletic Training*, vol. 45, no. 6, pp. 580–585, 2010.

[36] N. Pujol, P. Colombet, T. Cucurulo et al., "Natural history of partial anterior cruciate ligament tears: asystematic literature review," *Orthopaedics & Traumatology: Surgery & Research*, vol. 98, no. 8, pp. S160–S164, 2012.

[37] K. Bak et al., "Isolated partial rupture of the anterior cruciate ligament. Long-term follow-up of 56 cases," *Knee Surg Sports Traumatol Arthrosc*, vol. 5, no. 2, pp. 66–71, 1997.

[38] S. L. Buckley, R. L. Barrack, and A. H. Alexander, "The natural history of conservatively treated partial anterior cruciate ligament tears," *The American Journal of Sports Medicine*, vol. 17, no. 2, pp. 221–225, 2016.

[39] D. Y. Lee, S. A. Karim, and H. C. Chang, "Return to sports after anterior cruciate ligament reconstruction—a review of patients with minimum 5-year follow-up," *Annals of the Academy of Medicine, Singapore*, vol. 37, no. 4, pp. 273–278, 2008.

[40] A. Notarnicola, "Returning to sport after anterior cruciate ligament reconstruction in amateur sports men: a retrospective study," *Muscle, Ligaments and Tendons Journal*, vol. 6, no. 4, pp. 486–491, 2016.

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Research Article

Select Biomarkers on the Day of Anterior Cruciate Ligament Reconstruction Predict Poor Patient-Reported Outcomes at 2-Year Follow-Up: A Pilot Study

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Background. The majority of patients develop posttraumatic osteoarthritis within 15 years of anterior cruciate ligament (ACL) injury. Inflammatory and chondrodegenerative biomarkers have been associated with both pain and the progression of osteoarthritis; however, it remains unclear if preoperative biomarkers differ for patients with inferior postoperative outcomes. *Hypothesis/Purpose*. The purpose of this pilot study was to compare biomarkers collected on the day of ACL reconstruction between patients with "good" or "poor" 2-year postoperative outcomes. We hypothesized that inflammatory cytokines and chondrodegenerative biomarker concentrations would be significantly greater in patients with poorer outcomes. *Study Design*. Prospective cohort design. *Methods*. 22 patients (9 females, 13 males; age = 19.5 ± 4.1 years; BMI = 24.1 ± 3.6 kg/m^2) previously enrolled in a randomized trial evaluating early anti-inflammatory treatment after ACL injury. Biomarkers of chondrodegeneration and inflammation were assessed from synovial fluid (sf) samples collected on the day of ACL reconstruction. Participants completed Knee Injury and Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee (IKDC) questionnaires two years following surgery. Patients were then categorized based on whether their KOOS Quality of Life (QOL) score surpassed the Patient Acceptable Symptom State (PASS) threshold of 62.5 points or the IKDC PASS threshold of 75.9 points. *Results*. Patients that failed to reach the QOL PASS threshold after surgery (n = 6, 27%) had significantly greater sf interleukin-1 alpha (IL-1α; p = 0.004), IL-1 receptor antagonist (IL-1ra; p = 0.03), and matrix metalloproteinase-9 (MMP-9; p = 0.01) concentrations on the day of surgery. Patients that failed to reach the IKDC PASS threshold (n = 9, 41%) had significantly greater sf IL-1α (p = 0.02). *Conclusion*. These pilot data suggest that initial biochemical changes after injury may be an indicator of poor outcomes that are not mitigated by surgical stabilization alone. Biological adjuvant treatment in addition to ACL reconstruction may be beneficial; however, these data should be used for hypothesis generation and more definitive randomized clinical trials are necessary.

1. Introduction

Whether isolated or in concert with concomitant meniscal or articular cartilage injury, anterior cruciate ligament (ACL) rupture initiates a cascade of cytokine and catabolic enzyme activity [1–4]. Regardless of surgical or conservative management, the majority of patients develop posttraumatic osteoarthritis (PTOA) within 15 years of ACL injury [5–7]. In addition to magnetic resonance imaging (MRI) and/or radiographic evidence of cartilage degeneration [8–11], the

Table 1: Concomitant injuries and surgical treatments (n (%)) performed at the time of ACL reconstruction.

	Not injured	Injured, not treated	Debrided	Repaired
Meniscus				
Medial	8 (36%)	0 (0%)	1 (5%)	13 (59%)
Lateral	8 (36%)	0 (0%)	3 (14%)	11 (50%)
Tibial Articular Cartilage				
Medial	22 (100%)	0 (0%)	0 (0%)	0 (0%)
Lateral	22 (100%)	0 (0%)	0 (0%)	0 (0%)
Femoral Articular Cartilage				
Medial	21 (95%)	1 (5%)	0 (0%)	0 (0%)
Lateral	22 (100%)	0 (0%)	0 (0%)	0 (0%)

onset of PTOA is associated with increased concentrations of chondrodegenerative and inflammatory biomarkers [12, 13]. Increased biomarkers of cartilage turnover have not only been reported as a late consequence of ACL injury, but also been reported to be significantly elevated immediately following ACL injury [2–4, 14]. This may indicate chronically increased cartilage turnover and a progressively destructive process that may have long-term clinical consequences. However, while inflammatory and chondrodegenerative biomarkers are elevated in the period between ACL injury and reconstruction [3, 4], there is a substantial knowledge gap with regard to the role of preoperative biomarker concentrations and their association with either successful or suboptimal clinical outcomes.

One method to objectively quantify a successful outcome is to determine whether a patient has achieved a Patient Acceptable Symptom State (PASS) following surgery [15–18]. The PASS represents a threshold for a given postoperative outcome score above which the patient is defined as having a satisfactory outcome. Patients that fail to achieve the PASS threshold are then considered to have a suboptimal postoperative outcome. The purpose of this pilot study was to compare biomarkers assessed from samples collected preoperatively on the day of ACL reconstruction between patients with 2-year postoperative patient-reported outcome scores above and below previously established PASS thresholds [18]. We hypothesized that synovial fluid and urine concentrations of inflammatory cytokines and chondrodegenerative biomarkers would be significantly greater in patients with poorer outcomes.

2. Methods

Participants included 22 patients (9 females, 13 males; age= 19.5 ± 4.1 years (mean ± standard deviation); BMI= 24.1 ± 3.6 kg/m^2, Table 1) that had previously consented to participate at one site of an IRB-approved, multicenter prospective randomized clinical trial evaluating early anti-inflammatory treatment after ACL injury (clinicaltrials.gov ID: NCT01692756) [3]. At the time of enrollment, patients with an isolated ACL injury between the ages of 14 and 32 with closed growth plates were included. Other inclusion criteria included a normal contralateral knee, no history of previous traumatic ipsilateral knee injury, and an ACL injury that occurred during sports activity with no clinical evidence of posterior cruciate ligament injury and with no more than grade 1 medial or lateral collateral ligament injury. Patients were excluded if the injury occurred more than eight days prior to enrollment or they had a history of previous ipsilateral knee surgery, a known allergy to triamcinolone acetonide, intra-articular cortisone injection into either knee within three months of injury, or a history of any inflammatory disease or immunocompromise [3].

In the initial trial, biomarkers were assessed at three time points prior to surgery to determine if early anti-inflammatory treatment could alter the expected progressive increases in inflammatory and chondrodegenerative biomarker concentrations [3]. The three time points from the initial study were (1) mean 4 days after injury, (2) mean 11 days after injury, and (3) the day of ACL reconstruction (mean 37 days after injury). For the current study, we used only biomarker data from samples acquired on the day of ACL reconstruction to assess if inflammatory and chondrodegenerative biomarker concentrations differed between those with good versus poor postoperative outcomes. In original study, patient-reported outcomes on the day of surgery did not differ between patients treated with preoperative intra-articular corticosteroid and the placebo group. In addition, the surgical intervention and postoperative rehabilitation and medications did not differ between groups and no between-group differences were noted in either postoperative Knee Injury and Osteoarthritis Outcome Score (KOOS) Quality of Life scores (QOL; corticosteroid = 72.7 ± 16.1 versus placebo = 67.8 ± 31.1, p = 0.82) or International Knee Documentation Committee scores (IKDC; corticosteroid = 74.8 ± 12.9 versus placebo = 71.2 ± 12.3, p = 0.46). As such, we therefore pooled data for all patients for the current analysis.

Knee aspiration was performed aseptically at the time of surgery via a superolateral suprapatellar approach, and intra-articular placement was confirmed using the "squish" test [19]. Patients were fasting as both urine and synovial fluid (sf) samples were collected on the morning of surgery. Synovial fluid and urine samples were spun at 3500 RPM for 10 minutes and the supernatant aliquoted according to an allotment protocol. Once all samples were collected they were shipped to the Duke University biomarker laboratory (VBK/JLH) for analysis [3].

A number of chondrodegenerative biomarkers and inflammatory cytokines were assessed using previously described methods (Table 2) [3, 4]. All biomarker concentrations were assessed from synovial fluid samples with the exception of CTX-II which was assessed in both the synovial fluid (CTX-II) and urine (uCTX-II). Urinary CTX-II was normalized to creatinine concentration (ng/mmol) [13]. Biomarker variability, linear range of standard, and need for repeat were carefully assessed. Several commercially-available ELISA kits provided controls, which were used with every run to confirm that values were within the acceptable range according to the manufacturer and to assess interassay (plate to plate) variability. In addition, synovial fluid from a human subject with knee OA that had previously been aliquoted and frozen at −80°C was used as the control for all assays. A fresh aliquot of this control synovial fluid was thawed and used on every plate to calculate intra- and interassay variance of the assay each day that analyses were performed. Due to limited sf sample volume available, samples were run in singlicate; however, all standards and controls were run in duplicate and used to determine the precision of the assay and to establish an acceptable control range for the assay. The mean of the control sample for all assays plus or minus two standard deviations was defined as the acceptable control range. All control samples were within the acceptable control range for all plates and assays. Mean intra-assay coefficients of variation for each assay are reported in Table 2. Mean interassay coefficients of variation were all <15% with the exception of IL-1α and IL-1β. The manufacturer reported that interassay CVs for these assays are 6.6% and 6.4%, respectively; however due to the human control SF sample having values at or below the level of detection, this calculation was not possible. For values of IL-1α and IL-1β that were below the lower limit of detection, 1/2 LLOD (lowest level of detection) was reported for statistical purposes.

Patients were contacted two years after surgery to complete standardized patient-reported outcomes, including IKDC and KOOS Scores [18, 21–25]. The volume of preoperative bone bruises was calculated from each patient's preoperative magnetic resonance imaging (MRI) scan using previously described methods [26]. MRIs were considered adequate for inclusion if they included T2 or PD sequences in the coronal, axial, and sagittal plane as well as slice thicknesses < 5 mm. The bone bruise volumes in the medial tibial plateau, medial femoral condyle, lateral tibial plateau, and lateral femoral condyle were measured from the T2 or PD weighted coronal images in a modification of Roemer and Bohndorf's technique [26, 27]. Bone bruises volumes from each of the four bony regions were then summed and expressed as the total bone bruise volume (mm^3) [26].

2.1. Statistical Analysis. Mann–Whitney U tests were performed to determine if inflammatory cytokines and chondrodegenerative biomarkers assessed from samples collected on the day of surgery (Table 2) differed from those with either a good or poor outcome based on postoperative IKDC and KOOS QOL scores. Due to the high number of IL-1β samples that were below the lower limits of detection (11/22, 50%), for this cytokine we also used Fisher Exact tests to compare the prevalence of concentrations below the lower limits of detection (LLOD) between groups. Patients were categorized as having a good or poor outcome based on whether they reported IKDC or KOOS QOL scores above or below previously established Patient Acceptable Symptom State (PASS) thresholds following ACL reconstruction of 62.5 points for KOOS QOL and 75.9 points for the IKDC [18]. As the KOOS QOL and IKDC may be assessing different aspects of the patient's outcome, separate analyses were run based on the KOOS QOL PASS definition and IKDC PASS definition. Cohen's d effect sizes calculations were also performed in order to identify potentially clinically-meaningful findings within these pilot data, with $d > 0.80$ considered a large effect size [28]. Analyses were performed using SPSS Statistics 24 (IBM, Armonk, NY) and Excel 2016 (Microsoft, Redmond, WA) with $p < 0.05$ considered statistically significant. All data and results are stored at the Department of Orthopaedic Surgery and Sports Medicine at the University of Kentucky.

3. Results

At a mean follow-up of 2.4 years, 6/22 patients (27%) had postoperative KOOS QOL scores below the PASS threshold of 62.5 points (Table 3). Patients that failed to reach the QOL PASS threshold had significantly greater sf IL-1α (p=0.004), sf IL-1ra (p=0.02), and sf MMP-9 (p=0.01). While not statistically significant, markers of type I and type II collagen breakdown (sf NTX-I [p=0.055] and uCTX-II [p=0.08]) tended to be greater for those that failed to reach the QOL PASS threshold. Graft type, the prevalence of meniscus injury, and bone bruise volumes did not differ between QOL PASS groups (Table 3).

Nine of 22 patients (41%) failed to reach the IKDC PASS threshold of 75.9 (Table 4). Patients that failed to reach the IKDC PASS threshold had significantly greater sf IL-1α (p=0.02). While not statistically significant, sf IL-1ra (p=0.057), sf MMP-1 (p=0.10), and sf MMP-9 (p=0.10) tended to be greater for those that failed to reach the IKDC PASS threshold. No other biomarker differences were noted between those that did or did not surpass the IKDC or QOL PASS thresholds. Graft type, the prevalence of meniscus injury, and bone bruise volumes did not differ between IKDC PASS groups (Table 4).

4. Discussion

The purpose of this pilot study was to compare biomarkers assessed from samples collected on the day of ACL reconstruction between patients with postoperative patient-reported outcome scores above and below previously established PASS thresholds [18]. We hypothesized that synovial fluid and urinary concentrations of inflammatory cytokines and chondrodegenerative biomarkers would be significantly greater in patients with poorer outcomes, and our hypotheses were, in part, supported by the current results.

Table 2: Inflammatory cytokines and chondrodegenerative markers evaluated on the day of ACL reconstruction [3, 4].

Biomarker∗	Abbreviation	Volume (Dilution)	CV†	LLOD	Number (%) below LLOD‡
Cartilage oligomeric matrix protein (μg/mL) Catalog #RD194080200, BioVendor, Asheville, NC	COMP	5 μl (1:2500)	1.9%	0.4 ng/ml	0 (0%)
Synovial C-terminal crosslinked telopeptide of type II collagen (ng/mL) Cartilaps®, Catalog # AC-10F1, Immunodiagnostic Systems, Inc, Fountain Hills, AZ	CTX-II	40 μl (None)	4.3%	0.20 μg/L	0 (0%)
Urinary CTX-II normalized to creatinine concentration (ng/mmol) Cartilaps®, Catalog # AC-10F1, Immunodiagnostic Systems, Inc, Fountain Hills, AZ	uCTX-II	40 μl (None)	3.3%	0.20 μg/L	0 (0%)
Sulfated glycosaminoglycan (μg/mL) Catalog # BP-004, Kamiya Biomedical Company, Seattle, WA	sGAG	25 μl (None)	1.8%	N/A	0 (0%)
Interleukin-1 alpha (pg/mL) Catalog # K151RBD, Meso Scale Discovery, Rockville, MD	IL-1α	25 μl (1:2)	9.9%	0.238 pg/ml	4 (18%)
Interleukin-1 beta (pg/mL) Catalog #K151QPD, Meso Scale Discovery, Rockville, MD	IL-1β	25 μl (1:2)	5.7%	0.033 pg/ml	11 (50%)
Interleukin-1 receptor antagonist (pg/mL) Catalog # DRA00B, R&D Systems, Minneapolis, MN	IL-1ra	100 μl (None)	4.4%	6.3 pg/ml	0 (0%)
Matrix metalloproteinase 3 plex (MMP-1, MMP-3, MMP-9) (pg/mL) Catalog # K15043C, Meso Scale Discovery, Rockville, MD	MMP-1	5 μl (1:20)	3.5%	1.74 pg/ml	0 (0%)
	MMP-3	5 μl (1:20)	4.5%	4.34 pg/ml	0 (0%)
	MMP-9	5 μl (1:20)	3.5%	14.3 pg/ml	0 (0%)
N-terminal crosslinked telopeptide of type I collagen (nM BCE) Catalog # 9021, Osteomark ® NTx; Alere, Scarborough, ME	NTX-I	25 μl (1:5)	2.3%	N/A	0 (0%)
Tumor necrosis factor-inducible gene 6 activity In-house ELISA assay developed by Kraus Laboratory[20]	TSG-6	4 μl (1:100)	12.9%	1.0U	0 (0%)

∗ All biomarkers measured in synovial fluid with the exception of urinary CTX-II.
† CV = mean interassay coefficient of variation.
‡ LLOD = lower limits of detection.

Table 3: Comparison of inflammatory cytokines and chondrodegenerative markers (mean ± standard deviation) evaluated on the day of ACL reconstruction between patients with KOOS QOL scores above and below the PASS threshold of 62.5 points.

Biomarker	< PASS	≥ PASS	p[a]	d[e]
N	6	16	-	-
Female/Male (n)	3/3	6/10	0.66	-
Steroid/Placebo (n)	4/2	12/4	> 0.99	-
Age (years)	18.0 ± 2.6	20.0 ± 4.5	0.42	-
BMI (kg/m^2)	22.4 ± 2.9	24.8 ± 3.6	0.15	-
Graft (BTB/Hamstring)	5/1	13/3	> 0.99	-
Medial meniscus injury	5	9	0.35	-
Lateral meniscus injury	2	12	0.12	-
Bone bruise volume (mm^3)	7.99 ± 8.93	11.07 ± 9.33	0.50	0.30
COMP (μg/ml)	32.3 ± 12.5	39.3 ± 14.0	0.42	0.51
CTX-II (ng/ml)	1.57 ± 0.93	1.52 ± 1.97	0.38	0.03
uCTX-II[d] (μg/mmol)	5.72 ± 4.86	2.42 ± 2.09	0.08	0.99
sGAG (μg/ml)	190.9 ± 69.9	264.7 ± 168.3	0.83	0.49
IL-1α (pg/ml)	***9.47 ± 7.65***	***2.21 ± 2.20***	***0.004***	***1.36***
IL-1β[c] (pg/ml)	0.11 ± 0.13	0.45 ± 1.48	0.76	0.26
IL-1ra (pg/ml)	***2,593.2 ± 3,576.4***	***2,086.3 ± 5,507.0***	***0.03***	***0.10***
MMP-1 (ng/ml)	640.07 ± 81.58	394.06 ± 667.06	0.27	0.35
MMP-3 (ng/ml)	4,017.2 ± 4,576.41	2,532.80 ± 3,066.43	0.56	0.43
MMP-9 (ng/ml)	***30.99 ± 35.96***	***6.94 ± 10.30***	***0.01***	***1.07***
NTX-I (nM BCE)	30.3 ± 7.9	22.7 ± 7.1	0.055	0.97
TSG-6 (U)	286.4 ± 165.7	260.1 ± 157.3	0.83	0.11

[a] Statistically significant differences denoted with ***bold and italics font.***

[b] Number of patients in the corticosteroid or placebo group from the original randomized trial.

[c] There was also no difference in the number of samples below LLOD between groups.

< Pass=3/6 versus ≥ PASS=8/16, p > 0.99.

[d] u = urinary, the remaining biomarkers were measured in synovial fluid. Urinary CTX-II normalized to creatinine level (μg/mmol).

[e] Cohen's d effect sizes calculations were also performed in order to identify potentially clinically-meaningful findings within these pilot data, with d > 0.80 considered a large effect size.

The current pilot results support the previously described cascade of increased IL-1α stimulating the production of matrix metalloproteinases thereby reducing proteoglycan content and altering cartilage mechanical properties. Previous studies have demonstrated that ACL injury triggers a biochemical cascade that worsens over the first 4-6 weeks after injury [2–4]. Inflammation is initiated early by the injury-related hemarthrosis and subsequent intra-articular pathogenic processes at the time of injury, including the downregulation of proteoglycan synthesis and upregulation of matrix metalloproteinases [29–31]. It is widely accepted that IL-1 and IL-1ra are critical in the regulation of the pathological processes involved in joint tissue breakdown [32, 33]. Synovial fluid IL-1 levels are elevated in patients with ACL rupture and correlate with severity of chondral damage [34]. Synovial fluid levels of the chondroprotective IL-1ra cytokine are reported to decrease significantly after ACL injury, resulting in relatively unopposed activity of IL-1 [1]. Additionally, levels of IL-1ra decrease as the severity of chondral damage is increased [34]. The superficial cartilage layers have been shown to be more susceptible to IL-1 induced damage than deeper layers *in vitro* [35]. Porcine cartilage explants have been demonstrated to be more sensitive to the chondrodegenerative effects of IL-1α than IL-1β [36].

The current pilot results suggest that initial biochemical changes after injury may be prognostic of long-term consequences of injury of the knee that are not mitigated by surgical stabilization alone. Inflammatory cytokine and degradative enzyme concentrations on the day of ACL reconstruction have been previously shown to correlate with cartilage changes on MRI during the first three years after surgery [37], and the current results further demonstrate a connection between cytokine and degradative enzyme concentrations and the potential progression of posttraumatic OA. In the current study, both IL-1α and MMP-9 concentrations on the day of surgery were significantly higher for patients that failed to postoperatively achieve the KOOS QOL-based PASS compared to those with better clinical outcomes. In addition to increased IL-1a and MMP-9 concentrations, biomarkers of bone and cartilage turnover (sf NTX-I, d = 0.97 and uCTX-II, d = 0.99) were also increased for patients that failed to achieve KOOS QOL-based PASS. This overall state of upregulated catabolism and inflammation may lead to recurrent effusions and/or persistent synovitis which also appears to potentially have long-term implications for knee health.

In addition to playing a contributing role in the progression of structural posttraumatic OA changes [37], increased

Table 4: Comparison of inflammatory cytokines and chondrodegenerative markers (mean ± standard deviation) evaluated on the day of ACL reconstruction between patients with IKDC scores above and below the PASS threshold of 75.9 points.

Biomarker	< PASS	≥ PASS	p[a]	d[e]
N	9	13	-	-
Female/Male (n)	5/4	4/9	0.38	-
Steroid/Placebo[b] (n)	6/3	10/3	0.66	-
Age (years)	18.9 ± 3.5	19.9 ± 4.6	0.82	-
BMI (kg/m^2)	24.1 ± 3.9	24.2 ± 3.5	0.84	-
Graft (BTB/Ham)	8/1	10/3	0.62	-
Medial meniscus injury	7	7	0.38	-
Lateral meniscus injury	4	7	> 0.99	-
Bone bruise volume (mm^3)	9.19 ± 7.94	10.94 ± 10.18	0.67	0.17
COMP (μg/ml)	30.9 ± 10.2	41.9 ± 14.3	0.10	0.81
CTX-II (ng/ml)	1.16 ± 0.72	1.79 ± 2.16	0.92	0.37
uCTX-II[d] (μg/mmol)	3.92 ± 4.08	2.91 ± 2.77	0.62	0.30
sGAG (μg/ml)	199.5 ± 70.1	275.8 ± 183.2	0.82	0.51
IL-1α (pg/ml)	***5.48 ± 4.56***	***3.29 ± 5.80***	***0.02***	***0.41***
IL-1β[c] (pg/ml)	0.08 ± 0.09	0.55 ± 1.64	0.60	0.37
IL-1ra (pg/ml)	1,899.1 ± 3,014.8	2,621.5 ± 6,332.1	0.057	0.11
MMP-1 (ng/ml)	597.22 ± 689.63	366.96 ± 715.61	0.10	0.33
MMP-3 (ng/ml)	3,217.23 ± 4,074.67	2,744.09 ± 3,180.20	0.87	0.14
MMP-9 (ng/ml)	21.85 ± 31.59	7.71 ± 11.31	0.10	0.63
NTX-I (nM BCE)	26.6 ± 8.6	23.5 ± 7.5	0.33	0.40
TSG-6 (U)	260.9 ± 196.8	271.7 ± 129.3	0.53	0.40

[a] Statistically significant differences denoted with ***bold and italics font.***

[b] Number of patients in the corticosteroid or placebo group from the original randomized trial.

[c] There was also no difference in the number of samples below LLOD between groups.
< Pass=5/9 ersus ≥ PASS=6/13, p > 0.99.

[d] u = urinary, the remaining biomarkers were measured in synovial fluid. Urinary CTX-II normalized to creatinine level (μg/mmol).

[e] Cohen's d effect sizes calculations were also performed in order to identify potentially clinically-meaningful findings within these pilot data, with d > 0.80 considered a large effect size.

inflammatory cytokine and degradative enzyme concentrations on the day of ACL reconstruction also appear to affect postoperative patient-reported outcomes. In OA knees, nerve growth factor expression in the synovium has been shown to modulate pain by increasing local nociceptor sensitization [38, 39]. Nerve growth factor expression is increased in the synovium of OA knees [40], and by regulating nerve growth factor expression, proinflammatory cytokine IL-1 and other degradative enzymes may play an integral role in modulating knee pain [40]. While attention is given the potential role of the innate immune response on cartilage degradation and the progression of OA [41], it should be noted that, after adjusting for age, peripheral cytokine concentrations are similar between patients with knee OA and fibromyalgia [42]. Hypersensitivity and nociceptor sensitization secondary to increased proinflammatory cytokine concentrations may then explain the increased IL-1α and MMP-9 concentrations for those that failed to achieve a Patient Acceptable Symptom State in the current study.

Early anticatabolic and/or anti-inflammatory interventions after ACL injury or reconstruction may need to be further investigated as adjunctive treatment strategies to mitigate both the structural changes and symptoms of posttraumatic OA. CTX-II has been reported to be predictive of OA progression based on both radiographic and arthroscopic evidence [43–45]. Particularly relevant to the current results suggesting a link between CTX-II concentrations and patient-reported outcomes, Ishijima et al. reported that urinary CTX-II was associated with concurrent OA-related pain [46]. The association between CTX-II, pain, and inferior outcomes may be tied to the combination of both changes to the articular cartilage and to bone metabolism. Garnero et al. first reported that urinary CTX-II concentrations in early OA patients were predictive of bone marrow lesion progression [47]. More recently, in a cluster analysis of a wide spectrum of OA-related biomarkers, van Spil reported that CTX-II tended to cluster with other biomarkers associated with bone metabolism [48]. Bone marrow lesions are common following ACL injury [26, 49], and many resolve over time [50]. However, subjective symptoms of early OA are more common six years after ACL reconstruction for those noted to have local articular cartilage damage combined with bone marrow lesions at the time of surgery [26]. The size and progression of bone marrow lesions have been previously linked to OA-related pain as the subchondral bone is rich with nociceptors whereas the articular cartilage is not [51–53]. Taken together with our data, links between CTX-II, NTX-I, IL-1α, pain, and both cartilage and bone metabolism

may all contribute to KOOS QOL and IKDC outcomes at 2 years.

This study had several limitations. First and foremost, the results of this preliminary work are based on a small sample size and additional studies are necessary to confirm these results. Second, some patients had received corticosteroid injections prior to surgery which could have influenced biomarker concentrations on the day of surgery. As mentioned previously, KOOS QOL and IKDC scores did not differ between patients treated with preoperative intra-articular corticosteroid and the placebo group, and the surgical intervention and postoperative rehabilitation and medications did not differ between groups and no between-group differences were noted in either postoperative KOOS QOL or IKDC scores. Third, the prevalence of patients with postoperative KOOS QOL and IKDC scores below the PASS threshold was higher in the current study than those originally reported by Muller et al. [18]. This may be due, in part, to the differences in patient populations between the two studies. In the current study, all patients were injured during athletic participation with an average age at the time of surgery of 19.5 years compared to 26.1 in the study by Muller et al. [18]. The lingering effects of athletic injuries have been reported to negatively impact quality of life years after competition has ended, and both physical and mental aspects of function are significantly lower in former collegiate athletes compared to college attendees who did not participate in sport [54]. It remains unclear if the increased prevalence of patients with inferior patient-reported outcomes in the current study was perhaps due to the strict inclusion criteria of athletic ACL injuries. Fourth, while inferior patient-reported outcome scores have been associated with early OA changes, postoperative imaging or biomarker evidence of OA will be necessary to establish the potential connection between biomarkers on the day of surgery, KOOS QOL, IKDC scores, and evidence of structural features of knee OA. Finally, future work may require more sensitive methods to quantify synovial fluid IL-1β concentrations as 50% of the samples in the current study had values below the lower limits of detection.

In conclusion, the results of this preliminary investigation demonstrated that higher inflammatory cytokine activity (IL-1α) and a trend towards greater bone and cartilage collagen degradation (NTX-I and uCTX-II) at the time of surgery were associated with failure to achieve an acceptable symptom state two years after ACL reconstruction. These data suggest that initial biochemical changes after injury may be prognostic of long-term consequences of ACL injury that are not mitigated by surgical stabilization alone; however, due to the small sample size these data should be used for hypothesis generation and more definitive randomized clinical trials are necessary.

Data Availability

The datasets used to support the findings of this study are restricted by the University of Kentucky Institutional Review Board in order to protect patient privacy. Data are available from the corresponding author for researchers who meet the criteria for access to confidential data.

Disclosure

This study was conducted at the University of Kentucky and all analyses of biological specimens were performed at Duke University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Arthroscopy Association of North America. This study was presented in part at the 2018 International Cartilage Regeneration & Joint Preservation Society World Congress (ID 9981).

Conflicts of Interest

The authors have no conflicts of interest related to this work.

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References

[1] M. Cameron, A. Buchgraber, H. Passler et al., "The natural history of the anterior cruciate ligament-deficient knee. Changes in synovial fluid cytokine and keratan sulfate concentrations," *The American Journal of Sports Medicine*, vol. 25, no. 6, pp. 751–754, 1997.

[2] J. B. Catterall, T. V. Stabler, C. R. Flannery, and V. B. Kraus, "Changes in serum and synovial fluid biomarkers after acute injury (NCT00332254)," *Arthritis Research & Therapy*, vol. 12, no. 6, article R229, 2010.

[3] C. Lattermann, C. A. Jacobs, M. Proffitt Bunnell et al., "A Multicenter Study of Early Anti-inflammatory Treatment in Patients With Acute Anterior Cruciate Ligament Tear," *The American Journal of Sports Medicine*, vol. 45, no. 2, pp. 325–333, 2016.

[4] C. Lattermann, C. A. Jacobs, M. P. Bunnell et al., "Logistical challenges and design considerations for studies using acute anterior cruciate ligament injury as a potential model for early posttraumatic osteoarthritis," *Journal of Orthopaedic Research*, vol. 35, no. 3, pp. 641–650, 2017.

[5] L. S. Lohmander, P. M. Englund, L. L. Dahl, and E. M. Roos, "The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis," *The American Journal of Sports Medicine*, vol. 35, no. 10, pp. 1756–1769, 2007.

[6] L. S. Lohmander and H. Roos, "Knee ligament injury, surgery and osteoarthrosis: Truth or consequences?" *Acta Orthopaedica*, vol. 65, no. 6, pp. 605–609, 1994.

[7] B. E. Øiestad, L. Engebretsen, K. Storheim, and M. A. Risberg, "Knee osteoarthritis after anterior cruciate ligament injury: a systematic review," *The American Journal of Sports Medicine*, vol. 37, no. 7, pp. 1434–1443, 2009.

[8] D. Hunter, A. Guermazi, G. Lo et al., "Evoluation of semiquantitative whole joint assement of knee OA: MOAKS (MRI Osteoarthritis Knee Score)," *Osteoarthritis and Cartilage*, vol. 19, no. 8, pp. 990–1002, 2011.

[9] F. P. Luyten, M. Denti, G. Filardo, E. Kon, and L. Engebretsen, "Definition and classification of early osteoarthritis of the knee," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 20, no. 3, pp. 401–406, 2012.

[10] H. Madry, E. Kon, V. Condello et al., "Early osteoarthritis of the knee," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 24, no. 6, pp. 1753–1762, 2016.

[11] R. W. Wright and T. M. Group, "Osteoarthritis classification scales: interobserver reliability and arthroscopic correlation," *Journal of Bone and Joint Surgery*, vol. 96, no. 14, pp. 1145–1151, 2014.

[12] V. B. Kraus, F. J. Blanco, M. Englund et al., "OARSI Clinical Trials Recommendations: Soluble biomarker assessments in clinical trials in osteoarthritis," *Osteoarthritis and Cartilage*, vol. 23, no. 5, pp. 686–697, 2015.

[13] V. B. Kraus, J. E. Collins, D. Hargrove et al., "Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium," *Annals of the Rheumatic Diseases*, vol. 76, no. 1, pp. 186–195, 2016.

[14] S. J. Svoboda, T. M. Harvey, B. D. Owens, W. F. Brechue, P. M. Tarwater, and K. L. Cameron, "Changes in serum biomarkers of cartilage turnover after anterior cruciate ligament injury," *The American Journal of Sports Medicine*, vol. 41, no. 9, pp. 2108–2116, 2013.

[15] M. Dougados, "It's good to feel better but it's better to feel good," *The Journal of Rheumatology*, vol. 32, no. 1, pp. 1-2, 2005.

[16] J. C. Keurentjes, F. R. Van Tol, M. Fiocco et al., "Patient acceptable symptom states after total hip or knee replacement at midterm follow-up," *Bone & Joint Research*, vol. 3, no. 1, pp. 7–13, 2014.

[17] T. K. Kvien, T. Heiberg, and K. B. Hagen, "Minimal clincally important improvement/difference (MCII/MCID) and the patient acceptable symptom state (PASS): what do these concepts mean?" *Annals of the Rheumatic Diseases*, vol. 66, no. 3, pp. 40-41, 2007.

[18] B. Muller, M. A. Yabroudi, A. Lynch et al., "Defining Thresholds for the Patient Acceptable Symptom State for the IKDC Subjective Knee Form and KOOS for Patients Who Underwent ACL Reconstruction," *The American Journal of Sports Medicine*, vol. 44, no. 11, pp. 2820–2826, 2016.

[19] R. C. Glattes, K. P. Spindler, G. M. Blanchard, M. T. Rohmiller, E. C. McCarty, and J. Block, "A simple, accurate method to confirm placement of intra-articular knee injection," *The American Journal of Sports Medicine*, vol. 32, no. 4, pp. 1029–1031, 2004.

[20] C. Chou, D. Attarian, H. Wisniewski, P. Band, and V. Kraus, "TSG-6 – a double-edged sword for osteoarthritis (OA)," *Osteoarthritis and Cartilage*, vol. 26, no. 2, pp. 245–254, 2018.

[21] M. Englund, E. M. Roos, and L. S. Lohmander, "Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls," *Arthritis & Rheumatology*, vol. 48, no. 8, pp. 2178–2187, 2003.

[22] S. R. Filbay, I. N. Ackerman, T. G. Russell, E. M. Macri, and K. M. Crossley, "Health-related quality of life after anterior cruciate ligament reconstruction: a systematic review," *The American Journal of Sports Medicine*, vol. 42, no. 5, pp. 1247–1255, 2014.

[23] J. J. Irrgang, A. F. Anderson, A. L. Boland et al., "Development and validation of the international knee documentation committee subjective knee form," *The American Journal of Sports Medicine*, vol. 29, no. 5, pp. 600–613, 2001.

[24] E. M. Roos, H. P. Roos, L. S. Lohmander, C. Ekdahl, and B. D. Beynnon, "Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 28, no. 2, pp. 88–96, 1998.

[25] D. Schiphof, J. Waarsing, E. Oei, and S. Bierma-Zeinstra, "KOOS subscale and individual items associate with onset of structural knee osteoarthritis within five years," *Osteoarthritis and Cartilage*, vol. 24, p. S438, 2016.

[26] C. Lattermann, C. A. Jacobs, E. K. Reinke et al., "Are Bone Bruise Characteristics and Articular Cartilage Pathology Associated with Inferior Outcomes 2 and 6 Years After Anterior Cruciate Ligament Reconstruction?" *Cartilage*, vol. 8, no. 2, pp. 139–145, 2017.

[27] F. W. Roemer and K. Bohndorf, "Long-term osseous sequelae after acute trauma of the knee joint evaluated by MRI," *Skeletal Radiology*, vol. 31, no. 11, pp. 615–623, 2002.

[28] J. Cohen, *Statistical power analysis for the behavioral sciences*, vol. 2nd, Lawrence Earlbaum Associates, Hillsdale, NJ, 1988.

[29] S. Chandrasekhar, A. K. Harvey, and P. S. Hrubey, "Intra-Articular Administration of Interleukin-1 Causes Prolonged Suppression of Cartilage Proteoglycan Synthesis in Rats," *Matrix Biology*, vol. 12, no. 1, pp. 1–10, 1992.

[30] M. B. Goldring, J. Birkhead, L. J. Sandell, T. Kimura, and S. M. Krane, "Interleukin 1 suppresses expression of cartilage-specific types II and IX collagens and increases types I and III collagens in human chondrocytes," *The Journal of Clinical Investigation*, vol. 82, no. 6, pp. 2026–2037, 1988.

[31] C. Lundberg, I. Åsberg, M. Lonescu, A. Reiner, G. Smedegård, and A. Robin Poole, "Changes in cartilage proteoglycan aggrecan after intra-articular injection of interleukin-1 in rabbits: Studies of synovial fluid and articular cartilage," *Annals of the Rheumatic Diseases*, vol. 55, no. 8, pp. 525–534, 1996.

[32] C. Jacques, M. Gosset, F. Berenbaum, and C. Gabay, "The Role of IL-1 and IL-1Ra in Joint Inflammation and Cartilage Degradation," *Vitamins & Hormones*, vol. 74, pp. 371–403, 2006.

[33] M. Lotz, "Cytokines in cartilage injury and repair," *Clinical Orthopaedics and Related Research*, no. 391, pp. S108–S115, 2001.

[34] P. H. Marks and M. L. C. Donaldson, "Inflammatory cytokine profiles associated with chondral damage in the anterior cruciate ligament-deficient knee," *Arthroscopy: The Journal of Arthroscopic and Related Surgery*, vol. 21, no. 11, pp. 1342–1347, 2005.

[35] H. J. Hauselmann, J. Flechtenmacher, and L. Michal, "The superficial layer of human articular cartilage is more susceptible to interleukin-1-induced damage than the deeper layers," *Arthritis & Rheumatism*, vol. 39, no. 3, pp. 478–488, 1996.

[36] A. L. McNulty, N. E. Rothfusz, H. A. Leddy, and F. Guilak, "Synovial fluid concentrations and relative potency of interleukin-1 alpha and beta in cartilage and meniscus degradation," *Journal of Orthopaedic Research*, vol. 31, no. 7, pp. 1039–1045, 2013.

[37] K. Amano, J. L. Huebner, T. V. Stabler et al., "Synovial Fluid Profile at the Time of Anterior Cruciate Ligament Reconstruction and Its Association With Cartilage Matrix Composition 3 Years After Surgery," *The American Journal of Sports Medicine*, vol. 46, no. 4, pp. 890–899, 2018.

[38] S. Pezet and S. B. McMahon, "Neurotrophins: mediators and modulators of pain," *Annual Review of Neuroscience*, vol. 29, pp. 507–538, 2006.

[39] C. J. Woolf, B. Safieh-Garabedian, Q.-P. Ma, P. Crilly, and J. Winter, "Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity," *Neuroscience*, vol. 62, no. 2, pp. 327–331, 1994.

[40] S. Takano, K. Uchida, G. Inoue et al., "Nerve growth factor regulation and production by macrophages in osteoarthritic synovium," *Clinical & Experimental Immunology*, vol. 190, no. 2, pp. 235–243, 2017.

[41] F. Berenbaum, "Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!)," *Osteoarthritis and Cartilage*, vol. 21, no. 1, pp. 16–21, 2013.

[42] M. Imamura, R. A. Targino, and W. T. Hsing, "Concentrations of cytokines in pateints with osteoarthritis of the knee and fibromyalgia," *Clinical Interventions in Aging*, vol. 9, pp. 939–944, 2014.

[43] P. Garnero, X. Ayral, J.-C. Rousseau et al., "Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis," *Arthritis & Rheumatology*, vol. 46, no. 10, pp. 2613–2624, 2002.

[44] J. Kumm, A. Tamm, M. Lintrop, and A. Tamm, "The value of cartilage biomarkers in progressive knee osteoarthritis: cross-sectional and 6-year follow-up study in middle-aged subjects," *Rheumatology International*, vol. 33, no. 4, pp. 903–911, 2013.

[45] M. Reijman, J. M. Hazes, S. M. Bierma-Zeinstra et al., "A new marker for osteoarthritis: Cross-sectional and longitudinal approach," *Arthritis & Rheumatism*, vol. 50, no. 8, pp. 2471–2478, 2004.

[46] M. Ishijima, T. Watari, K. Naito et al., "Relationships between biomarkers of cartilage, bone, synovial metabolism and knee pain provide insights into the origins of pain in early knee osteoarthritis," *Arthritis Research & Therapy*, vol. 13, article R22, 2011.

[47] P. Garnero, C. Peterfy, S. Zaim, and M. Schoenharting, "Bone marrow abnormalities on magnetic resonance imaging are associated with type II collagen degradation in knee osteoarthritis: A three-month longitudinal study," *Arthritis & Rheumatology*, vol. 52, no. 9, pp. 2822–2829, 2005.

[48] W. E. Van Spil, N. W. D. Jansen, J. W. J. Bijlsma et al., "Clusters within a wide spectrum of biochemical markers for osteoarthritis: Data from CHECK, a large cohort of individuals with very early symptomatic osteoarthritis," *Osteoarthritis and Cartilage*, vol. 20, no. 7, pp. 745–754, 2012.

[49] H. G. Potter, S. K. Jain, Y. Ma, B. R. Black, S. Fung, and S. Lyman, "Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up," *The American Journal of Sports Medicine*, vol. 40, no. 2, pp. 276–285, 2012.

[50] M. Costa-Paz, D. L. Muscolo, M. Ayerza, A. Makino, and L. Aponte-Tinao, "Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures," *Arthroscopy: The Journal of Arthroscopic and Related Surgery*, vol. 17, no. 5, pp. 445–449, 2001.

[51] D. T. Felson, C. E. Chaisson, C. L. Hill, and etal., "The association of bone marrow lesions with pain in knee osteoarthritis," *Annals of Internal Medicine*, vol. 134, pp. 591–593, 2001.

[52] D. T. Felson, S. McLaughlin, J. Goggins et al., "Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis," *Annals of Internal Medicine*, vol. 139, no. 5 I, pp. 330–I33, 2003.

[53] D. T. Felson, J. Niu, A. Guermazi et al., "Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging," *Arthritis & Rheumatology*, vol. 56, no. 9, pp. 2986–2992, 2007.

[54] J. E. Simon and C. L. Docherty, "Current health-related quality of life is lower in former division i collegiate athletes than in non-collegiate athletes," *The American Journal of Sports Medicine*, vol. 42, no. 2, pp. 423–429, 2014.

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Research Article

Age-Related Changes of Elastic Fibers in Shoulder Capsule of Patients with Glenohumeral Instability: A Pilot Study

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Background. Recurrent shoulder dislocations occur much more frequently in adolescents than in the older population but a clear explanation of this incidence does not exist. The aim of the present study was to define the age-related distribution of the elastic fibers (EFs) in the shoulder capsule's extracellular matrix as a factor influencing shoulder instability. *Materials and Methods*. Biopsy specimens were obtained from the shoulder capsule of patients divided preoperatively into three groups: Group 1 consisted of 10 male patients undergoing surgery for unidirectional traumatic anterior instability (TUBS); Group 2 consisted of 10 male patients undergoing surgery for multidirectional instability (MDI); Group 3 represents the control, including 10 patients with no history of instability. In addition to the group as a whole, specific subgroups were analyzed separately on the basis of the age of subjects: > 22 or < to 22 years. All the samples were analyzed by histochemical (Weigert's resorcinol fuchsin and Verhoeff's iron hematoxylin), immunohistochemical (monoclonal antielastin antibody), and histomorphometric methods. *Results*. Both the elastin density and the percentage of area covered by EFs were significantly higher in younger subjects (<22 years old). Furthermore, the elastin density and the percentage of area covered by EFs were significantly higher in specimens of group of patients affected by multidirectional shoulder instability in comparison to the other two groups. *Conclusion*. Data of the present study confirmed the presence of an age-related distribution of EFs in the human shoulder capsule. The greater amount of EFs observed in younger subjects and in unstable shoulders could play an important role in predisposing the joint to first dislocation and recurrence.

1. Introduction

Glenohumeral instability is usually defined as a clinical syndrome characterized by shoulder pain related to abnormal displacement of the humeral head in the glenoid [1]. It represents a wide spectrum of pathologies and can be classified according to the timing of diagnosis and frequency of the event, the degree, the direction(s), and the etiology of the first occurrence (traumatic or atraumatic). With respect to direction, glenohumeral instability may be anterior, posterior, inferior, or multidirectional [1, 2]. Several authors showed the importance of distinguishing traumatic unidirectional instability (TUBS) from atraumatic multidirectional instability (AMBRI) [3–7].

In the pathogenesis of unidirectional recurrent shoulder instability, several factors have a recognised role: age under 22 years at time of trauma, male sex, involvement in competitive or contact sport, large Hill Sachs lesion, large Bankart or bony Bankart lesion, rotator cuff and biceps deficiency, glenohumeral dysplasia and abnormal version, and scapulothoracic dyskinesia [1, 2]. About the role of age, higher incidence of shoulder instability has been reported at

the second and third decade and different authors showed that recurrent dislocation occurs much more frequently in adolescents than in the older population but a clear explanation of this incidence does not exist [8–11]. These studies just noted that age is one of the major risk factors for primary shoulder dislocation and recurrence [9]. Alterations of the capsulo-ligamentous structures are also commonly considered important predisposing factor to first dislocation and recurrence [1, 9], but the biological nature of these alterations has not been well investigated yet. They include constitutional glenohumeral laxity and acquired capsule alterations, which consist in a plastic deformation of the capsule and the inferior glenohumeral ligament complex that can occur also with a single anterior dislocation, even though tissue elongation is difficult to document both at MRI and intraoperatively [4, 12].

On the other hand, the pathogenesis of multidirectional instability is still not clear. It may be multifactorial, but capsular laxity (i.e., a loose, redundant inferior capsule) is a pathological predisposing condition that has been implicated as one of the main pathogenetic factors. The entity of laxity is related to age, sex, and genetic factors which control the histological structure and biochemical composition of articular capsule [1, 13–15].

The glenohumeral articular capsule is a dense fibrous connective tissue composed mainly of water, proteoglycans, collagen, and elastic fibers [16]. Collagen fibril diameter has been shown to be correlated with the tensile strength of shoulder capsule [17]. The elastic fibers (EFs) are one of the main components of the connective tissue that provide physiologic elasticity to it, and may affect capsular strength [18]. Abnormalities in EFs and specifically in the fibrillin component have been demonstrated in Marfan's syndrome, a condition that is associated with connective tissue laxity [19, 20]. The distribution of elastic fibers is related to the different functional role and biomechanical behaviour of each tissue and the amount of elastic fibers in the various tissues changes with age [18, 21, 22]. Very few studies have analyzed the histological and biochemical composition of the human shoulder capsule and age-related modifications of extracellular matrix are still poorly known [17, 23–26].

The aim of the present pilot study was to analyze the eventual age-related distribution of the elastic fibers in unaffected shoulder capsule and in patients with traumatic anterior and atraumatic multidirectional instability at first surgery. The hypothesis was that a different pattern of distribution of the elastic fibers might be associated with shoulder instability.

2. Materials and Methods

2.1. Patients and Specimen Collection. Biopsy specimens were obtained from the shoulder capsule of three groups of male patients from the senior authors practice between 2015 and 2017. All subjects gave informed written consent for the use of their specimens to the purpose of the present trial. The diagnosis of instability was made when there was a history of subluxation with spontaneous reduction or a history of dislocation requiring manual reduction, and patients had a positive anterior apprehension and relocation test (anterior instability) or anterior and posterior apprehension and positive sulcus test (multidirectional instability).

The patients were divided preoperatively into three different groups on the basis of history, clinical and instrumental (MRI/TAC) evaluation, and arthroscopic findings. The indication for arthroscopic shoulder stabilization was given independently from the study protocol.

Group 1 consisted of 10 consecutive male patients with a history of traumatic shoulder dislocation/s and persistent clinical or radiographic evidence of anteroinferior shoulder instability (labral detachment, anterior labroligamentous and periosteal sleeve avulsion lesion [ALPSA]).

Inclusion criteria were at least 1 shoulder dislocation, traumatic onset before 6 months, and unidirectional instability with or without hyperlaxity (grades B2 or B3 according to Gerber and Nyffeler [18]. Exclusion criteria were multidirectional instability or evidence of bony glenoid defects (>25% as obtained on Bernageau radiographic profile or 3-dimensional computed tomography scans). The number of reported dislocations varied from 3 to 11 episodes (median value: 5). The average age of these patients was 28 years (ranging from 17 to 40).

All patients were treated by arthroscopic capsulolabral repair and refixation with sutures and anchors technique.

Group 2 consisted of 10 consecutive patients with clinical symptoms and signs (lasting for at least 6 months) indicating instability in an inferior direction and at least one other direction (anterior or posterior), without history of trauma [21].

The hyperabduction test, or Gagey test, was conducted to evaluate passive abduction, which occurs within the glenohumeral joint and is controlled by the inferior glenohumeral ligament. In patients with instability, 85%, show a range of passive abductions of over 105 degrees versus 90 degrees in the contralateral shoulder, the former associated with lengthening and laxity of the inferior glenohumeral ligament [27]. The number of reported dislocations varied from 5 to 10 episodes (median value: 6). The average age of these patients was 30 years (ranging from 16 to 42).

Findings at arthroscopy and imaging reflected the dominant direction of instability. The most common arthroscopic finding was increased capsular volume based on redundant axillary recess without intra-articular associated lesions. All patients were treated by arthroscopic capsular plications for MDI.

Group 3: the control group consisted of samples from shoulder capsule of 10 male patients with no history of instability: 3 patients underwent arthroscopic repair of acute traumatic glenoid fracture and 7 underwent open reduction and osteosynthesis of proximal humeral fracture. The average age of these patients was 34 years (ranging from 16 to 45).

Only male patients were enrolled in this study in order to limit histological variations due to sex.

In addition to the group as a whole, specific subgroups were analyzed separately on the basis of the age of subjects: > 22 or < to 22 years. In particular, Groups 1A, 2A, and 3A included subjects with age < 22 years whereas Groups 1B, 2B, and 3B included subjects with age > 22 years. Age represents an important prognostic factor for redislocations [28, 29].

Some authors have defined the cut-off for increased risk of redislocation in the early third decade (20 years [27], 22 years, and 25 years [11]), whereas others have found different risks in patients aged less than 20 years (64%) versus greater than 40 years (6%) [30].

In our study, age was categorized into clusters of younger than 22 years and 22 years or older, based on the findings from a previous study by the senior authors, where it was shown that patients younger than 22 have a greater risk of redislocation after arthroscopic treatment of instability [29].

We excluded from the study all subjects affected by shoulder instability associated with voluntary dislocations, unequivocal diagnosis of genetic disorders (i.e., Marfan Syndrome and Ehler-Danlos Syndrome), and cervical or other neurological diseases predisposing to shoulder instability.

At the time of surgery, a capsular biopsy was harvested from the capsule in the interval between the middle and the inferior glenohumeral ligaments (Rouviere Foramen), in all patients of Groups 1 and 2 during the capsular shift procedure. The specimens were obtained by an arthroscopic biopsy punch about 1 cm lateral to the glenoid rim. The average size of the specimens used for analysis was 3 x 3 mm. Biopsy from the same region was taken from the control group subjects (Group 3) by arthroscopy in 3 cases and by open procedure in 7 cases. All the samples were analyzed by immunohistochemical and histomorphometric methods. The images were evaluated separately by two senior experts on soft tissue histology blinded to all clinical parameters. The independent evaluations were then discussed by the two observers to reach consensus and to obtain the final evaluation on each slide.

2.2. Histochemistry. For light microscopy, specimens were fixed by immersion in 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4, at 4°C for 24 hours, decalcified in 4 N formic acid and sodium citrate for 72 hours, embedded in paraffin, cut into transverse and longitudinal sections (3 to 5 μm thick), and stained with haematoxylin-eosin for assessment of the quality of the tissue, with specific methods for EFs (Weigert's resorcinol fuchsin and Verhoeff's iron hematoxylin) and with Van Gieson (for collagen fibers).

2.3. Immunohistochemistry. Sections were deparaffinized in xylene and rehydrated in graded ethanol. Intrinsic peroxidase activity was blocked by immersion in distilled water containing 3% hydrogen peroxidase for 6 min. Nonspecific binding was blocked with 3% normal goat serum in phosphate-buffered saline (PBS), pH 7.4, for 30 min at room temperature. Slides were then incubated overnight at 4°C with the primary antibodies. A monoclonal antielastin antibody (Sigma-Aldrich, Milan, Italy) was used at 1:5000 dilution. Rabbit and mouse immunoglobulins at the same dilutions as the primary antibodies were used as controls. The reactions were revealed using the DAKO LSAB + kit, HRP (Dako, Carpinteria, CA, USA). The analysis of immunolabeling of elastin was performed on two slides per specimen by evaluating five fields in each slide and defining three different grades: 1 low, 2 moderate, and 3 high immunolabeling. Staining was viewed and photographed with a Leica Microscope.

2.4. Histomorphometry. Computerized morphometric analysis of EFs was performed by using the Leica Q500 MC Image Analysis System (Leica Cambridge Ltd., Cambridge, England) on two slides per specimen stained with Verhoeff's iron hematoxylin. All morphometric steps, except the section of the first microscopic field, were automated. EFs were counted electronically and labelled with different colors to facilitate their identification. The software for mathematical morphology calculated the area fraction (Area%) occupied by EF (i.e., pixels of EFs/256"pixels); five fields in each slide were studied.

2.4.1. Statistical Analysis. Data were expressed as mean +- SD of the mean, and the statistical evaluation was carried out by ANOVA test. A value of $p < 0.05$ was considered significant. All statistical analysis was performed with SPSS, version 19.0 (IBM, Armonk, New York).

3. Results

Data of the specimens from the patients with shoulder instability and control group were summarised in Figures 1 and 2. The topographic distribution of the EFs was similar, but both the elastin density and the percentage of area covered by EFs were higher in younger subjects (Groups 1A, 2A, and 3A) in comparison to older subjects (Groups 1B, 2B, and 3B). These differences were in all cases statistically significant ($p<0.05$). The elastin density and the percentage of area covered by EFs were higher in specimens of Group 2 (Multidirectional instability) in comparison to the other Groups ($p<0.001$), and this difference was statistically significant, as was the difference between Group 1 and Group 3 ($p<0.001$). No differences in the cellularity and vascularisation were observed between the specimens from different groups of subjects. EFs stained a bright violet or purple were flame-shaped and varied in length. Numerous EFs were homogeneously distributed in all the specimens analyzed. They were arranged in bundles with a preferential orientation (Figures 3, 4, and 5), as previously observed in human and rabbit articular capsules of the knee [25].

4. Discussion

The main finding of the present pilot study is that there is a significant difference in terms of elastin and elastic fibers density among patients younger or older than 22, especially in case of multidirectional shoulder instability, where the highest density of both elastin and EFs is documented.

Very few studies analyzed the biochemical composition and the histological structure of human normal and pathological shoulder capsule. Kaltsas et al. identified collagen types I,III, and V in shoulder capsule by gel electrophoresis, but no further biochemical and histological characterization was reported [13]. Ticker et al. showed that the overall biochemical composition of the inferior glenohumeral ligament

	Group 1 *TUBS*		*Group 2* *MULTIDIRECTIONAL*		*Group 3* *CONTROLS*	
	<22yy	>22yy	<22yy	>22yy	<22yy	>22yy
Number of patients	5	5	5	5	5	5
Elastin density	1.9±0.7	1.7±0.7	2.6±0.5	2.0±0.5	1.5±0.5	1.1±0.3
Elastic fibers density (mean Area% ± sd)	9.3±1.1	7.3±0.6	12.6±1.1	10.5±1.3	6.4±0.5	4.6±0.4

Figure 1: Number of patients, immunohistochemical and histomorphometric data of specimens from patients affected with traumatic instability (Group 1), multidirectional instability (Group 2), and control subjects (Group 3). All intragroup differences (<22 yy vs >22 yy) were statistically significant (see arrows with asterisks). All intergroup differences (Group 1 vs Group 2, Group 2 vs Group 3, and Group 1 vs Group 3) were statistically significant (see arrows with asterisks).

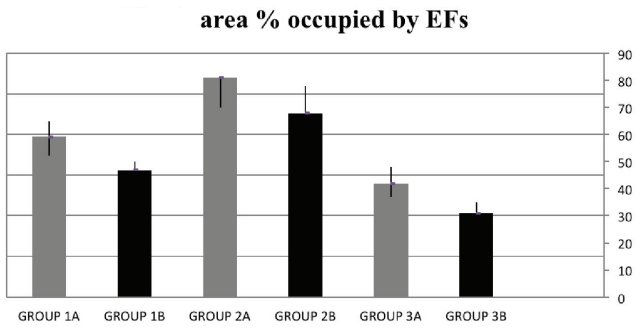

Figure 2: Histomorphometric data of EFs distribution (mean area % occupied by EFs ± SD) from patients with shoulder instability (Groups 1 and 2) and control subjects (Group 3). Subgroup A: patients < 22 yy old; Subgroup B: patients >22 yy old.

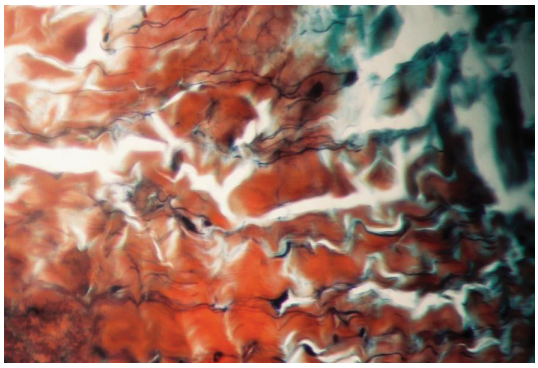

Figure 3: Shoulder articular capsule of an 18-year-old patient affected with MDI. Many elastic fibers are homogeneously distributed and arranged in bundles with a course parallel to collagen fibers, showing a crimp feature (Verhoeff's iron hematoxylin, staining, and original magnification, x 400; elastic fibers are stained in violet or purple, whereas collagen is in red).

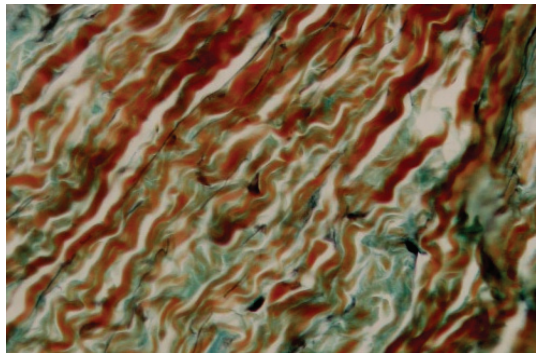

Figure 4: Shoulder articular capsule of a 33-year-old patient affected with MDI. Many elastic fibers maintain the normal orientation in the different layer but are reduced in number in comparison with patients of the same group with age < 22 yy (Verhoeff's iron hematoxylin staining, and original magnification x 400; elastic fibers are stained in violet or purple, whereas collagen is in red).

in specimens from subjects with a mean age of 60 years was similar to the composition of other ligaments [31]. Hirakawa et al. reported the presence of abundant immature collagen fibers (increased cysteine content) in shoulder capsule from loose shoulders compared to controls [24]. Mc Farland et al. documented the histologic changes that occur in the capsule of patients with traumatic instability of the shoulder as a denuded synovial layer, subsynovial edema, increased cellularity, and increased vascularity [11]. Rodeo et al. analyzed collagen cross-links, collagen fibril diameter and density, amino acid composition, and elastic fibers in shoulder capsule and skin in four patient groups: (1) unidirectional anterior instability; (2) multidirectional instability/primary surgery; (3) multidirectional instability/revision surgery; and (4) no history of instability. The age-related changes were not

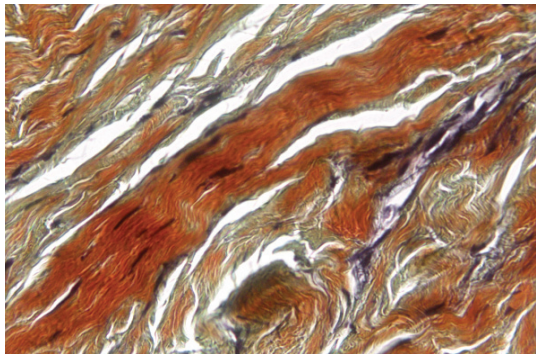

Figure 5: Shoulder articular capsule from a subject 40 years old of control group. Very few elastic fibers are detectable; their number is dramatically reduced in comparison with the patients of the other groups (Verhoeff's iron hematoxylin staining, original magnification x 400; elastic fibers are stained in violet or purple, whereas collagen is in red).

considered. They did not find significant differences between the unidirectionally and multidirectionally unstable capsule, but samples from multidirectional instability/revision surgery subjects contained significantly more reducible cross-links, smaller-diameter collagen fibrils, decreased collagen fibril density, and an increased density of elastin staining. The authors showed that collagen fibrils could play a major role in shoulder instability and hypothesized that repeated capsular deformation in patients with shoulder instability may provide the stimulus for adaptive changes that increase the strength of the capsule in an attempt to diminish instability. Thus they interpreted the differences in EFs distribution in shoulder capsule as a consequence rather than as predisposing factor of shoulder instability [20].

To the best of our knowledge, no previous studies have measured the age-related distribution of EFs in normal and unstable shoulder capsule. The present study attempted to elucidate some age-related histological aspects of the capsule that may contribute to capsular laxity and predispose to first shoulder dislocation and recurrence. We decided to consider only male subjects and subjects under and over the age of 22 years because male sex and age under 22 years at time of surgery have been found as significant risk factors for recurrence [9].

Our observations showed the presence of numerous EFs in shoulder capsule of young and adult subjects. The topographic distribution of the EFs was similar, but their number (elastin density and percentage of area covered by EFs) was significantly higher in younger subjects in comparison to older subjects (age > 22y). Furthermore, shoulder capsule from patients with shoulder instability had higher density of EFs compared with normal capsule, particularly in the samples taken from patients affected with multidirectional instability.

The mechanical properties of articular capsule and ligaments are due to their extracellular matrix that is mainly composed of water, glycosaminoglycans, collagen, and elastic fibers [16]. EFs consist of an amorphous core of elastin and closely associated microfibrils that are composed of fibrillin and microfibrillar associated glycoproteins. Elastin, the major component of mature EFs, should provide the elastomeric properties required. Microfibrils, which constitute the so-named oxytalan fibers, probably do not elongate much under mechanical stress. They are more abundant in location where resistance to mechanical stress is required, such as periodontium and osteoperiosteal junction. To date, however, the functional role of EFs in the joint capsule has not been clarified yet, even though they could have a role in the rapid recovery of the initial length after deformation. Previous studies demonstrated the topographic distribution and the mechanical role of EFs in several musculoskeletal tissues. Some of us described the age-related distribution of the EFs in the rabbit knee and in the human epiphyseal region and made hypotheses on the possible role of these fibers in maintaining joint stability and in affecting the growth process of long bones [18, 21, 32]. We found that the type and the quantity of fibers varied according to the age of the subjects in various skeletal tissues, including articular capsule of the knee.

Some studies have suggested the involvement of these fibers in several genetic and acquired pathological conditions, including some affecting the musculo-skeletal system [28, 29, 33]. In previous studies we observed that in human and bovine Marfan syndrome the structural abnormalities of EFs in articular capsule could make the capsule functionally incompetent to resist normal stress, predisposing to joint laxity and dislocations [27, 34, 35].

Data of the present study confirmed also in human articular capsule of the shoulder the presence of an age-related distribution of EFs, and showed a greater amount of these fibers in unstable shoulder. These data confirm the observations of Rodeo et al. about increased density of elastin staining in samples from patients affected by multidirectional instability [20].

This study however presents some weakness related to the small number of subjects included, the limited area of the capsule sampled, the histological analyses limited to EFs, and the fact that just the 22-year-old cut-off was considered. In particular, the biopsy location may affect the histological results: we took biopsy samples from the Rouviere Foramen, close to the middle glenohumeral ligament, 1 cm lateral to the capsulolabral edge. Future studies should sample different areas of the capsule in order to verify whether the extracellular matrix composition changes inherently. We focused the analyses on the EFs. However, the mechanical properties of ligaments and articular capsule are also due to other extracellular matrix components such as glycosaminoglycans/water and collagen fibers, which will be age-related analysis in further studies [31]. The choice of the cut-off at the age of 22 was performed based on the findings coming from clinical trials previously published: anyway we cannot exclude the fact that other age-related differences might exist and the preliminary results of the present pilot study could be used to design a bigger trial to eventually detect those difference. Unfortunately, due to ethical reasons, it was not possible to include more biopsies in this study and our sample size did not allow for further statistically sounding analysis. In light of these findings, it is difficult to understand all the factors

affecting capsular strength and to know if the extracellular matrix composition is the cause rather than consequence of shoulder instability.

5. Conclusion

Based on the findings of this pilot study, a greater elastin density and EFs distribution in capsular biopsies of younger subjects with unstable shoulders compared to healthy controls may represent an important factor in predisposing the joint to first dislocation and recurrence, particularly in the subgroup of patients with multidirectional shoulder instability.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

All the authors of the present paper declare no conflicts of interest and nothing to disclose.

Acknowledgments

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References

[1] L. U. Bigliani, R. Kelkar, E. L. Flatow, R. G. Pollock, and V. C. Mow, "Glenohumeral stability: Biomechanical properties of passive and active stabilizers," *Clinical Orthopaedics and Related Research*, no. 330, pp. 13–30, 1996.

[2] C. L. Baker III, R. Mascarenhas, A. J. Kline, A. Chhabra, M. W. Pombo, and J. P. Bradley, "Arthroscopic treatment of multidirectional shoulder instability in athletes: A retrospective analysis of 2-to 5-year clinical outcomes," *The American Journal of Sports Medicine*, vol. 37, no. 9, pp. 1712–1720, 2009.

[3] P. Boileau, M. Villalba, J. Y. Hery, F. Balg, P. Ahrens, and L. Neyton, "Risk factors for recurrence of shoulder instability after arthroscopic Bankart repair," *The Journal of Bone and Joint Surgery—American Volume*, vol. 88, no. 8, pp. 1755–1763, 2006.

[4] J. Deitch, C. T. Mehlman, S. L. Foad, A. Obbehat, and M. Mallory, "Traumatic anterior shoulder dislocation in adolescents," *The American Journal of Sports Medicine*, vol. 31, no. 5, pp. 758–763, 2003.

[5] C. B. Dewing, F. McCormick, S. J. Bell et al., "An analysis of capsular area in patients with anterior, posterior, and multidirectional shoulder instability," *The American Journal of Sports Medicine*, vol. 36, no. 3, pp. 515–522, 2008.

[6] T. Flinkkilä, P. Hyvönen, P. Ohtonen, and J. Leppilahti, "Arthroscopic Bankart repair: Results and risk factors of recurrence of instability," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 18, no. 12, pp. 1752–1758, 2010.

[7] J. R. Ralphs and M. Benjamin, "The joint capsule: structure, composition, ageing and disease," *Journal of Anatomy*, vol. 184, part 3, pp. 503–509, 1994.

[8] A. Gigante, N. Specchia, S. Nori, and F. Greco, "Distribution of elastic fiber types in the epiphyseal region," *Journal of Orthopaedic Research*, vol. 14, no. 5, pp. 810–817, 1996.

[9] C. M. Kielty, "Elastic fibres in health and disease," *Expert Reviews in Molecular Medicine*, vol. 8, pp. 1–23, 2006.

[10] B. Lee, M. Godfrey, E. Vitale et al., "Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes," *Nature*, vol. 352, no. 6333, pp. 330–341, 1991.

[11] E. G. McFarland, T. K. Kim, P. Banchasuek, and E. F. McCarthy, "Histologic evaluation of the shoulder capsule in normal shoulders, unstable shoulders, and after failed thermal capsulorrhaphy," *The American Journal of Sports Medicine*, vol. 30, no. 5, pp. 636–642, 2002.

[12] L. J. Smith and N. L. Fazzalari, "The elastic fibre network of the human lumbar anulus fibrosus: Architecture, mechanical function and potential role in the progression of intervertebral disc degeneration," *European Spine Journal*, vol. 18, no. 4, pp. 439–448, 2009.

[13] D. S. Kaltsas, "Comparative study of the properties of the shoulder joint capsule with those of other joint capsules," *Clinical Orthopaedics and Related Research*, vol. 173, pp. 20–26, 1983.

[14] F. Postacchini, S. Gumina, and G. Cinotti, "Anterior shoulder dislocation in adolescents," *Journal of Shoulder and Elbow Surgery*, vol. 9, no. 6, pp. 470–474, 2000.

[15] C. R. Rowe, B. Zarins, and J. V. Ciullo, "Apparent causes of failure and treatment recurrent anterior dislocation of the shoulder after surgical repair," *The Journal of Bone & Joint Surgery*, vol. 66, pp. 159–168, 1984.

[16] P. J. MacMahon and W. E. Palmer, "Magnetic resonance imaging in glenohumeral instability," *Magnetic Resonance Imaging Clinics of North America*, vol. 20, no. 2, pp. 295–312, 2012.

[17] C. S. Neer II and C. R. Foster, "Inferior capsular shift for involuntary inferior and multidirectional instability of the shoulder: a preliminary report," *The Journal of Bone & Joint Surgery*, vol. 83, no. 10, p. 1586, 2001.

[18] C. Gerber and R. W. Nyffeler, "Classification of glenohumeral joint instability," *Clinical Orthopaedics and Related Research*, vol. 400, pp. 65–76, 2002.

[19] L. Hovelius, A. Olofsson, B. Sandström et al., "Nonoperative treatment of primary anterior shoulder dislocation in patients forty years of age and younger: A prospective twenty-five-year follow up," *The Journal of Bone & Joint Surgery*, vol. 90, no. 5, pp. 945–952, 2008.

[20] S. A. Rodeo, K. Suzuki, M. Yamauchi, M. Bhargava, and R. F. Warren, "Analysis of collagen and elastic fibers in shoulder capsule in patients with shoulder instability," *The American Journal of Sports Medicine*, vol. 26, no. 5, pp. 634–643, 2016.

[21] A. Gigante, C. Chillemi, and F. Greco, "Changes of elastic fibers in musculoskeletal tissues of Marfan syndrome: A possible mechanism of joint laxity and skeletal overgrowth," *Journal of Pediatric Orthopaedics*, vol. 19, no. 3, pp. 283–288, 1999.

[22] A. Gigante, C. Chillemi, K. A. Potter, C. Bertoni-Freddari, and F. Greco, "Elastic fibers of musculoskeletal tissues in bovine Marfan syndrome: A morphometric study," *Journal of Orthopaedic Research*, vol. 17, no. 4, pp. 624–628, 1999.

[23] A. Gigante, N. Specchia, and F. Greco, "Age-related distribution of elastic fibers in the rabbit knee," *Clinical Orthopaedics and Related Research*, no. 308, pp. 33–42, 1994.

[24] M. Hirakawa, "On the etiology of the loose shoulder—biochemical studies on collagen from joint capsules," *Nippon Seikeigeka Gakkai Zasshi*, vol. 65, article 550, 1991.

[25] M. P. Jacob, "Alterations of elastic fibers in genetically modified mice and human genetic diseases," *Frontiers in Bioscience*, vol. E3, no. 3, pp. 994–1004, 2011.

[26] C. M. Robinson, J. Howes, H. Murdoch, E. Will, and C. Graham, "Functional outcome and risk of recurrent instability after primary traumatic anterior shoulder dislocation in young patients," *The Journal of Bone and Joint Surgery—American Volume*, vol. 88, no. 11, pp. 2326–2336, 2006.

[27] O. J. Gagey and N. Gagey, "The hyperabduction test," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 83, no. 1, pp. 69–74, 2001.

[28] L. Hovelius, "Anterior dislocation of the shoulder in teen-agers and young adults. Five-year prognosis," *The Journal of Bone & Joint Surgery*, vol. 69, no. 3, pp. 393–399, 1987.

[29] G. Porcellini, F. Campi, F. Pegreffi, A. Castagna, and P. Paladini, "Predisposing factors for recurrent shoulder dislocation after arthroscopic treatment," *The Journal of Bone & Joint Surgery*, vol. 91, no. 11, pp. 2537–2542, 2009.

[30] S. C. Thomas and F. A. Matsen III, "An approach to the repair of avulsion of the glenohumeral ligaments in the management of traumatic anterior glenohumeral instability," *The Journal of Bone & Joint Surgery*, vol. 71, no. 4, pp. 506–513, 1989.

[31] J. B. Ticker, E. L. Flatow, R. J. Pawluk et al., "The inferior glenohumeral ligament: A correlative investigation," *Journal of Shoulder and Elbow Surgery*, vol. 15, no. 6, pp. 665–674, 2006.

[32] C. D. Geier Jr. and G. A. Paletta Jr., "Shoulder instability in the skeletally immature athlete," *Operative Techniques in Sports Medicine*, vol. 14, no. 3, pp. 159–164, 2006.

[33] H. Uhthoff and M. Piscopo, "Anterior capsular redundancy of the shoulder: congenital or traumatic? An embryological study," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 67-B, no. 3, pp. 363–366, 1985.

[34] N. Hadley-Miller, B. Mims, and D. M. Milewicz, "The potential role of the elastic fiber system in adolescent idiopathic scoliosis," *The Journal of Bone & Joint Surgery*, vol. 76, no. 8, pp. 1193–1206, 1994.

[35] P. Tsipouras, R. Del Mastro, M. Sarfarazi et al., "Genetic linkage of the marfan syndrome, ectopia lentis, and congenital contractural arachnodactyly to the fibrillin genes on chromosomes 15 and 5," *The New England Journal of Medicine*, vol. 326, no. 14, pp. 905–909, 1992.

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Review Article

Radial Head Resection versus Arthroplasty in Unrepairable Comminuted Fractures Mason Type III and Type IV: A Systematic Review

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Unrepairable comminuted fractures of the radial head Mason type III or type IV have poor outcomes when treated by open reduction and internal fixation. Radial head resection has been proposed as good option for surgical treatment, while in the last decades, the development of technology and design in radial head prosthesis has increased efficacy in prosthetic replacement. The present review was conducted to determine the best surgical treatment for comminuted radial head when ORIF is not possible. Better outcomes are reported for radial head arthroplasty in terms of elbow stability, range of motion, pain, and fewer complications compared to radial head excision. Nevertheless, radial head resection still can be considered an option of treatment in isolated radial head fractures with no associated ligament injuries lesion of ligaments or in case of older patients with low demanding function.

1. Introduction

Surgical treatment for comminuted and unrepairable fractures of the radial head may be challenging. These types of fractures are often associated with multiple ligamentous injuries amounting to elbow instability. Radial head resection has been proposed as good option for surgical treatment, while in the last decades, the development of technology and design in radial head prosthesis has increased efficacy in prosthetic replacement.

The radial head is a secondary valgus stabilizer of the joint and it is involved in transmission of axial force load through the elbow during flexion [1]. It is also a varus and external rotatory constrainer [2]. Comminuted radial head fractures Mason type III and type IV are commonly associated with other injures of the elbow as capitellum and coronoid fractures and/or ligaments disruption, both medial and lateral ligaments and interosseus membrane [3–6]. Primary goal in surgical treatment is to restore elbow stability in order to preserve the complex physiologic elbow kinematics. In this respect, medial collateral ligament is the primary constrainer in valgus stress. Radial head contributes secondarily to valgus stability [1, 7] and its preservation is mandatory in case of fractures that involve soft tissue and ligaments to avoid chronic instability. Many authors have described serious complications in case of resection of the radial head such as proximal migration of radius and longitudinal instability, humeroulnar osteoarthritis [2, 7–9], decrease in grip strength, cubitus valgus, and ulnar neuropathy [10, 11]. Therefore, radial head arthroplasty has obtained a large consensus in orthopaedic surgeons as primary option of treatment in fractures Mason types III and IV. It allows an anatomical reconstruction and it maintains stability and physiologic kinematics of the elbow if associated with ligament reconstruction. However, oversizing or overstuffing of radial head prosthesis, malpositioning, and aseptic mobilization may lead to a high rate of complications and failure of this surgical procedure. Recent reviews of literature [10, 12] on elbow arthroplasties have reported satisfactory results in radial head replacement studies due to improvement of biomaterials and operative techniques.

The purpose of this review was to investigate the current literature on surgical treatment of unrepairable comminuted

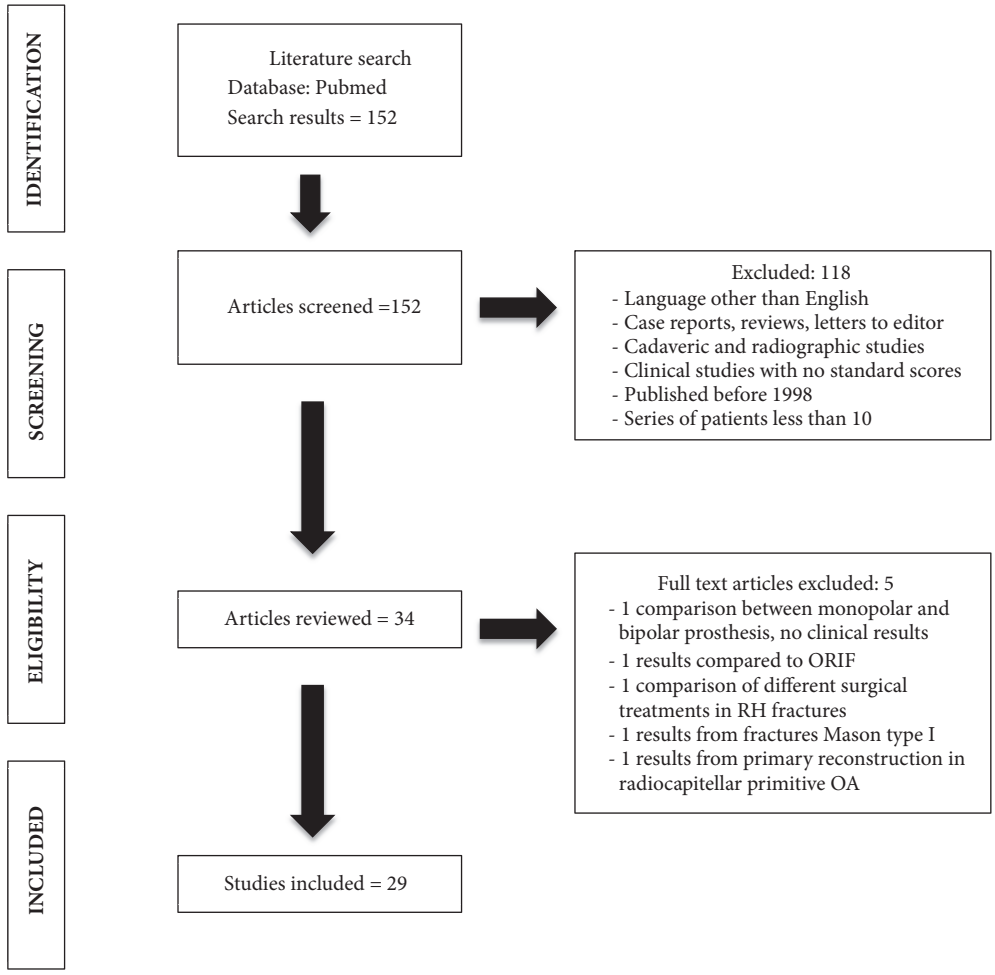

Figure 1

radial head fractures Mason type III or type IV to assess results and indications for radial head replacement or resection.

2. Materials and Methods

We searched in PubMed electronic database the words (radial head fractures) AND ((artrhoplasty) OR (prosthesis)) AND ((resection) OR (excision)). The guidelines for preferred reporting items for systematic reviews and meta-analysis (PRISMA) were used (Figure 1). We selected articles of the last 20 years, from 1998 to December 2017. We created an Excel database for collecting data extracted from articles in English language, selecting papers with series of 10 or more patients. Exclusion criteria were articles written in other languages, case reports or reviews, cadaveric or instrumentals studies, clinical studies with no standard questionnaires or scores, and studies in which posttraumatic outcomes were not separated from primary reconstruction of the radial head.

We extracted relevant data from the selected articles: type of study, number of patients, age, follow-up, type of surgery performed, clinical results (ROM, DASH score, MEPS score, and VAS), and radiographic results.

3. Results

The database search identified 152 potentially relevant articles. Abstracts have been analyzed following inclusion and exclusion criteria and a total of 29 papers were selected for the present review. Most of retrospective studies on metal radial head prosthesis have been published in the last ten years in comparison to a lack of studies for radial head excision in the last two decades. Moreover, few articles on comparison of the two surgical techniques have been found. Because of heterogeneity in level of evidence, surgical technique, type of implants, and rehabilitation protocol, we did not perform statistical data analysis. Articles selected are reported in Table 1.

4. Discussion

From our review of literature clinical results for radial head replacement are reported in Table 2. Most of retrospective studies involve modular monopolar or bipolar prosthesis implanted for irreparable Mason type III or type IV fractures. For most of authors, mid term follow-up has shown satisfactory results in range of motion recovery (average

Table 1: Studies selected. Number and age of patients, type of treatment, and follow-up.

Author	Type of study and year of publication	N. of patients	Age	Type of treatment	Follow up
Carità E	Retrospective 2017	28 (Mason type III – IV)	49 yo (18-71)	Cementless monopolar prostheses (Acumed – Tornier)	49 months (6-118)
Laflamme M	Retrospective 2017	46 (21 Mason III; 36 Mason IV)	Porous stem: 52.8 yo Smooth stem: 45.6	Modular monopolar head – uncemented loose fitting stem (Evolve, Wright) Modular monopolar head - porous press-fit stem (ExploR, Biomet)	6,3 years (1,2-15,1)
Tarallo L	Retrospective 2017	31 Mason III	-	31Radial head replacement (Anatomic RHA, Acumed)	30 months (12 months to 7 years)
Nestorson J	Restrospective 2017	32 Mason IV	50 yo (29-70)	18 pts radial head arthroplasty 14 radial head resection	58 months (RHA) 108 months (RH resection)
Laumonerie P	Retrospective 2017	77 (65 Mason type III, 2 Mason type II; 10 radial neck fractures)	52 yo (20-82)	Guepar radial head prosthesis (SBi/Stryker) Evolutive (Aston Medical) rHead Recon (SBi/Stryker) rHead STANDARD (SBi/Stryker)	74 months (24 to 141)
Lopiz	Retrospective 2016	25 Mason III	Excixion 53 yo Arthroplasty 54.4yo	11 patients radial head resection 14 Radial head prosthesis	Excision 60.3 months Arthroplasty 42 months
Van Hoecke	Retrospective 2016	21 Mason III	53,2 yo	Judet bipolar head prosthesis	113 months
Heijink	Retrospective 2016	25 Mason type III	55 yo	Cemented bipolar radial head artrhoplasty (Tornier)	50 months
Kodde	Retrospective 2016	27	48 yrs (24-63)	Press fit bipolar radial head arthroplasty	48 months (28-73)
Marsh JP	Retrospective 2016	55	61 yrs	Modular smooth-stemmed radial head implant (Evolve, Wright)	8.2 yrs
Gauci MO	Retrospective 2016	65 (10 ORIF revision 42 Mason III 12 post traumatic radiohumareal sequelae, 1 swanson prosthesis revision)	52 yrs (22-85)	Modular Pyrocarbon (MoPyc) radial head prosthesis (Tornier)	42 months (24-108)
Solarino G.	Retrospective 2015	30 (12 Mason II; 18 Mason III)	71 yo (65-80)	Radial head resection	40 months (24-72)
Allavena C	Retrospective 2014	22 (16 fractures Mason type III; 6 fractures of the radial neck)	44 yrs (22-65)	Modular bipolar radial head prostehesis (Guepar,De Puy)	50 months
Yalcinkaya M	Retrospective 2013	14 fractures Mason type III	38 yrs (20-67)	Radial head resection	14,7 yrs (9-26)
Flinkkila T.	Retrospective 2012	42 (34 Mason type III; 8 type II)	56 yrs (23-85)	Metallic radial head artrhoplasty	50 months (12-107)
Sarris IK	Retrospective 2012	5 Mason type III; 15 type IV; 10 complex elbow injuries; 2 malunion	54 yrs (32-68)	MoPyc pyrocarbon prosthesis (Bioprofile, Tornier)	27 months (21-46)

Table 1: Continued.

Author	Type of study and year of publication	N. of patients	Age	Type of treatment	Follow up
Ricon F	Retrospective 2012	28 Mason III	54 yrs	Pyrocarbon radial head prosthesis (Bioprofile Lab.)	32 months (12-62)
Muhm M	Retrospective 2011	25 radial head fractures type III and type IV	-	Uncemented modular metallic prosthesis (Evolve)	Short term 1,6yrs Mid term 5,1 yrs
Iftimie	Retrospective 2011	22 (16 Mason type III; 6 type IV)	54 yrs (28-81)	Resection head arthroplasty	16,9 yrs (10-24)
Celli A	Retrospective 2010	16 patients (9Mason type III 7 Mason type IV)	46.1 yrs (27-74)	Bipolar Judet radial head arthroplasty (Tornier)	41,7 months (12,3 – 86,3)
Antuna SA	Retrospective 2010	26 patients (6 type III 20 type IV)	29 yrs (15-39)	Radial Head Resection	24,9 yrs (15-34)
Dotzis A	Retrospective 2006	14 patients (6 Mason type III; 8 type IV)	44.8 years (18 – 85)	Judet prosthesis (Tornier)	5.3 years (1-12 yrs)
Ashwood N	Retrospective 2004	16 Mason type III	45 yrs (21- 72)	Metallic monoblock radial head prosthesis (Wright Med Tec.)	2.8 years (1.2-4.3)
Herbertsson P.	Retrospective 2004	61 patients 39 Mason type II 10 Mason III 12 Mason IV	44 yrs (9-69)	Radial head resection Primary RHE=39 Delayed RHE=18	18 years (11-33)
Moro JK	Retrospective 2001	25 (10 Mason type III;15 Mason type IV)	54 yrs	Metal Radial head arthroplasty	39 months
Sanchez Sotelo J.	Retrospective 2000	10 Mason type III	39 yrs (26-57)	Radial head resection	4.62 years (24-86 months)
Ikeda M	Retrospective 2000	11 Mason type III	40 yrs (25-70)	Radial head resection	11 years (3-18)
Smets A	Retrospective 2000	13 Mason type III	-	Floating radial head prosthesis	25.2 months
Jansen RP	Retrospective 1998	18 Mason III	-	Radial head resection	16 to 30 years

flexion-extension arc of motion: 116°). Good results in DASH scores (from 7 to 24) and MEPS scores (from 79 to 100) and low VAS pain evaluation scale (from 0 to 2.2) are reported [13–32]. A certain loss of grip strength compared to contralateral side is often described (average loss of strength: 10% respect to the contralateral side). Authors highlight the importance of ligament reconstruction in case of associated injuries. Intraoperative assessment of stability and acute repair of torn ligaments is mandatory for a successful procedure.

Most common radiological modifications include osteoarthritic changes of ulnohumeral joint, capitellum wear for oversizing of radial head prosthesis, periarticular heterotopic ossifications, and radiolucency lines around the stem. Some modifications in radiographic appearance seem to not correlate directly with clinical symptoms: bone resorption around the prosthesis does not correlate with loosening of the prosthesis and does not affect clinical scores. Marsh [21] reports favorable clinical outcomes from short to long follow-up despite a high evidence of radiolucency around the stem and arthritis in his series. Gauci [20] has found no association between neck bone resorption and postoperative symptoms.

Complications (Table 3) described in radial head replacement are in common in almost all the papers: aseptic mobilization of the stem, overstuffing, erosion of the capitellum, osteoarthritis, and heterotopic ossification clinically arising with lateral elbow pain or loss of motion, and posterior subluxation for undersizing. Rare temporary ulnar and radial nerve sensory neuropathies are reported. Though, few papers seem to discourage radial head arthroplasty. Moro [31] reports mild to moderate impairment of ROM and pain for both elbow and wrist in patients treated with a metal radial head implant. Laumonerie [16] describes unsatisfactory result from bipolar radial head prosthesis because of malposition in varus and valgus and oversizing leading to a high rate of reintervention during the three first months after implantation. Flinkkila [23] reports poor results from press

Table 2: Mean clinical results for radial head arthroplasty.

Author	Type of prosthesis	ROM	VAS	DASH	Meps/Mepi	Other clinical evaluations
Carità E	Cementless monopolar prostheses (Acumed – Tornier)	Flexion- extension arc 107° pronosupination 159°	1.8	14,2	Meps 89	Patient Rated Wrist Evaluation score (PRWE) = 29
Laflamme	Modular monopolar head – uncemented loose fitting stem (Evolve, Wright) Modular monopolar head - porous press-fit stem (ExploR, Biomet)	Mean elbow flexion difference compared with the normal side: 4°; extension 14 pronation 8° supination 15°	1.11	7.7	Mepi 96.5	Grip strength compared with the normal side (Jamar dynamometer kg/force): 1.0 (-24-13)
Tarallo	Anatomic RHA, Acumed)	Flexion-extension arc 112° (95°-112° Pronosupination 134°	-	-	Meps: 24 excellent (77%) 3 good (10%) 4 fair (13%)	-
Laumonerie	Guepar radial head prosthesis (SBi/Stryker) Evolutive (Aston Medical) rHead Recon (SBi/Stryker) rHead STANDARD (SBi/Stryker)	*Acute treatment* Flexion 132° Extension -12.9° Supination 67.8° Pronation 76°	-	13.1	Meps 91.5	Force compared to contralateral side: flexion 87.2 extension 93.6
Nestorson	Radial head arthoplasty	Flexion-extension arc 130° (95°-155°) Forearm rotation 30° (10°-85°)	-	13	Meps: 85	-
Lopiz	Radial head arthoplasty	Flexion-extension arc 85.5°	-	24.8	Meps: 6 Excellent 3 good 2 fair 2 poor	-
Van Hoecke	Judet bipolar head prosthesis	Flexion 121.8° Extension 24,8° Pronation: 62.4° Supination 58.8°	-	23.1	Mepi 88,6	-
Heijink	Cemented bipolar radial head artrhoplasty (Tornier)	Flexion-extension arc 129° Forearm rotation 131°	Pain: 13 absent 7 mild 3 moderate 1 severe	-	Meps 13 Excellent 7 good 3 fair 1 poor	-
Kodde	Press fit bipolar radial head arthroplasty (Tornier)	Flexion-extension arc 126° Forearm rotation 138°	Pain: 17 absent 3 mild 7 moderate	-	Meps 17 Excellent 2 good 7 fair 1 poor	-

Table 2: Continued.

Author	Type of prosthesis	ROM	VAS	DASH	Meps/Mepi	Other clinical evaluations
Marsh	Modular smooth-stemmed radial head implant (Evolve, Wright)	Flexion-extension arc 126°+/- 21° Pronation 79° Supination 67°	-	14	Mepi 91+/- 13 points	Patient-Rated Elbow Evaluation (PREE): 14 Mean grip strength: 97% of that of the unaffected limb
Gauci	Modular Pyrocarbon (MoPyc) radial head prosthesis (Tornier)	Flexion 136° Extension -9° Pronation 71° Supination 76°	1		Meps 96	-
Allavena	Modular bipolar radial head prostehesis (De Puy)	Flexion-extension arc 100° Rotation arc 143°	-	21	Meps 79	Mean wrist strength 86% compared to contralateral side Mean elbow strength 67% compared to contralateral side
Flinkkila T.	Metallic radial head artrhoplasty	Flexion-extension arc 117° extension deficit 20°	-	23	Meps 86	-
Sarris IK	MoPyc pyrocarbon prosthesis (Bioprofile, Tornier)	Flexion-extension arc 130° Pronation 74° Supination 72°	-	-	Meps excellent 80% good 17% fair 3%	Mean grip strength 96% compared to contralateral side
Ricon F	Pyrocarbon radial head prosthesis (Bioprofile Lab.)	Flexion-extension arc 105° Pronation 85° Supination 80°	-	-	92	Mean grip strength reduced of 10% on the injured side
Muhm M	Uncemented modular metallic prosthesis (Evolve)	mid-term (15 patients) flexion 127.3 extension 15.7 pronation 74.3 supination 71.7	-	24,9	-	Broberg and Morrey scoring system 85,2
Celli A	Bipolar Judet radial head arthroplasty (Tornier)	Flexion-extension arc 117° Pronosupination 120°	1.38 at rest 2.25 at work	11.4	Meps 89.4	-
Dotzis A	Judet prosthesis (Tornier)	Flexion-extension arc 14°-140° pronation 87.5° supination 84°	-	23.9	Excellent 6 Good 4 Fair 1 Poor 1	Mean grip strength 90% compared to contralateral side
Ashwood N	Metallic monoblock radial head prosthesis (Wright)	Loss of flexion 10° Loss of pronation 12° Loss of supination 12°	17 (0-100 vas scale)	-	87	Mean grip strength reduced of 12% on the injured side
Moro JK	Metal Radial head arthroplasty	Flexion 140° Extension -8° Pronation 78° Supination 68°	-	17	Mepi 80 Excellent, good 17 Poor 3 Fair 5	SF-36 score: physical component 47; mental component 49 Mean PRWE score: 17 Mean WOS score: 60
Smets A	Floating radial head prosthesis		-	-	Mepi Excellent 7 Good 3 Fair 1 Poor 2	-

Table 3: Complications in radial head replacement.

Author	N. of patients	Complications
Carità E	28	1 osteolysis and stem mobilization 1 overstuffing (erosion of the capitellum) 2 periprosthetic calcification(asymptomatic) 6 resorption of the neck of the radius (asymptomatic) 3 removal of the implant (1 mobilization; 3 painful elbow)
Laflamme M	46	22 osteolysis >2mm (48%) 4 Overstuffing 1 degenerative changes (Broberg and Morrey grade III) 5 heterotopic ossification Brooker grade II, 1 grade IV
Tarallo L	31	8 heterotopic ossification (26%) 2 radiolucent lines (asymptomatic)
Nestorson J	18	4 surgical revision (3 aseptic loosening, 1 proximal radio-ulnar synostosis, 1 CPRS) 5 late osteoarthritis
Laumonerie P	54 acute injuries 23 delayed surgery	8 painful loosening 4 radiohumeral conflict 3 radiocapitellar instability 5 ulnar nerve palsy 4 CPRS 30 reoperations (38.9%) (19 implants removed; 11 retention of the implant)
Lopiz	14	3 elbow stiffness 2 oversizing 1 periprosthetic fracture 2 neuropathies (ulnar and radial) 4 elbow arthritis grade I, 9 cases grade II, 1 case grade III (Broberg and Morrey classification) 11 periarticular ossification (asymptomatic) 5 bone lucencies (asymptomatic)
Van Hoecke	21	14 capitellar erosion 10 ulnohumeral arthritis 1 radiolucent lines 1 overlenghtening 1 ulnar plus 1 prosthesis removed
Heijink	25	3 radiolucency lines (asymptomatic) 5 periarticular ossification (asymptomatic) 7 osteolysis of proximal radius (asymptomatic) 4 erosion of the capitellum 13 ulnohumeral arthritis 2 radial nerve neuropraxia 1 luxation (dissociation of the prostheses) – removed 2 subluxation
Kodde IF	27	3 revisions for chronic instability 5 revision for ulnar nerve dysfunction, elbow stiffness, symptomatic arthritis 23 radial neck osteolysis 13 ulnohumeral degeneration 7 erosion of the capitellum 5 heterotopic ossification (asymptomatic) 1 posterior subluxation 2 persistent pain for medial and lateral epicondylitis
Marsh JP	55	25 periprosthetic lucency 21 ulnohumeral arthritis 20 heterotopic ossification 12 capitellar osteopenia 1 abnormal radiocapitellar alignment
Gauci MO	65	48 (92%) cortical resorption around prosthesis neck 9 capitellum wear 1 radio-ulnar synostosis

Table 3: Continued.

Author	N. of patients	Complications
Allavena C	22	6 early posterior subluxation 5 sensory ulnar nerve dysfunction 2 CPRS type I 3 lateral elbow pain 1 symptomatic loosening 8 osteolysis 1 advanced osteoarthritis 6 capitellar erosions 4 anterior ossifications
Flinkkila T.	42	1 infection 1 radial nerve palsy 21 osteoarthritis (3 severe) 14 capitellar erosion 9 prostheses removed (6 painful, 2 loosed)
Sarris IK	32	2 stem-neck dissociation 1 stiffness 2 periprosthetic lucencies (asymptomatic) 7 heterotopic ossification (asymptomatic) 4 radiographic sign of stress shielding (asymptomatic)
Ricon F	28	2 posterior subluxation (overstuffing) 11 radial neck resorption 5 ossification in collateral ligament 1 mild periprosthetic ossification
Muhm M	Mid term 15	12 periprosthetic radiolucency 12 (70%) heterotopic ossification 12 (70%) osteoarthritis
Iftimie	22	24 degenerative changes
Celli A	16	2 heterotopic ossification 2 proximal radio-ulnar synostosis 2 capitellar erosion (overstuffing) 1 proximal bone resorption
Dotzis A	14	1 CPRS and stiffness 1 periprosthetic lucency 7 heterotopic ossification (asymptomatic)
Ashwood N	16	1 CPRS 3 ulnar neuropathies 2 superficial wound infections
Moro JK	25	17 bone radiolucency (asymptomatic) 1 CPRS 1 ulnar neuropathy 1 PIN palsy 1 elbow stiffness 1 wound infection
Smets A	13	3 wrist pain 1 implant removed for stiffness

fit radial head prosthesis due to a high rate of loosening. Difficulties on technique of implantation are described by Ashwood [30] for mono-block prosthesis.

Retrospective studies on radial head resection have a longer follow-up and clinical and radiological results are reported in Table 4 [33–42]. Clinical and radiological complications at long-term follow-up are reported (Table 5). Clinical results show good outcomes in Mayo Elbow Performance Scores (MEPS, from 79 to 100) and Disabilities for Arm Shoulder and Harm scores (DASH, from 4 to 15), a satisfactory recovery of elbow range of motion (average flexion-extension arc of motion: 120°) and low scores in VAS scale (from 0 to 4.6). However common complications of this surgical procedure involve ulnohumeral joint due to an higher load compression force that leads to degenerative changes and progressive worsening of cubitus valgus associated to ulnar nerve neuropathy and UCL elongation leading to chronic elbow instability [3, 4]. Moreover, proximal migration of radius is often assessed (80% of papers), complications that involve DRUJ impairment

Table 4: Mean clinical results for radial head resection.

Author	ROM	VAS	DASH	Meps/Mepi	Other clinical evaluations
Nestorson J	Flexion-extension arc 127,5° (105°-150°)	-	12	Meps: 100	-
Lopiz	Flexion-extension arc 105.2°	-	13.5	Meps 6 excellent 3 good 2 fair 0 poor	-
Solarino G.	flexion 124° extension -11° pronation 78° supination 82°	Pain Absent 14 Mild 8 Moderate 8	13	Meps 79	-
Yalcinkaya M	Flexion-extension arc 127° Pronation 83,2° Supination 84,6°	4,6	6,6	Meps 88,6	-
Iftimie	flexion 135° extension -5° pronation 83° supination 79°	0.48	4,89	-	Grip strength 88% compared to the contralateral side
Antuna SA	flexion 84° extension -9° pronation 84° supination 85°	9	6	95	Grip strength loss 16% compared to contralateral side
Herbertsson P.	*Primary RHA* flexion 140° extension -7° supination 77° pronation 85°	-	-	-	Steinberg system for clinical outcomes: 25 good; 26 fair; 10 poor 28 no symptoms, 27 occasional pain; 6 daily pain
Sanchez Sotelo J.	Flexion-extension 7.5-140 Pronation 85.5° Supination 83.5°	0	0.66 to 15.9	-	Grip strength loss 15% compared to contralateral side Broberg and Morrey performance index: excellent 5; good 5; poor 1
Ikeda M	flexion 132° extension -14° supination 82° pronation 80°	-	-	-	Grip strength loss 17% compared to contralateral side
Jansen RP	-	-	-	Mepi Excellent 17 Good 3 Fair 1 Poor 2	-

leading to wrist pain hand strength reduction and distal radio-ulnar arthritis. Preoperative or intraoperative setting of elbow stability and correction of ligaments injuries is mandatory to avoid early complications. Despite of complications, many authors approve the surgical technique due to good outcomes in mid to large term. Yalcinkaya [36] found no significant correlation between radiological degenerative modifications in elbow and outcomes of clinical scores in patients treated by radial head resection. Antuna [38] reports good clinical results in a large series of patients less than forty years old treated by radial head excision after a mean follow-up of 25 years. Herbertsson [39] reports worst outcomes in excision for Mason type IV fractures although delayed radial arthroplasty is suggested for pain relief and preservation of range of motion in case of failure of other treatments.

Finally, few papers compare radial head resection and radial head arthroplasty [34, 35] where authors recommend resection as primary option of treatment because of a lack of statistical clinical differences between the two surgical procedures, in case of isolated radial head fractures not associated to ligaments injuries. Nestorson [33] did not found better outcomes by using a press fit radial head prosthesis in Mason type IV fractures and he reports similar functional results after radial head resection despite more osteoarthritic changes. Lopiz [34] suggests resection as a good option of

Table 5: Complications in radial head resection.

Author	N. Of patients	Complications
Nestorson J	14	2 surgical revision (stiffness) 1 ulnar nerve dysfunction 1 radial nerve dysfunction 13 late osteoarthritis
Lopiz	11	Average radial shortening 2.3mm 1 elbow stiffness 1 valgus instability All patients: elbow arthritis grade I 2 heterotopic ossification (asymptomatic)
Solarino G.	30	Arthritic changes: 4 mild; 3 moderate 5 heterotopic ossification 5 ulnar minus (mean value 3.5) and DRUJ instability
Yalcinkaya M	14	8 degenerative changes in elbow 4 degenerative changes in wrist 3 heterotopic ossification 8 proximal migration of radius Mean ulnar variance: 1.7mm Mean carrying angle 11.2°
Iftimie	22	24 Degenerative changes (Broberg and Morrey 1 patient grade 3; 13 grade 2; 10 grade 1
Antuna SA	26	2 postero-lateral instability 2 valgus laxity 1 DRUJ instability Osteoarthritic changes (17 mild; 9 moderate) 8 heterotopic ossification (asymptomatic) Average radial shortening 3.1mm
Herbertsson P.	61	16 ulnar plus >2 mm Degenerative changes: 42 cysts; 40 irregular subchondral bone; 43 osteophytes
Sanchez Sotelo J.	10	4 heterotopic ossification 8 degenerative arthritis mean proximal radius migration: 1.6mm mean carrying angle decrease: 5.4°
Ikeda M	11	Mean ulnar variance +1.6mm Mean increase in carrying angle 8° Mild to severe degenerative arthritis in all patients
Jansen RP	18	ROM limitations 11 Degenerative changes 7 increase of cubitus valgus, 7 periarticular ossification, 7 osteoporosis of capitellum, 12 proximal radius migration (from 1 to 5 mm)

treatment when ORIF is not possible, reporting a higher rate of complications in the group of patient treated by radial head arthroplasty.

5. Conclusion

From our review of literature almost all the retrospective studies on radial head arthroplasty report convincing results in terms of elbow stability, range of motion, and pain. Nevertheless, papers on radial head resection report good clinical outcomes in isolated radial head resection with no associated ligament injuries. Few papers compare the two techniques with no substantial differences in terms of clinical outcomes at medium and long follow-up.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

[1] B. F. Morrey, K. N. An, and T. J. Stormont, "Force transmission through the radial head.," *The Journal of Bone & Joint Surgery*, vol. 70, no. 2, pp. 250–256, 1988.

[2] S. L. Jensen, B. S. Olsen, S. Tyrdal, J. O. Søjbjerg, and O. Sneppen, "Elbow joint laxity after experimental radial head excision and lateral collateral ligament rupture: Efficacy of prosthetic replacement and ligament repair," *Journal of Shoulder and Elbow Surgery*, vol. 14, no. 1, pp. 78–84, 2005.

[3] R. P. Van Riet, "Associated injuries complicating radial head fractures: a demographic study," *Clinical Orthopaedics and Related Research*, 2005.

[4] N. F. Hilgersom, D. Eygendaal, and M. P. van den Bekerom, "Is radial head resection the first choice treatment of comminuted radial head fractures without associated instability?" *Injury*, vol. 48, no. 2, pp. 560–562, 2017.

[5] J. Itamura, N. Roidis, R. Mirzayan, S. Vaishnav, T. Learch, and C. Shean, "Radial head fractures: MRI evaluation of associated injuries," *Journal of Shoulder and Elbow Surgery*, vol. 14, no. 4, pp. 421–424, 2005.

[6] J. C. McGinley, G. Gold, E. Cheung, and J. Yao, "MRI Detection of Forearm Soft Tissue Injuries with Radial Head Fractures," *HAND*, vol. 9, no. 1, pp. 87–92, 2014.

[7] B. F. Morrey, S. Tanaka, and K. An, "Valgus Stability of the Elbow," *Clinical Orthopaedics and Related Research*, no. 265, pp. 187–195, 1991.

[8] N. Bonnevialle, "Radial head replacement in adults with recent fractures," *Orthopaedics & traumatology, surgery & research : OTSR*, vol. 102, no. 1, pp. S69–S79, 2016.

[9] Z. D. Mikic and S. M. Vukadinovic, "Late results in fractures of the radial head treated by excision," *Clinical Orthopaedics and Related Research*, vol. 181, pp. 220–228, 1983.

[10] G. Giannicola, F. M. Sacchetti, G. Antonietti, A. Piccioli, R. Postacchini, and G. Cinotti, "Radial head, radiocapitellar and total elbow arthroplasties: A review of recent literature," *Injury*, vol. 45, no. 2, pp. 428–436, 2014.

[11] A. L. Lindenhovious, "Open reduction and internal fixation compared with excision for unstable displaced fractures of the radial head," *The Journal of Hand Surgery*, 2007.

[12] M. N. Kaur, "Functional outcomes post-radial head artrhoplasty: a systematic review of literature," *Shoulder and Elbow*, 2014.

[13] E. Carità, A. Donadelli, L. Cugola, and P. Perazzini, "Radial head prosthesis: results overview," *Musculoskeletal Surgery*, vol. 101, pp. 197–204, 2017.

[14] M. Laflamme, P.-P. Grenier-Gauthier, A. Leclerc, S. Antoniades, and A.-M. Bédard, "Retrospective cohort study on radial head replacements comparing results between smooth and porous stem designs," *Journal of Shoulder and Elbow Surgery*, vol. 26, no. 8, pp. 1316–1324, 2017.

[15] L. Tarallo, R. Mugnai, M. Rocchi, F. Capra, and F. Catani, "Mason type III radial head fractures treated by anatomic radial head arthroplasty: Is this a safe treatment option?" *Orthopaedics & Traumatology: Surgery & Research*, vol. 103, no. 2, pp. 183–189, 2017.

[16] Laumonerie, "Mid term oucome of 77 modular radial head prostheses," *Bone Joint Journal*, 2017.

[17] V. Hoecke, "Long term results after bipolar radial head arthroplasty," *Acta Orthopaedica Belgica*, 2016.

[18] A. Heijink, I. F. Kodde, P. G. H. Mulder, C. N. Van Dijk, and D. Eygendaal, "Cemented bipolar radial head arthroplasty: midterm follow-up results," *Journal of Shoulder and Elbow Surgery*, vol. 25, no. 11, pp. 1829–1838, 2016.

[19] Kodde, "Press-fit bipolar radial head arthroplasty, mide term results," *Journal of Shoulder and Elbow Surgery*, 2016.

[20] M.-O. Gauci, M. Winter, C. Dumontier, N. Bronsard, and Y. Allieu, "Clinical and radiologic outcomes of pyrocarbon radial head prosthesis: Midterm results," *Journal of Shoulder and Elbow Surgery*, vol. 25, no. 1, pp. 98–104, 2016.

[21] J. P. Marsh, R. Grewal, K. J. Faber, D. S. Drosdowech, G. S. Athwal, and G. J. King, "Radial Head Fractures Treated with Modular Metallic Radial Head Replacement," *The Journal of Bone & Joint Surgery*, vol. 98, no. 7, pp. 527–535, 2016.

[22] C. Allavena, S. Delclaux, N. Bonnevialle, M. Rongières, P. Bonnevialle, and P. Mansat, "Outcomes of bipolar radial head prosthesis to treat complex radial head fractures in 22 patients with a mean follow-up of 50 months," *Orthopaedics & Traumatology: Surgery & Research*, vol. 100, no. 7, pp. 703–709, 2014.

[23] T. Flinkkilä, T. Kaisto, K. Sirniö, P. Hyvönen, and J. Leppilahti, "Short- to mid-term results of metallic press-fit radial head arthroplasty in unstable injuries of the elbow," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 94, no. 6, pp. 805–810, 2012.

[24] I. K. Sarris, M. J. Kyrkos, N. N. Galanis, K. A. Papavasiliou, F. E. Sayegh, and G. A. Kapetanos, "Radial head replacement with the MoPyC pyrocarbon prosthesis," *Journal of Shoulder and Elbow Surgery*, vol. 21, no. 9, pp. 1222–1228, 2012.

[25] F. J. Ricón, P. Sánchez, F. Lajara, A. Galán, J. A. Lozano, and E. Guerado, "Result of a pyrocarbon prosthesis after comminuted and unreconstructable radial head fractures," *Journal of Shoulder and Elbow Surgery*, vol. 21, no. 1, pp. 82–91, 2012.

[26] M. Muhm, R. de Castro, and H. Winkler, "Radial head arthroplasty with an uncemented modular metallic radial head prosthesis: Short- and mid-term results," *European Journal of Trauma and Emergency Surgery*, vol. 37, no. 1, pp. 85–95, 2011.

[27] A. Celli, F. Modena, and L. Celli, "The acute bipolar radial head replacement for isolated unreconstructable fractures of the radial head," *Musculoskeletal Surgery*, vol. 94, pp. S3–S9, 2010.

[28] A. Dotzis, G. Cochu, C. Mabit, J. L. Charissoux, and J. P. Arnaud, "Comminuted fractures of the radial head treated by the Judet floating radial head prosthesis," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 88, no. 6, pp. 760–764, 2006.

[29] J.-M. Brinkman, F. T. G. Rahusen, M. J. De Vos, and D. Eygendaal, "Treatment of sequelae of radial head fractures with a bipolar radial head prosthesis: Good outcome after 1-4 years follow-up in 11 patients," *Acta Orthopaedica*, vol. 76, no. 6, pp. 867–872, 2005.

[30] N. Ashwood, G. I. Bain, and R. Unni, "Management of Mason Type-III Radial Head Fractures with a Titanium Prosthesis, Ligament Repair, and Early Mobilization," *The Journal of Bone & Joint Surgery*, vol. 86, no. 2, pp. 274–280, 2004.

[31] J. K. Moro, J. Werier, J. C. MacDermid, S. D. Patterson, and G. J. W. King, "Arthroplasty with a metal radial head for unreconstructible fractures of the radial head," *The Journal of Bone & Joint Surgery*, vol. 83, no. 8, pp. 1201–1211, 2001.

[32] S. Smets, "The floating radial head prosthesis for comminuted radial head fractures: a multicentric study," *Acta Orthopaedica Belgica*, 2000.

[33] J. Nestorson, P.-O. Josefsson, and L. Adolfsson, "A radial head prosthesis appears to be unnecessary in Mason-IV fracture dislocation," *Acta Orthopaedica*, vol. 88, no. 3, pp. 315–319, 2017.

[34] Y. Lópiz, A. González, C. García-Fernández, J. García-Coiradas, and F. Marco, "Comminuted fractures of the radial head: resection or prosthesis?" *Injury*, vol. 47, pp. S29–S34, 2016.

[35] G. Solarino, G. Vicenti, A. Abate, M. Carrozzo, G. Picca, and B. Moretti, "Mason type II and III radial head fracture in patients

older than 65: is there still a place for radial head resection?" *Aging Clinical and Experimental Research*, vol. 27, pp. 77–83, 2015.

[36] M. Yalcinkaya, A. E. Bagatur, S. Erdogan, and G. Zorer, "Resection arthroplasty for mason type III radial head fractures yield good clinical but poor radiological results in the long term," *Orthopedics*, vol. 36, no. 11, pp. e1358–e1364, 2013.

[37] P. P. Iftimie, J. Calmet Garcia, I. de Loyola Garcia Forcada, J. E. Gonzalez Pedrouzo, and J. Giné Gomà, "Resection arthroplasty for radial head fractures: Long-term follow-up," *Journal of Shoulder and Elbow Surgery*, vol. 20, no. 1, pp. 45–50, 2011.

[38] S. A. Antuña, J. M. Sánchez-Márquez, and R. Barco, "Long-term results of radial head resection following isolated radial head fractures in patients younger than forty years old," *The Journal of Bone & Joint Surgery*, vol. 92, no. 3, pp. 558–566, 2010.

[39] P. Herbertsson, P. O. Josefsson, R. Hasserius, J. Besjakov, F. Nyqvist, and M. K. Karlsson, "Fractures of the radial head and neck treated with radial head excision," *The Journal of Bone & Joint Surgery*, vol. 86, no. 9, pp. 1925–1930, 2004.

[40] J. Sanchez-Sotelo, O. Romanillos, and E. G. Garay, "Results of acute excision of the radial head in elbow radial head fracture-dislocations," *Journal of Orthopaedic Trauma*, vol. 14, no. 5, pp. 354–358, 2000.

[41] M. Ikeda and Y. Oka, "Function after early radial head resection for fracture: A retrospective evaluation of 15 patients followed for 3-18 years," *Acta Orthopaedica*, vol. 71, no. 2, pp. 191–194, 2000.

[42] R. P. Janssen and J. Vegter, "Resection of the radial head after Mason type-III fractures of the elbow," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 80-B, no. 2, pp. 231–233, 1998.

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Research Article

Failure Predictor Factors of Conservative Treatment in Pediatric Forearm Fractures

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The aim of this study is to evaluate the predictive efficacy of the radiographic parameters and the relationship between the radiographic results and the clinical data. We carried out a retrospective study analyzing the data of 225 pediatric patients with forearm fractures treated conservatively. Two orthopaedists examined 4 different radiographic parameters. They compared CI and radial translation parameters at T0, in terms of indication of type of treatment and predictive efficacy. Afterwards, the two orthopaedists analyzed X-rays performed at T1, evaluating radiographic results according to radial shortening and angle parameters. From the analysis of the CI measured by Observer 1, 135 patients out of 225 had retrospective indication to conservative treatment; the frequency of failure was 18/135 (13.3%). Observer 2 indicated conservative treatment in 144 patients out of 225 and the proportion of failure was 21/144 (14.6%). As regards the radial translation, Observer 1 reported a frequency of failure of 78/225 (34.7%) and Observer 2 reported 75/222 (33.8%). Furthermore the authors detected a deficit of pronosupination for the patients considered to have failure according to radiographic results. The authors defined the greater reliability of CI with respect to the radial translation parameter and the direct relationship between radiographic failure and clinical-functional data.

1. Introduction

Forearm fractures are among the most common lesions in pediatric patients [1, 2]. 20-30% of the cases involve distal metaphysis [3, 4].

81% of forearm fractures happen to children over the age of 5, with the peak of incidence between 10 and 12 years of age in females and 12 and 14 in males. The mechanism of trauma is directly related to falling on the palm of the hands [5].

Conservative treatment consists in carrying out a reduction on manoeuvre and long arm cast [5, 6]; in 85% of cases this achieves a good clinical-functional result [7].

Osteosynthesis is indicated in cases of open fractures and physis fractures or when conservative treatment fails [8].

As regards conservative treatment the most common complication is loss of the reduction [9, 10]. For this reason recent literature reports an increase in the use of k-wires as a first treatment [11, 12].

This renders the study of radiographic parameters even more important in understanding the predictive efficacy of conservative treatment [13]. The therapeutic strategy adopted depends principally on radiographic parameters even though there is no clear scientific evidence to support this given that in literature the vast majority of works analyze either radiographic indices linked to the type of fracture or the parameters linked to the manoeuvre reduction but not both together.

The aim of this study is to evaluate the predictive efficacy of the radiographic parameters, the interobserver

reproducibility, and the relationship between the radiographic results and the clinical data.

2. Material and Methods

We carried out a cohort retrospective study analyzing the clinical-radiographic records of 225 pediatric patients with diaphyseal forearm fractures according to Orthopaedic Trauma Association Classification (22 D/2.1, D/4.1, and D/5.1). The subjects, aged between 2 and 15, had been treated conservatively in our hospital in the period 2010-2014 with an average follow-up of 18 months.

The conservative treatment consisted in the reduction manoeuvre of the fracture and cast moulding. The casts were applied above the elbow. The elbow was immobilized at 90° degrees. The casts were composed of Cellona Plaster of Paris Bandages.

The reduction manoeuvre and the cast application were performed by two trauma surgeons (B.M. and V.P.) with at least 10 years of experience in the pediatric field.

Inclusion criteria for the study were

(i) monoosseous forearm fracture,

(ii) biosseous forearm fracture,

(iii) age range of 2-15.

Exclusion criteria were

(i) open or pathological forearm fracture,

(ii) physeal fracture,

(iii) patients who did not complete follow-up and those for whom there was no complete radiographic documentation.

The study population was divided into 3 groups: Group 1 < 5 years, Group 2 with range of 5-10 years, and Group 3 > 10 years. The data collected regarded sex, age, side of fractures (left/right), and type.

The radiographic parameters examined were

(i) Cast Index (CI), described for the first time by Chess et al. in 1994 [14],

(ii) radial translation, which evaluates the translation of distal radius segment with respect to proximal segment [15],

(iii) shortening of radius with respect to ulna [16],

(iv) angle between bone segments in lateral view [17].

The CI evaluates the efficacy of the reduction manoeuvre and the geometry of the cast. It calculates the ratio between the distance of internal margins of the cast in lateral view (x) and anteroposterior view (y) at the point of fracture. In the literature a high risk of loss of reduction when CI is ≥0.84 is reported [14].

The radial translation allows the distinguishing of 4 different groups: the first without any translation; the second with translation of distal radius segment <50%; the third > 50%;the fourth when there is no contact between the segments. Mani found that in 60% of patients in Groups III and IV there was a secondary failure of reduction manoeuvre [15].

The shortening of radius with respect to ulna is responsible for pronosupination deficits if the value reaches a pathological range > 5mm [16].

The angle subtended between bone segments in lateral view allows us to define a pronosupination limit if the value is >15° in patients aged under 10 years and >10° in children aged over 10 years [17, 18].

The measurements of radiographic parameters, described previously, were calculated on digital X-rays which were performed at a distance of 100cm in 2 projections (anteroposterior and lateral views). ROMAN v 1.7 software was used to calculate 4 parameters after the calibration of the system in order to convert pixel into mm.

Two orthopaedists with an experience greater than 10 years performed measurements blindly and independently.

All the patients were followed up at 1 year (T_1) after the trauma. Follow-up examinations included measurements of forearm range of motion for both sides using a goniometer. The position of the arm was adducted and elbow flexed at 90°.

The two orthopaedists indicated retrospectively the type of treatment (surgical or conservative) according to CI and radial translation values measured at T_0 by emergency X-ray. As defined in literature, in the presence of the values of CI and radial translation, respectively, ≥0.84 and >50% of bone diameter, the two observers suggested surgical treatment.

Afterwards, the two orthopaedists analyzed X-rays performed at T_1, evaluating radiographic results according to radial shortening and angle parameters. As reported in literature, an angle value greater than 15° in children under 10 years and greater than 10° in patients over 10 years and a radial shortening value greater than 5mm are indicative of poor result and pronosupination deficit. Furthermore, the two surgeons compared poor radiographic data to pronosupination range of motion.

For each patient enrolled, a data collection form structured in different sections was compiled:

(i) Anagraphic variables (name, surname, age), type, and side of fracture

(ii) variables measured by two observers: CI and radial translation at T_0 and radius shortening and inclination of segments in lateral view at T_0 and T_1

(iii) Treatment performed.

The compiled forms were put into a database using the fileMaker Pro software and analyzed with STATA software.

The qualitative variables (sex, age groups, side, indication of surgical treatment based on CI and radial translation, and patients with poor outcome based on inclination and radial shortening parameters) were described in percentages; the chi-square test was used to evaluate the differences between the percentages.

The quantitative variables (age, CI, radial shortening, and inclination) were expressed in mean values with standard deviation. The Student t-test for paired samples was used to evaluate the differences between the mean values measured by the two observers.

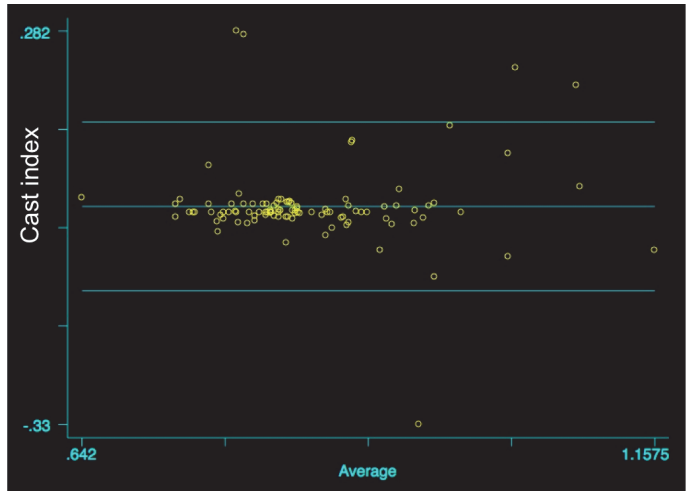

Figure 1: Comparison of CI values between the two measurements, Bland Altman graph (r=0.027; p=0.79).

To evaluate the level of agreement between the two measuring processes (Observers 1 and 2) in relation to the indication of surgical treatment according to CI and radial translation at T_0 and indication for failure based on inclination and radial shortening, the K-test agreement was used.

The Bland Altman graph, calculating the values of r and Z, was developed to quantify any eventual differences between the measurements of the two observers of CI at T_0 and radial shortening and inclination at T_0 and T_1.

For each test used, the p value <0.05 was considered significant.

3. Results

In the study 225 patients were enrolled; of these 183 (81.3%) were male and 42 (18.7%) female. The average age was 8.4±3.5 years (range 2-15); in particular 36 (16%) were under 5, 111 (49.3%) were between 5 and 10, and 78 (34.7%) were over 10.

The affected side was right in 93 (41.3%) and left in 132 (58.7%). Among the 225 recruitment patients, 84 (37.3%) presented monoosseous radius fracture, 9 (4%) monoosseous ulna fracture, and 132 (58,7%) biosseous fracture.

The mean value of CI, measured by Observer 1, was 0.85±0.09 and 0.84±0.9, by Observer 2 (t=1.41; p=0.08). The Bland Altman test, used to compare the measurements, did not give evidence of any statistically significant differences (r=0.027; p=0.79; Figure 1). In particular, Observer 1 indicated retrospectively surgical treatment according to CI in 90 patients (40%), whilst Observer 2 indicated it in 81 (36%); between the two measurements a high agreement level (agreement 86.4%; expected agreement 49.9%; Kappa=0.72; z=7.44; p<0.0001) emerged.

At T_0, the mean value of radial shortening, measured by Observer 1, was 2.6±2.1 (t=0.56; p=0.29) and 2.6±2.2, by Observer 2. Also in this case, the Bland Altman analysis did not give evidence of significant differences between the two measurements (r=-0.125; p=0.209; Figure 2).

At T_1, the mean values of radial shortening measured by the two observers were, respectively, 2.8±1.4 and 2.8±1.5 (t=0.16; p=0.43). There were not any statistically significant differences (r=-0.19; p=0.06; Figure 3).

As regards pathological ranges compatible with functional or anatomical deficits, these were found in 18 patients (8%) according to Observer 1 and 27 (12%) according to Observer 2. The agreement level between the two evaluations was high (agreement 97.1%; expected agreement 86.4%; K=0.78; z=8.16; p<0.0001).

At T_0, the mean angular value, measured by Observer 1, was 18.6±10.0 whilst for Observer 2 it was 18.9±10.0 (t=0.16; p=0.44). Also, in this case, Bland Altman analysis did not show any significant differences between the two measurements (r=-0.004; p=0.964; Figure 4).

At T_1 the angular mean values, measured by the two observers, were 7.7±5.8 for Observer 1 and 7.8±5.8 for Observer 2 (t=1.18; p=0.12). Also, in this case, the authors did not reveal any statistically significant differences (r=0.041; p=0.678; Figure 5).

The percentage of failures according to angular value at T_1, was 26.7% (n=60) for Observer 1 and 22.7% (n=51) for Observer 2; the agreement level in this evaluation was very high (agreement: 99%; expected agreement: 69.3%; K=0.97; z=9.83; p<0.0001).

Analyzing the agreement between CI and radial translation with reference to the surgical indication, there was statistical significance for the measurements performed by Observer 2 (agreement 59.2%; expected agreement: 54.7%; k=0.01; p=0.025), whilst no statistically significant differences in the comparison between the measurements calculated by Observer 1 emerged (agreement 50.5%; expected agreement 49.5%; k=0.02; p=0.16).

Observer 1 indicated retrospectively surgical treatment in 90 (40%) of the 225 enrolled patients according to CI values. Observer 2 indicated retrospectively surgical treatment in 81 (36%) of the 225 enrolled patients.

As regards radial translation parameter, Observer 1 did not indicate retrospectively the surgical treatment, whilst Observer 2 indicated retrospectively the surgical treatment only in 3 cases out of 225.

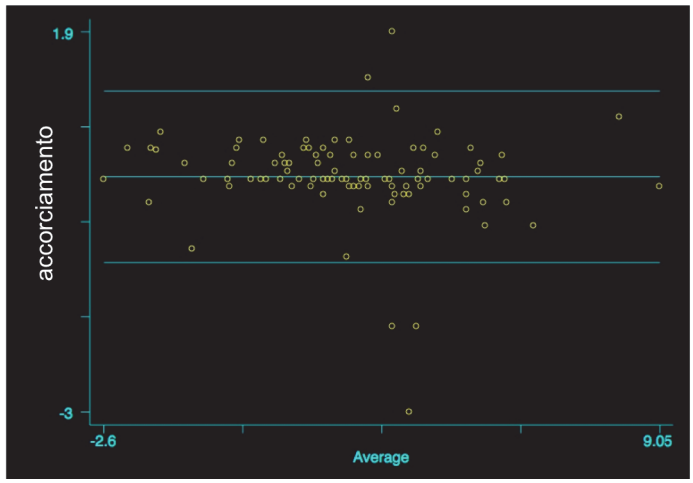

Figure 2: Comparison of radial shortening between the two measurements at T_0, Bland Altman graph (r=-0.125; p=0.209).

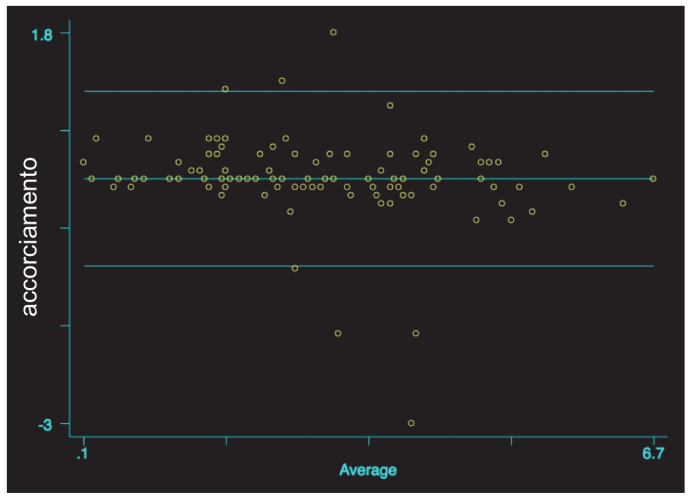

Figure 3: Comparison of radial shortening values measured by the two observers at T_1, Bland Altman graph (r=-0.19; p=0.06).

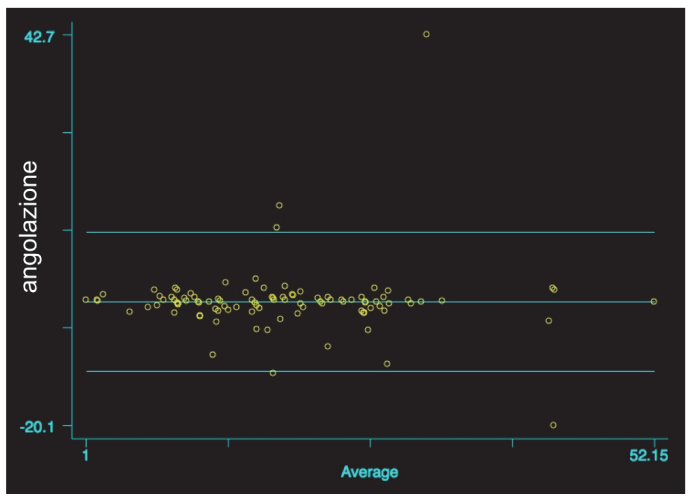

Figure 4: Comparison of angular values between the two measurements at T_0, Bland Altman graph (r=-0.0004; p=0.964).

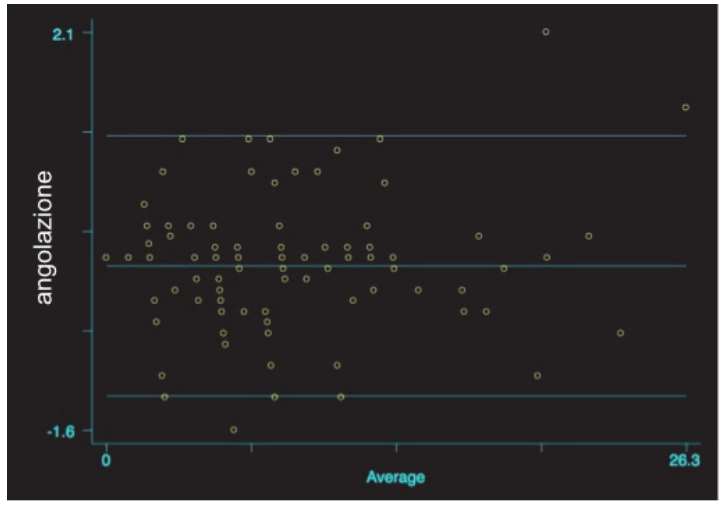

Figure 5: Comparison of angular values between the two measurements at T_1, Bland Altman graph (r=0.041; p=0.678).

Table 1: The proportion of patients according to age groups and poor result who received a retrospective indication to surgical treatment in relation to CI.

Age Groups	Observer 1	Observer 2
<5 years	9/21 (42.8%)	9/21 (42.8%)
5-10 years	15/33 (45.4%)	15/27 (55.5%)
>10 years	36/36 (100%)	33/33(100%)

In the study group the two observers reported a poor radiographic result in 78 patients (34.7%) according to shortening and angulation measured at T_1.

Analyzing the CI measured by Observer 1, 90 patients out of 225 had retrospective indication to surgical treatment, whilst the remaining 135 received a conservative treatment indication. The frequency of failure was 18/135 (13.3%) for patients with a conservative treatment indication and 69/90 (66.6%) for patients with surgical treatment indication (chi-square=22.6; p<0.0001). The same analysis was carried out by Observer 2 and he indicated retrospectively the surgical treatment in 81/225. The proportion of failure was 21/144(14.6%) for the patients with retrospective conservative treatment indication and 57/81 (70.4%) for the patients with surgical treatment indication (chi-square=23.7 p<0.0001).

Furthermore, analyzing age groups, the proportion of patients with a retrospective surgical treatment indication characterized by poor results is described in Table 1.

As regards radial translation parameter, Table 2 describes the distribution for class assigned by the two observers. Observer 1 did not report any retrospective surgical indications in patients enrolled. The frequency of failure was 78/225 (34,7%) for patients with conservative treatment indication, whilst Observer 2 reported only 3/225 patients with retrospective surgical indication and those who had failure. The proportion of failure was 75/222 (33,8%) for the patients with retrospective indication to conservative treatment.

Moreover, as regards Observer 1, 78 patients with a poor result received a retrospective indication to conservative treatment according to radial translation; for the second observer the proportion was 75/222.

The results of measurements revealed at T_1 of both affected and unaffected arm are described in Table 3. The mean value of the difference of pronation range between affected and unaffected arm in the patients with poor result was 4.3°±1.4° (range 0-9); in particular 48 out of the 78 patients who had failure (61.5%) presented a difference of pronation range >5°.

In these patients the mean value of the difference of supination range was 4.3°±1.3° (range: 3°-10°); in detail 42 out of the 78 patients who had failure (53.9%) presented a difference of supination range >5°.

4. Discussion

The authors evaluated the radiographic data of 225 patients, affected by forearm fractures, who had been treated conservatively; first they defined retrospectively the treatment indication according to CI and radial translation parameters. Then they revealed the poor results according to shortening and angulation parameters measured at T_1 in the patients with retrospectively conservative indication. In this second step the poor radiographic results were linked to clinical-functional data.

To define the efficacy of radiographic parameters in terms of predictive conservative treatment failure, the measurements performed by the two observers with an experience greater than 10 years were analyzed statistically at T_0 and T_1.

As regards the first parameter (CI), the comparison of the mean values of measurements performed by the two observers did not evidence any statistically significant differences (r=0.027; p=0.79). Indeed, there was a high agreement level (agreement 86.4%).

As regards shortening, analyzing the values observed at T_0 and T_1, no statistically significant differences between

Table 2: Distribution of patients analyzed for radial translation class measured by the two observers and agreement level.

Radial translation class	Observer 1	Observer 2	Agreement	Expected agreement	Z	P
1	177 (78.7%)	171 (76%)	94.2%	56.4%	8.8	<0.001
2	48 (21.3%)	51 (22.7%)	93.2%	59.1%	8.5	<0.001
3	0	0	97.1%	95.2%	5.0	<0.001
4	0	3 (1.3%)	98.1%	98.1%	NA	NS

the two measurements (T_0: r=-0.125; p=0.209) (T_1: r=-0.19; p=0.06) emerged. The reliability of the measurements performed by the two observers was very high as demonstrated by agreement level of 95.1%.

In relation to the angulation, the Bland Altman analysis did not evidence any statistically significant differences between T_0 and T_1 (T_0: r=-0.004; p=0.964) (T_1: r=0.041; p=0.678). Even though the evaluation of Figure 5 and the dispersion of values may appear contradictory, indeed, if we analyze in depth the dispersion grade, we may note that the range of values is very small, being in the order of up to 0.5° with a very high agreement level (agreement: 99%). The percentage of patients with pathological angular values was 26.7% for Observer 1 and 22.7% for Observer 2; we related the high agreement between the measurements to the accuracy detection of angular value with respect to the linear values which are influenced by variables of X-ray execution. In literature numerous works reported the measurements errors due to the variability of distance between the patient and X-ray tube, i.e., magnification concept and right radiographic position [19].

As regards radial translation a high agreement level emerged as demonstrated in Table 2. This was linked to the easiness of identification so to assign the class. Indeed, over 76% of patients presented a translation of distal segment and so were assigned to class 1.

In the last few years, though surgical treatment of forearm fracture, in particular biosseous, has become more frequent [12, 20, 21], conservative treatment is still by far the most common approach [21].

According to recent data of bibliography, also in our experience we verified a predominance of conservative treatment with respect to surgery.

For this reason, the predictive factors failure of conservative treatment plays the main role in recent literature taking into consideration that the causes of loss of reduction in forearm pediatric fractures are related to bone injury pattern [6], to the surgeon and to the patient [9].

Among the predictive failure factors linked to the pattern of injury, we reported the angulation and radial translation [15, 17], whilst among those related to surgeon and/or patient we highlighted the role of CI, padding index and Canterbury index [9].

Our study is the first in literature that compares two different parameters (CI and radial translation) in order to report the superiority in terms of reliability of each one or both of them in predicting failure.

As pointed out by the authors, the failure risk, in terms of angulation and shortening after reduction manoeuvre, is very low (about 7%) [22, 23].

The angulation parameter value changes according to the age [24, 25]. The value greater than 15° in the child aged <10 and 10° for the child aged >10 may affect aesthetic and/or pronosupination defects.

Furthermore, a radial shortening greater than 5 mm with respect to the ulna is not tolerated and causes pronosupination defects [16].

In the observation group, the authors revealed a percentage of failure equal to 34.7% according to the parameters (angulation and radial shortening described previously).

As defined by results, the authors observed a high agreement level between CI and radial translation for the measurements performed by both observers.

The analysis of CI, measured by Observer 1, showed that among the 135 patients out of 225 with a conservative retrospective indication (CI<0.84), 18 subjects presented a failure of reduction manoeuvre (13.3%). In the remaining 90 patients a value that indicated high risk for conservative treatment failure emerged (CI >0.84); in fact, 60 out of 90 patients had failure (66.6%) (chi-square = 22.6; p<0.0001).

The same analysis was carried out by Observer 2 who reported that 144 out of 225 patients had CI <0.84, and 21 of these had failure (14.6%). Similarly 57 out of 81 with CI that indicated the need for surgery (70.4%) had failure (chi-square = 23.7; p<0.0001).

As regards radial translation parameter, a 33.8% failure was observed in subjects whose retrospective indication was conservative treatment. This parameter therefore proved to be statistically less reliable than the CI. Indeed CI, the radiological parameter that regards both the surgeon and the patient, reflects the skill in applying the cast.

As reported in literature the respect of the principle of three-point system appears fundamental [14]. Another factor responsible for incorrect application of the cast is dependent on the age of the patients since in children >10 the increase of muscle mass means greater difficulty in modelling the cast [26]. In our experience, the analyses of different age groups for the patients with CI >0.84 and poor results showed failure increased with age. In the measurements performed by both observers in children >10 years, the failure rate was 100%. In fact, with an increase in age, we observed an increase of retrospective indication for surgery according to CI due to an increase in muscle mass and so also to the radiographic parameters.

The second aim of this study was to link the radiographic failure to clinical data. As described in Table 3, the authors verified a close link between the radiographic and functional results. As regards pronation deficit, a >5° mean value deficit of the pronation range with respect to unaffected arm was observed in 61.5% of the patients considered to have failure.

Table 3: Description of ROM values of both the affected and unaffected arm measured at T_1.

	Range of Motion
AFFECTED ARM PRONATION	75.45° (66°-85°)
UNAFFECTED ARM PRONATION	79.90° (72°-88°)
AFFECTED ARM SUPINATION	75.44° (66°-85°)
UNAFFECTED ARM SUPINATION	79.89° (71°-88°)

As regards supination a >5° mean value deficit of the supination range with respect to unaffected arm was observed in 53.9% of the patients considered to have failure. In literature, the minimal value to define a pronosupination deficit must be ≥5° considering possible errors related to precision of the instruments and objectivity of the surgeon [27]. The authors demonstrated a functional deficit of pronosupination more than 50% of the patients undergoing conservative treatment. Based on the results obtained, we observed the superiority, in terms of reliability, of the CI over radial translation; this could be linked to the greater accuracy of CI which measures two planes of both lateral and anteroposterior view.

Radial translation, however, measured only in anteroposterior view, is probably less accurate notwithstanding the four classes. Regarding the latter, the division into two classes (classes II and III) may not be sufficient.

Moreover, according to the data of our study, in the evaluation of conservative treatment option in cases of discordance between the two parameters, we suggest relying on the CI.

At the same time, as defined in the literature, given that the causes of loss of reduction may be linked to different variables, it is better not to analyze just one radiographic parameter but to evaluate also the fractures parameters [3, 28].

The weak point of our study is the lack of analysis of other accurate radiographic parameters such as three-point index and gap index. In a work in progress, the authors will study the other radiographic parameters comparing the results and revealing the predictive efficacy of the respective parameters.

5. Conclusions

The achievement of our initial objectives allowed us to define the greater reliability of CI with respect to the radial translation parameter and the direct relationship between radiographic failure and clinical-functional data. In the evaluation of reduction manoeuvre failure and conservative treatment of forearm pediatric fracture, in cases where there is a discordance, the CI is the much more reliable parameter. Moreover, we should not rely on just one predictive factor but should take into account multifactor analysis. It is opportune, therefore, to consider the characteristics of the fracture, the morphology of the patient, and the surgeon.

Data Availability

Readers are encouraged to contact the authors for details about the study population.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

[1] E. C. Rodríguez-Merchán, "Pediatric fractures of the forearm," *Clinical Orthopaedics and Related Research*, no. 432, pp. 65–72, 2005.

[2] D. S. Bae, "Pediatric Distal Radius and Forearm Fractures," *Journal of Hand Surgery*, vol. 33, no. 10, pp. 1911–1923, 2008.

[3] J. Pretell Mazzini and J. Rodriguez Martin, "Paediatric forearm and distal radius fractures: Risk factors and re-displacement-role of casting indices," *International Orthopaedics*, vol. 34, no. 3, pp. 407–412, 2010.

[4] B. A. Boyer, B. Overton, W. Schrader, P. Riley, and P. Fleissner, "Position of immobilization for pediatric forearm fractures," *Journal of Pediatric Orthopaedics*, vol. 22, no. 2, pp. 185–187, 2002.

[5] L. M. Hove and C. Brudvik, "Displaced paediatric fractures of the distal radius," *Archives of Orthopaedic and Trauma Surgery*, vol. 128, no. 1, pp. 55–60, 2008.

[6] M. T. Proctor, D. J. Moore, and J. M. Paterson, "Redisplacement after manipulation of distal radial fractures in children," *Journal of Bone & Joint Surgery*, vol. 75, no. 3, pp. 453-454, 1993.

[7] C. Creasman, D. J. Zaleske, and M. Ehrlich, "Analyzing forearm fractures in children," *Clinical Orthopaedics and Related Research*, vol. 188, pp. 40–53, 1984.

[8] R. Ortega, R. T. Loder, and D. S. Louis, "Open reduction and internal fixation of forearm fractures in children," *Journal of Pediatric Orthopaedics*, vol. 16, no. 5, pp. 651–654, 1996.

[9] M. Bhatia and P. H. Housden, "Redisplacement of paediatric forearm fractures: Role of plaster moulding and padding," *Injury*, vol. 37, no. 3, pp. 259–268, 2006.

[10] C. Bochang, Y. Jie, W. Zhigang, D. Wiegl, E. Bar-On, and K. Katz, "Immobilisation of forearm fractures in children. Extended versus flexed elbow," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 87, no. 7, pp. 994–996, 2005.

[11] K. B. Alemdaroglu, S. Iltar, O. Cimen et al., "Risk factors in redisplacement of distal radial fractures in children," *Journal of Bone & Joint Surgery*, vol. 90, no. 6, pp. 1224–1230, 2008.

[12] J. M. Flynn, K. J. Jones, M. R. Garner, and J. Goebel, "Eleven years experience in the operative management of pediatric forearm fractures," *Journal of Pediatric Orthopaedics*, vol. 30, no. 4, pp. 313–319, 2010.

[13] S. Iltar, K. B. Alemdaroglu, F. Say et al., "The value of the three-point index in predicting redisplacement of diaphyseal fractures of the forearm in children," *Bone & Joint Journal*, vol. 95, no. 4, pp. 563–567, 2013.

[14] D. G. Chess, J. C. Hyndman, J. L. Leahey, D. C. Brown, and A. M. Sinclair, "Short Arm Plaster Cast for Distal Pediatric Forearm Fractures," *Journal of Pediatric Orthopaedics*, vol. 14, no. 2, pp. 211–213, 1994.

[15] G. V. Mani, P. W. Hui, and J. C. Cheng, "Translation of the radius as a predictor of outcome in distal radial fractures of children," *Journal of Bone & Joint Surgery*, vol. 75, no. 5, pp. 808–811, 1993.

[16] A. J. Bronstein, T. E. Trumble, and A. F. Tencer, "The effects of distal radius fracture malalignment on forearm rotation: A cadaveric study," *Journal of Hand Surgery*, vol. 22, no. 2, pp. 258–262, 1997.

[17] J. W. Colaris, J. H. Allema, L. U. Biter et al., "Conversion to below-elbow cast after 3 weeks is safe for diaphyseal both-bone forearm fractures in children," *Acta Orthopaedica*, vol. 84, no. 5, pp. 489–494, 2013.

[18] J. A. Roberts, "Angulation of the radius in children's fractures," *Journal of Bone & Joint Surgery*, pp. 751–754, 1986.

[19] C. Merle, W. Waldstein, E. C. Pegg et al., "Prediction of three-dimensional femoral offset from AP pelvis radiographs in primary hip osteoarthritis," *European Journal of Radiology*, vol. 82, no. 8, pp. 1278–1285, 2013.

[20] M. Altay, C. N. Aktekin, B. Ozkurt, B. Birinci, A. M. Ozturk, and A. Y. Tabak, "Intramedullary wire fixation for unstable forearm fractures in children," *Injury*, vol. 37, no. 10, pp. 966–973, 2006.

[21] I. Helenius, T. S. Lamberg, S. Kääriäinen, A. Impinen, and M. P. Pakarinen, "Operative treatment of fractures in children is increasingA population-based study from Finland," *Journal of Bone & Joint Surgery*, pp. 2612–2616, 2009.

[22] S. J. Voto, D. S. Weiner, and B. Leighley, "Redisplacement after closed reduction of forearm fractures in children," *Journal of Pediatric Orthopaedics*, vol. 10, no. 1, pp. 79–84, 1990.

[23] E. Larsen, D. Vittas, and S. Trop-Pedersen, "Remodeling of angulated distal forearm fractures in children," *Clinical Orthopaedics and Related Research*, no. 237, pp. 190–195, 1988.

[24] L. S. Matthews, H. Kaufer, D. F. Garver, and D. A. Sonstegard, "The effect on supination-pronation of angular malalignment of fractures of both bones of the forearm," *Journal of Bone and Joint Surgery*, vol. 14, no. 7, 1982.

[25] A. Sarmiento, E. Ebramzadeh, D. Brys, and R. Tarr, "Angular deformities and forearm function," *Journal of Orthopaedic Research*, vol. 10, no. 1, pp. 121–133, 1992.

[26] A. Malviya, D. Tsintzas, K. Mahawar, C. E. Bache, and P. R. Glithero, "Gap index: A good predictor of failure of plaster cast in distal third radius fractures," *Journal of Pediatric Orthopaedics B*, vol. 16, no. 1, pp. 48–52, 2007.

[27] K. H. Teoh, Y.-H. Chee, N. Shortt, G. Wilkinson, and D. E. Porter, "An age- and sex-matched comparative study on both-bone diaphyseal paediatric forearm fracture," *Journal of Children's Orthopaedics*, vol. 3, no. 5, pp. 367–373, 2009.

[28] U. Debnath, A. Guha, and S. Das, "Distal forearm fractures in children: Cast index as predictor of re-manipulation," *Indian Journal of Orthopaedics*, vol. 45, no. 4, pp. 341–346, 2011.

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Research Article

The Dimensionless Squared Jerk: An Objective Parameter That Improves Assessment of Hand Motion Analysis during Simulated Shoulder Arthroscopy

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Purpose. Attempts to quantify hand movements of surgeons during arthroscopic surgery faced limited progress beyond motion analysis of hands and/or instruments. Surrogate markers such as procedure time have been used. The dimensionless squared jerk (DSJ) is a measure of deliberate hand movements. This study tests the ability of DSJ to differentiate novice and expert surgeons (construct validity) whilst performing simulated arthroscopic shoulder surgical tasks. *Methods*. Six residents (novice group) and six consultants (expert group) participated in this study. Participants performed three validated tasks sequentially under the same experimental setup (one performance). Each participant had ten performances assessed. Hand movements were recorded with optical tracking system. The DSJ, time taken, total path length, multiple measures of acceleration, and number of movements were recorded. *Results*. There were significant differences between novices and experts when assessed using time, number of movements with average and minimal acceleration threshold, and DSJ. No significant differences were observed in maximum acceleration, total path length, and number of movements with $10 m/s^2$ acceleration threshold. *Conclusion*. DSJ is an objective parameter that can differentiate novice and expert surgeons' simulated arthroscopic performances. We propose DSJ as an adjunct to more conventional parameters for arthroscopic surgery skills assessment.

1. Introduction

There is currently no accepted definition of arthroscopic skills competency or proficiency [1]. This makes it difficult for training institutions to set skills assessments for competency-based training [2, 3]. Broadly these assessments can be categorized as being subjective, objective, or assumption of competence by numbers.

Subjective assessment is the simplest and earliest form of assessment. It follows similar principles to an apprenticeship, where a trainer will give their trainee or apprentice a global assessment [4]. It has been shown that this form of assessment does not reflect the actual level of skill the trainee may possess [2, 5].

To improve the assessment, more objectively based assessment tools have been developed [1, 6–11], whilst remaining feasible and practical [12, 13]. Objective assessment tools described can be broadly defined into quantifiable outcome measurement (such as mean time to perform the task, force measurements, and motion analysis [12, 14–20] or procedural checklists/global ratings scores (GRS) [7, 21–25] (categorical subjective assessment of defined intraprocedural steps).

When a new skill is being learned, a learning curve can be plotted and maintained at a plateau if a skill is continuously practiced [26, 27]. An individual plateau point does not define competence, but it does assume that most novices should achieve the same skills performance plateau of experienced surgeons with continued practice [26, 27].

(a) (b)

Figure 1: Experimental setup. (a) Standardized preparation tool (red dash lines). (b) Motion capture system configuration. Yellow dots are reflective markers. Blue outlined prisms are optical cameras.

In shoulder arthroscopy skills evaluation, outcome measures that were able to discriminate skill level on simulators include time to completion of tasks, distance and path traveled by probe, and number of probe collisions [28–31].

Number of movements is difficult to define. It can be described as the number of deliberate movements above a threshold acceleration value. One study considered an arbitrary value of 10 m/s^2 as the threshold value to detect deliberate hand movements of the surgeon. [12] Another study considered the minimum acceleration value from each participant as the threshold value to detect the deliberate hand movement [16]. Hence, the lack of clarity on the optimal criteria to determine the number of movements is a key limitation of use of this parameter for skill assessment.

Limited progress has been made to quantify hand or instrument movement beyond motion analysis using the parameters above. The dimensionless squared jerk (DSJ) was designed to be less dependent on time and to place more emphasis on movement. In physics, jerk is defined as a rate of change for acceleration. Therefore, it is a derivative of acceleration with respect to time and distance and as such is the second derivative of velocity or the third derivative of position. Hogan and Sternad noted that jerk could well-quantify the smoothness of motion related to hand coordination, with superior thoroughness; as such the sensitivity needed to be dimensionless, so that there would be no natural dependency of movement duration, extent, and spurious peaks [4].

The dimensionless squared jerk (DSJ) has been accepted as an objective parameter to quantify hand motion in different disciplines, such as parkinsonism, kinetics, and optometry. [32–35] To date, there is no study in the published literature quantifying hand motion using DSJ during simulated arthroscopic surgery.

In this study, we compare the ability of conventional parameters (procedural time, total path length, multiple measures of acceleration, and number of movements) to differentiate between novices and experts performing simulated shoulder arthroscopic tasks. To improve objective assessment of arthroscopic performance, we evaluated the construct validity of DSJ. Our hypothesis is that DSJ can differentiate between novices and experts performing simulated shoulder arthroscopic tasks and can be used as a parameter to train and assess surgeons.

2. Methods

2.1. Participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Review Board was obtained from Asan Medical Center prior to study (no. 2017-0292). Informed consent was obtained from all individual participants included in the study. The two groups in this study were the novice group (no hands-on experience of arthroscopic surgery) and the expert group (shoulder arthroscopy consultant). A test study was performed to calculate the expected means of the performance parameters in both groups. A priori power analysis showed a minimum of 51 attempts in each group would be sufficiently powered (80%) at a significance level of 0.05. Twelve volunteers participated in this study. These included six residents (novice group) and six consultants (expert group). Each participant performed the simulated arthroscopic tasks ten times. All the participants were right handed; therefore, they controlled the arthroscope with the left hand and maneuvered the surgical instruments with their right hand.

2.2. Experiment Setup and Protocol. Each participant performed three simulated arthroscopic tasks with a standard 30° angle arthroscope with 105° field of view (Conmed–Linvatec Corporation, Largo, FL). Both groups performed the experiment under the same experimental protocols and design and were evaluated with an optical tracking system. The phantom model, arthroscope, and surgical instruments were arranged in accordance with their predesigned places on the preparation table (Figure 1(a)).

The optical tracking system consisted of seven large-volume-motion-capture cameras (Prime 41; Natural Point, Inc., Corvallis, OR, USA). These were organized in a circular order to ensure their ability to capture two reflective markers. The markers were attached on the dorsal aspect of hands

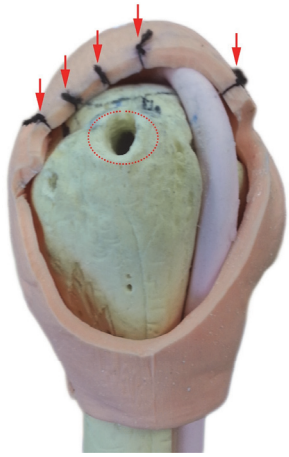

Figure 2: Modified human phantom shoulder model. Red-dots circle is a predesigned suture anchor site and red arrows are five predetermined points along the lateral border of rotator cuff.

of the participants, at the mid-shaft point of the third metacarpal (Figure 1(b)). Marker trajectory was recorded with an associated tracking software (Motive: Tracker; Natural Point, Inc.) at a sampling rate of 120 Hz.

A human shoulder phantom model (Arthrex Inc., Naples, FL, USA) was modified for shoulder arthroscopic simulation purposes. Five black silks were sutured at five different predetermined sites along the torn lateral border of the simulated rotator cuff (Figure 2).

All participants gave consent and were briefed about the experimental shoulder arthroscopic tasks. Each participant performed three validated shoulder arthroscopic tasks sequentially (Video 1) [2, 16]. Video is available as supplementary material. First, each participant touched five points along the rotator cuff with a grasper. Second, each participant inserted an anchor at a predetermined hole on the footprint of the rotator cuff on the greater tuberosity. Third, each participant pulled sutures through the anterior portal with grasper.

Participants placed their hand in a predetermined location on the preparation table before the start of the task and replaced to the initial position after completion of the task.

The optical tracking system was utilized to record three-dimensional (3D) movement of hand. Data were recorded from the time when the hands were off the preparation tool up to the time when all the surgical instruments were replaced to their initial locations for each task. All data generated or analyzed during this study are included within this article.

2.3. Data Collection and Analysis. The optical tracking system recorded the 3D position data (x, y, z) of each marker as a function of time. Total procedural time was calculated by adding the time for the three tasks cumulatively, without any intertask time. The total path length was defined as the distance traveled by the participant's hands during the three tasks (without any intertask distance). The acceleration parameter was analyzed in two ways: 1, computation of average acceleration; 2, computation of the maximum acceleration. The number of movements was defined by changes in velocity with respect to time, according to three threshold values: 1, acceleration above 10 m/s^2; 2, acceleration above minimum acceleration of each participant; 3, acceleration above average acceleration of each participant.

Each participant's total DSJ, which was the jerk without dimensions, was calculated with the following formula [4, 36, 37]:

$$\left(\int_{t_1}^{t_2} x'''(t)^2\, dt\right) * \frac{D^3}{v_{mean}^2} \quad (1)$$

where $\dddot{x}(t)^2 dt$ is squared jerk, D is the movement's duration, and v_{mean} is the movement's average velocity which was calculated using the 3D position data. The formula for calculating the DSJ was chosen based on the previous study by Hogan and Stenard [4]. We confine our observation to the earlier measure which has been used in the previous studies. [36, 37]

A Wilcoxon-Mann-Whitney Test was performed to analyze the differences in each parameter. Level of significance was set at 0.05 (p value).

3. Results

There were highly significant differences ($p < 0.001$) between novices and experts when assessed using time, number of movements (minimum acceleration, average acceleration), and DSJ. A significant difference was observed in average acceleration ($p = 0.050$) and range of acceleration ($p = 0.046$). No significant difference was observed in number of movements (10 m/s^2) (p = 0.371), maximum acceleration ($p = 0.545$), or total path length ($p = 0.395$) (Table 1). Master data table is available as supplementary material. The main result of this study has been presented at the 27th SECEC-ESSSE Congress, held in Berlin (Germany), September 13-16, 2017. [38]

Consultants were significantly quicker to complete all tasks and had a faster average and range of acceleration. They also had a highly significant lower DSJ indicating that consultants had less unwanted and more purposeful movements than novices. Novices had significantly more number of movements when the threshold was defined using minimum and average acceleration. Using 10m/s^2 as the acceleration threshold to define a movement [16], there was a tendency that novices had more movements, but this did not reach significance (Figures 3(a), 3(b), 3(c), and 3(d)).

4. Discussion

We have shown that DSJ as an objective parameter achieves construct validity in differentiating between novices and experts performing simulated shoulder arthroscopic tasks. This is logical as other studies have shown motion analysis to be a valid assessment tool in determining skill level. [12, 39–42]

Our results show that experts performed simulated arthroscopic tasks faster than novices in keeping with other

Table 1: The mean of the 10 performances stratified by participant and group (novice versus consultant). Wilcoxon-Mann-Whitney Test p values between groups. Min. acc.: minimum acceleration; Avg. acc.: average acceleration; Nov: novice. ∗∗ = statistically highly significant. ∗ = statistically significant.

	Time taken (s)		Average acceleration (m/s^2)		Maximum acceleration (m/s^2)		No. of movements ($>10m/s^2$)		No. of movements ($min.\ acc.$)		No. of movements ($avg.\ acc.$)		Total path length (m)		Range of acceleration (m/s^2)		DSJ	
	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert	Nov	Expert
1	62.29	41.86	0.56	0.45	14.37	5.17	13.91	0.00	14463.16	10040.20	3657.00	3068.70	15.52	8.86	14.37	5.17	3.03	2.83
2	74.73	52.32	0.83	0.47	44.73	5.69	27.20	0.00	11336.00	12552.60	3008.10	3805.70	16.47	10.54	44.73	5.69	6.61	5.32
3	43.46	46.15	0.52	0.99	8.28	85.62	0.00	41.30	13545.20	11454.60	3899.10	3508.40	13.92	13.36	8.28	85.62	3.84	1.82
4	55.99	54.15	0.61	1.13	21.43	29.80	19.21	5.20	16964.56	12989.50	4780.30	3351.60	13.05	22.37	21.43	29.80	5.31	2.08
5	51.84	51.84	0.48	1.80	6.20	38.06	0.00	4.80	12844.00	12435.30	3865.80	3226.20	10.69	28.41	6.20	38.06	4.89	1.99
6	87.60	63.53	1.19	0.62	96.28	19.43	24.30	2.20	20873.30	14395.50	5667.30	3619.00	29.99	29.43	96.28	64.13	15.22	1.76
Mean	62.56	51.64	0.70	0.91	31.88	30.63	14.10	8.92	15004.37	12311.28	4146.27	3429.93	16.61	18.83	31.88	38.08	6.48	2.63
Standard deviation	19.40	10.73	0.53	0.58	104.69	37.82	32.13	17.77	4653.71	2574.73	1291.92	568.00	6.86	9.01	104.69	47.21	5.75	2.06
p value	<0.001∗∗		0.050∗		0.545		0.371		<0.001∗∗		<0.001∗∗		0.395		0.046∗		<0.001∗∗	

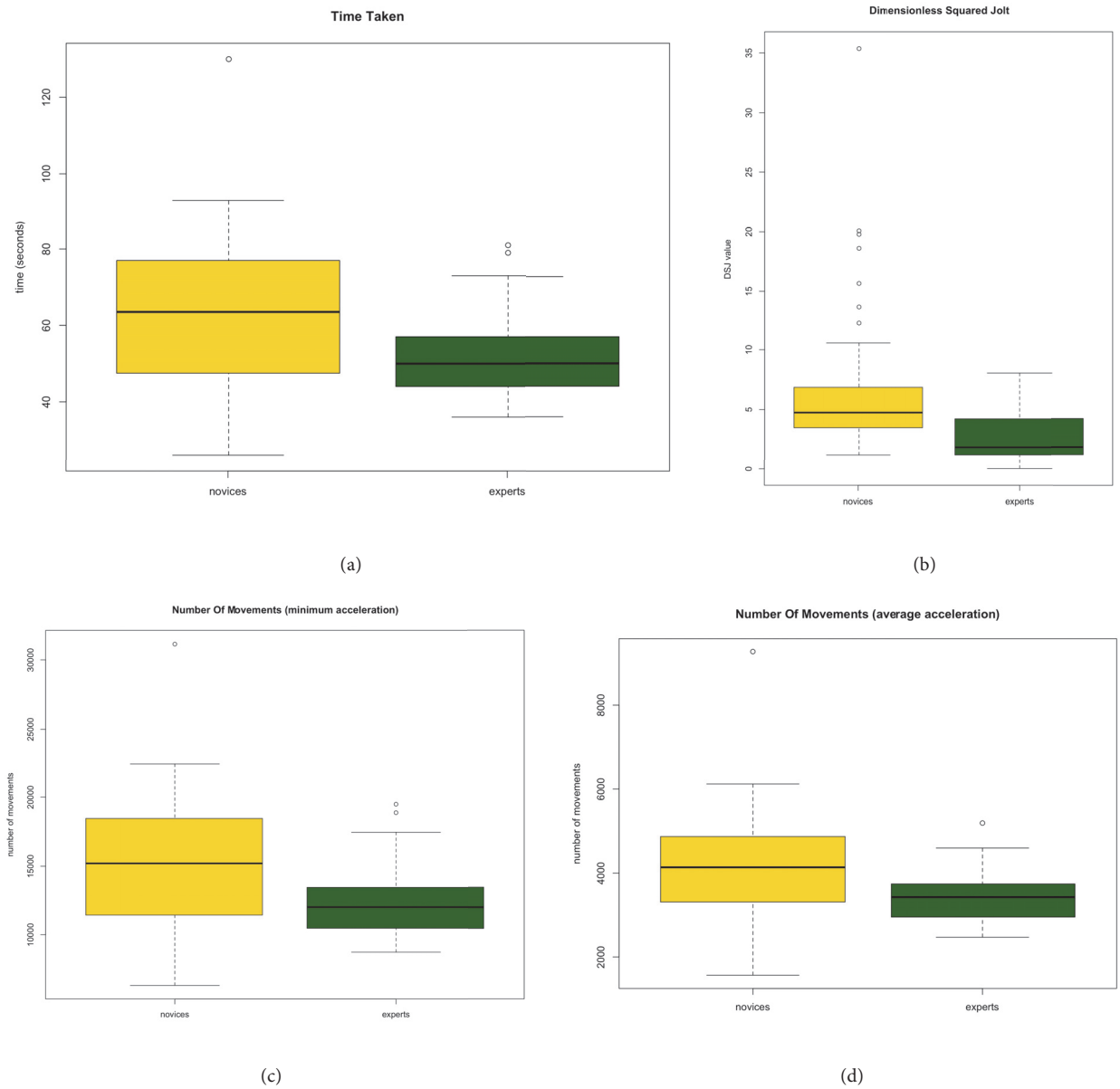

FIGURE 3: Whisker plots for (a) time, (b) dimensionless squared jerk, (c) number of movements (minimum acceleration), and (d) number of movements (average acceleration).

studies [12, 43]. However, we would not draw the conclusion that the fastest surgeons are the best surgeons as procedural time alone does not give information on movement control or quantify risk of unnecessary iatrogenic injury. We did see a significantly larger range of acceleration in the experts compared to the novices whilst other studies reported the experts proceeded with a higher velocity [12, 28, 41, 42, 44].

Number of movements may help quantify risk of iatrogenic injury. In this study, we observed novices consistently had more hand movements. This is in keeping with other studies which also showed the novice usually will demonstrate unnecessary hand movements compared to experts [41, 44].

Using number of movements as an objective parameter to measure arthroscopic performance is difficult. This is partly because of spurious peaks that may occur because of two or more submovements [45, 46] and partly due to there being no consensus on the definition of a purposeful movement. We have evaluated three methods of defining a purposeful movement and support Jung et al. definition of a purposeful movement: one that results in an acceleration that exceeds the threshold set by the minimum acceleration of the participant [16]. This achieved statistical significance along with a purposeful movement being defined as an acceleration that exceeds average acceleration of the participant.

Defining a purposeful movement can be avoided by using DSJ as it is a parameter that is based on rate of acceleration and thus is independent of any threshold value. This allows DSJ to provide a measure of deliberate hand movements only by taking cognizance of the changes in acceleration (jerk) and the area under the jerk's curve to eliminate the potential bias induced by spurious peaks [4, 45, 46].

Another parameter that has been used to differentiate skill level of surgeons for arthroscopy is total path length [12, 43]. In this study, the expert group hand motion tracked over a longer total path length as compared to that in the novice group. We postulate that longer total path length may reflect the care taken to avoid iatrogenic damage to intra-articular structures in this anatomical simulated arthroscopic study. The shortest path between 2 points is a straight line, but to avoid collision, a longer nonlinear path may have been adopted by the experts. Further studies that incorporate collision data alongside motion analysis would help investigate this further.

4.1. Limitations. We accept that this study has several limitations. First, the number of participants in each group was low. Second, we only considered three shoulder arthroscopy tasks for this analysis, whilst there are numerous techniques and skills utilized during arthroscopic surgery. Future studies need to expand the number of standardized arthroscopic tasks, as we could not assess the novices' ability to perform complicated tasks without some training, thereby interfering with the results. Third, the hand motions were represented only by two markers. Such simplified motions cannot analyze the wrist, forearm, or elbow motion. Fourth, the assumption is that the simulated arthroscopic tasks correlate with intraoperative performance. Fifth, there is no clear definition of an expert arthroscopist. Lastly, we acknowledged that there were several methods proposed in quantifying smoothness of movement. Nevertheless, we felt that jerk-based measurement proposed by previous study by Hogan et al. would meet our study's purposes [4].

5. Conclusion

DSJ is an objective parameter that can differentiate experts and novices at simulated shoulder arthroscopy. Modern day training requires objective skills assessment to support competency-based curricula, and the DSJ can function as a useful objective performance parameter to measure deliberate movements alongside other motion analysis parameters.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Level of evidence is diagnostic study, Level III.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Supplementary Materials

Video 1 in Methods and Master data table in Results are available as supplementary materials. Video shows three standardized arthroscopic tasks for each participant to complete. The performances data by participant and group (novice versus consultant). Wilcoxon-Mann-Whitney Test p values between groups. *(Supplementary Materials)*

References

[1] J. L. Hodgins and C. Veillette, "Arthroscopic proficiency: methods in evaluating competency," *BMC Medical Education*, vol. 13, no. 1, 2013.

[2] A. Darzi, S. Smith, and N. Taffinder, "Assessing operative skill. Needs to become more objective," *BMJ*, vol. 318, no. 7188, pp. 887-888, 1999.

[3] J. A. Milburn, G. Khera, S. T. Hornby, P. S. Malone, and J. E. Fitzgerald, "Introduction, availability and role of simulation in surgical education and training: review of current evidence and recommendations from the Association of Surgeons in Training," *International Journal of Surgery*, vol. 10, no. 8, pp. 393–398, 2012.

[4] N. Hogan and D. Sternad, "Sensitivity of Smoothness Measures to Movement Duration, Amplitude, and Arrests," *Journal of Motor Behavior*, vol. 41, no. 6, pp. 529–534, 2009.

[5] J. D. Mabrey, S. D. Gillogly, J. R. Kasser et al., "Virtual reality simulation of arthroscopy of the knee.," *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association*, vol. 18, no. 6, p. E28, 2002.

[6] A. Alvand, K. Logishetty, R. Middleton, T. Khan, W. F. Jackson, A. J. Price et al., "Validating a global rating scale to monitor individual resident learning curves during arthroscopic knee meniscal repair," *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, vol. 29, no. 5, pp. 906–912, 2013.

[7] N. R. Howells, H. S. Gill, A. J. Carr, A. J. Price, and J. L. Rees, "Transferring simulated arthroscopic skills to the operating theatre," *The Journal of Bone & Joint Surgery*, vol. 90-B, no. 4, pp. 494–499, 2008.

[8] A. Insel, B. Carofino, R. Leger, R. Arciero, and A. D. Mazzocca, "The development of an objective model to assess arthroscopic performance," *The Journal of Bone & Joint Surgery—American Volume*, vol. 91, no. 9, pp. 2287–2295, 2009.

[9] R. Koehler, T. John, J. Lawler, C. Moorman, and G. Nicandri, "Arthroscopic training resources in orthopedic resident education," *The Journal of Knee Surgery*, vol. 28, no. 1, pp. 67–74, 2015.

[10] J. A. Martin, G. Regehr, R. Reznick et al., "Objective structured assessment of technical skill (OSATS) for surgical residents," *British Journal of Surgery*, vol. 84, no. 2, pp. 273–278, 1997.

[11] R. M. Middleton, M. J. Baldwin, K. Akhtar, A. Alvand, and J. L. Rees, "Which global rating scale?: A comparison of the ASSET, BAKSSS, and IGARS for the assessment of simulated arthroscopic skills," *Journal of Bone and Joint Surgery - American Volume*, vol. 98, no. 1, pp. 75–81, 2016.

[12] N. R. Howells, M. D. Brinsden, R. S. Gill, A. J. Carr, and J. L. Rees, "Motion analysis: a validated method for showing skill levels in arthroscopy," *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, vol. 24, no. 3, pp. 335–342, 2008.

[13] R. S. Sidhu, E. D. Grober, L. J. Musselman, and R. K. Reznick, "Assessing competency in surgery: Where to begin?" *Surgery*, vol. 135, no. 1, pp. 6–20, 2004.

[14] A. Alvand, S. Auplish, H. Gill, and J. Rees, "Innate arthroscopic skills in medical students and variation in learning curves," *The Journal of Bone & Joint Surgery*, vol. 93, no. 19, p. e115.9, 2011.

[15] H. Fatima, D. K. Rex, R. Rothstein et al., "Cecal Insertion and Withdrawal Times With Wide-Angle Versus Standard Colonoscopes: A Randomized Controlled Trial," *Clinical Gastroenterology and Hepatology*, vol. 6, no. 1, pp. 109–114, 2008.

[16] K. Jung, D. Kang, A. L. Kekatpure, A. Adikrishna, J. Hong, and I. Jeon, "A new wide-angle arthroscopic system: a comparative study with a conventional 30◦ arthroscopic system," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 24, no. 5, pp. 1722–1729, 2016.

[17] K. Kim, D. Kim, K. Matsumiya, E. Kobayashi, and T. Dohi, "Wide FOV Wedge Prism Endoscope," in *Proceedings of the 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference*, pp. 5758–5761, Shanghai, China, January 2006.

[18] S.-i. Kim and T. S. Suh, "World Congress on Medical Physics and Biomedical Engineering 2006," in *Proccedings of the Imaging The Future Medicine*, Seoul, Korea, 2006.

[19] M. Pellisé, G. Fernández–Esparrach, A. Cárdenas et al., "Impact of Wide-Angle, High-Definition Endoscopy in the Diagnosis of Colorectal Neoplasia: A Randomized Controlled Trial," *Gastroenterology*, vol. 135, no. 4, pp. 1062–1068, 2008.

[20] D. K. Rex, V. Chadalawada, and D. J. Helper, "Wide angle colonoscopy with a prototype instrument: Impact on miss rates and efficiency as determined by back-to-back colonoscopies," *American Journal of Gastroenterology*, vol. 98, no. 9, pp. 2000–2005, 2003.

[21] R. Aggarwal, T. Grantcharov, K. Moorthy, T. Milland, and A. Darzi, "Toward feasible, valid, and reliable video-based assessments of technical surgical skills in the operating room," *Annals of Surgery*, vol. 247, no. 2, pp. 372–379, 2008.

[22] J. D. Doyle, E. M. Webber, and R. S. Sidhu, "A universal global rating scale for the evaluation of technical skills in the operating room," *The American Journal of Surgery*, vol. 193, no. 5, pp. 551–555, 2007.

[23] T. R. Eubanks, R. H. Clements, D. Pohl et al., "An objective scoring system for laparoscopic cholecystectomy," *Journal of the American College of Surgeons*, vol. 189, no. 6, pp. 566–574, 1999.

[24] M. C. Vassiliou, L. S. Feldman, C. G. Andrew et al., "A global assessment tool for evaluation of intraoperative laparoscopic skills," *The American Journal of Surgery*, vol. 190, no. 1, pp. 107–113, 2005.

[25] M. C. Vassiliou, P. A. Kaneva, B. K. Poulose et al., "Global assessment of gastrointestinal endoscopic skills (GAGES): A valid measurement tool for technical skills in flexible endoscopy," *Surgical Endoscopy*, vol. 24, no. 8, pp. 1834–1841, 2010.

[26] N. R. Howells, S. Auplish, G. C. Hand, H. S. Gill, A. J. Carr, and J. L. Rees, "Retention of arthroscopic shoulder skills learned with use of a simulator: Demonstration of a learning curve and loss of performance level after a time delay," *The Journal of Bone & Joint Surgery*, vol. 91, no. 5, pp. 1207–1213, 2009.

[27] W. M. Jackson, T. Khan, A. Alvand et al., "Learning and Retaining Simulated Arthroscopic Meniscal Repair Skills," *The Journal of Bone and Joint Surgery-American Volume*, vol. 94, no. 17, pp. e132–1-8, 2012.

[28] A. H. Gomoll, R. V. O'Toole, J. Czarnecki, and J. J. P. Warner, "Surgical experience correlates with performance on a virtual reality simulator for shoulder arthroscopy," *The American Journal of Sports Medicine*, vol. 35, no. 6, pp. 883–888, 2007.

[29] K. D. Martin, P. J. Belmont, A. J. Schoenfeld, M. Todd, K. L. Cameron, and B. D. Owens, "Arthroscopic Basic Task Performance in Shoulder Simulator Model Correlates with Similar Task Performance in Cadavers," *The Journal of Bone and Joint Surgery-American Volume*, vol. 93, no. 21, pp. e127(1)–e127(5), 2011.

[30] R. A. Pedowitz, J. Esch, and S. Snyder, "Evaluation of a virtual reality simulator for arthroscopy skills development," *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, vol. 18, no. 6, pp. E29–E39, 2002.

[31] S. Smith, A. Wan, N. Taffmder, S. Read, R. Emery, and A. Darzi, "Early experience and validation work with procedicus va - The prosolvia virtual reality shoulder arthroscopy trainer," *Studies in Health Technology and Informatics*, vol. 62, pp. 337–343, 1999.

[32] T. Flash and N. Hogan, "The coordination of arm movements: an experimentally confirmed mathematical model," *The Journal of Neuroscience*, vol. 5, no. 7, pp. 1688–1703, 1985.

[33] C. J. Ketcham, R. D. Seidler, A. W. Van Gemmert, and G. E. Stelmach, "Age-related kinematic differences as influenced by task difficulty, target size, and movement amplitude," *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, vol. 57, no. 1, pp. P54–P64, 2002.

[34] H. L. Teulings, J. L. Contreras-Vidal, G. E. Stelmach, and C. H. Adler, "Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control," *Experimental Neurology*, vol. 146, no. 1, pp. 159–170, 1997.

[35] H. J. Wyatt, "Detecting saccades with jerk," *Vision Research*, vol. 38, no. 14, pp. 2147–2153, 1998.

[36] K. Takada, K. Yashiro, and M. Takagi, "Reliability and sensitivity of jerk-cost measurement for evaluating irregularity of chewing jaw movements," *Physiological Measurement*, vol. 27, no. 7, article no. 005, pp. 609–622, 2006.

[37] K. Yashiro, T. Nakamura, T. Mizumori, H. Yatani, and K. Takada, "Clinical validity of measuring jerk-cost of jaw movement during speech: Effect of mouthguard design on smoothness of jaw movements," in *Proceedings of the SICE Annual Conference 2004*, pp. 2741–2744, Sapporo, Japan, August 2004.

[38] E. A. A. Kholinne, M. J. Gandhi, H. P. Hong, and I. H. Jeon, "The Dimensionless Squarred Jolt (DSJ) - A novel objective parameter that improves assessment of hand motion analysis during shoulder arthroscopy," in *Proceedings of the 27th SECEC-ESSSE Congress*, Berlin, Germany, 2017.

[39] V. Datta, A. Chang, S. Mackay, and A. Darzi, "The relationship between motion analysis and surgical technical assessments," *The American Journal of Surgery*, vol. 184, no. 1, pp. 70–73, 2002.

[40] J. D. Mason, J. Ansell, N. Warren, and J. Torkington, "Is motion analysis a valid tool for assessing laparoscopic skill?" *Surgical Endoscopy*, vol. 27, no. 5, pp. 1468–1477, 2013.

[41] A. Nasr, B. Carrillo, J. T. Gerstle, and G. Azzie, "Motion analysis in the pediatric laparoscopic surgery (PLS) simulator: Validation and potential use in teaching and assessing surgical skills," *Journal of Pediatric Surgery*, vol. 49, no. 5, pp. 791–794, 2014.

[42] Y. Tashiro, H. Miura, Y. Nakanishi, K. Okazaki, and Y. Iwamoto, "Evaluation of Skills in Arthroscopic Training Based on Trajectory and Force Data," *Clinical Orthopaedics and Related Research*, vol. 467, no. 2, pp. 546–552, 2009.

[43] G. S. J. Kirby, P. Guyver, L. Strickland et al., "Assessing arthroscopic skills using wireless elbow-worn motion sensors," *Journal of Bone and Joint Surgery - American Volume*, vol. 97, no. 13, pp. 1119–1127, 2014.

[44] V. Datta, S. Mackay, M. Mandalia, and A. Darzi, "The use of electromagnetic motion tracking analysis to objectively measure open surgical skill in the laboratory-based model," *Journal of the American College of Surgeons*, vol. 193, no. 5, pp. 479–485, 2001.

[45] M. Drakesmith, K. Caeyenberghs, A. Dutt, G. Lewis, A. S. David, and D. K. Jones, "Overcoming the effects of false positives and threshold bias in graph theoretical analyses of neuroimaging data," *NeuroImage*, vol. 118, pp. 313–333, 2015.

[46] B. Rohrer and N. Hogan, "Avoiding spurious submovement decompositions II: A scattershot algorithm," *Biological Cybernetics*, vol. 94, no. 5, pp. 409–414, 2006.

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Research Article

Usefulness of Serum Cardiac Biomarkers for Predicting In-Hospital Cardiac Complications in Acute Hip Fracture: A Prospective Cohort in 20 High Surgical Risk patients with Age over 55 Years

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Background. Serum cardiac biomarkers have recently been demonstrated to be useful for predicting perioperative complication after hip fracture (HF). However, no previous study has revealed the comparative efficacy of different cardiac biomarkers in high surgical risk HF patients. *Methods.* A prospective study was conducted, from June to December 2016, in 20 acute HF patients with American Society of Anesthesiologists (ASA) grade 3 or 4. All patients received blood test for high sensitivity Troponin-I (hsTnI) and N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) at the time of admission and 24 hours postoperatively. Perioperative data and in-hospital, 3-month, and 6-month postoperative complications were collected. The complications were classified as cardiac and noncardiac HF-related complications. *Results.* The average patients' age was 79±8 years. Six patients (30%) were male. The incidence of PCI was 30% (n=6). None of the patients (0%) died during the 6-month postoperative followup period. In-hospital overall cardiac and noncardiac complications were found in 12(60%), 5(30%), and 7(45%), respectively. The mean serum hsTnI levels in the patients with cardiac complication were significantly greater than those in the patients without cardiac complication at both time of admission (99.5 ng/mL vs 5.5 ng/mL, p=0.006) and 24 hours postoperatively (28.6 ng/mL vs 9.4 ng/mL, p=0.013). The mean serum NT-proBNP levels in patients with cardiac complication were also greater but nonsignificantly compared to those in the patients without cardiac complication at both time of admission (2299 pg/mL vs 281 pg/mL, p=0.239) and 24 hours postoperatively (2266 pg/mL vs 586 pg/mL, p=0.061). The other significant preoperative predictors for cardiac complication were low hemoglobin level (p=0.014), low glomerular filtration rate level (p=0.039), and ASA grade 4 (p=0.005). *Conclusion.* In-hospital cardiac complication in high-risk HF patients was significantly associated with the abnormal rise of serum hsTnI level. Therefore, we recommended using the hsTnI test in the perioperative evaluation in high-risk HF patients. *Trial registration number* is TCTR20160711002.

1. Introduction

Hip fracture (HF) is a common fracture in the elderly population and is frequently associated with significant postoperative complications and mortality [1, 2]. Regarding the complications after HF, the cardiac complication is one of the most fearsome perioperative complications that accounts for 59.7% of the death during the first 48 hours postoperatively [2]. Moreover, the cardiac complication during the perioperative period is very common as an incidence of 35-42%, which is mostly caused by heart failure, myocardial ischemia, and arrhythmia [3]. Theoretically, this cardiac complication

is a consequence of perioperative cardiac injury (PCI) that was triggered by many mechanisms related to fracture itself and the HF surgery, such as stress, blood loss, inflammation, hypercoagulation, or even in combination [4, 5]. However, the identification of PCI in HF patients is still problematic because PCI is often clinically unrecognized [6, 7] and the diagnosis requires the measurement of serum cardiac biomarkers, such as such as N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin. Recent studies showed that the increase of these cardiac biomarkers during admission is significant predictor for perioperative cardiovascular complication [8–14]. However, only few previous studies had been investigated on the relationship between the abnormal rise in cardiac biomarkers and the development of the complication after HF during perioperative period [14, 15]. Moreover, to our best knowledge, the comparative data between the efficacy of the perioperative assessment with different cardiac biomarkers for predicting the in-hospital or early postoperative morbidity or mortality has not been studied yet. Therefore, the aim of this study was to evaluate and compare the efficacy of the two commonly used cardiac biomarkers, high sensitivity Troponin-I (hsTnI), and NT-proBNP, for predicting the complication after HF during the in-hospital and 6-month postoperative period.

2. Materials and Methods

2.1. Study Population. This was a prospective single-centered observational cohort study in an academic university hospital from June to December 2015 in older patients with acute hip fracture. The study protocol was approved by our Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (protocol number 09-58-15). All patients were informed and gave their consent before participating in this study. The inclusion criteria were patients who were (1) 55 years or older, (2) presented with hip fracture within 1 week before admission, (3) treated with surgery, and (4) having American Society of Anesthesiologist (ASA) physical status grade 3 or 4. Patients were excluded if they (1) had serum creatinine >2.0 mg/dL, (2) died before surgery, (3) received neuropeptides therapy, and (4) had severe dementia or were uncooperative for assessments. All participants were followed postoperatively for 6 months.

2.2. Surgical Protocol and Perioperative Management. After the patients were diagnosed as hip fracture and gave their informed consent, they were allocated into this study and admitted to the orthopaedic trauma ward. Then preoperative medical consultation and surgical planning were performed. The surgery was scheduled as soon as possible after the medical clearance, and all operations were performed by one of the orthopaedic trauma experts (PS and NK). Displaced femoral neck fractures were treated with bipolar hip replacement (BHR) using anterolateral approach with anterior hemimyotomy. Prosthesis selection, as cementless or cemented type, was based on the quality of proximal femoral geometry. Dynamic hip screw (DHS) was used in stable intertrochanteric fracture, and proximal femoral nail antirotation (PFNA) was used in unstable intertrochanteric fracture. All patients received blood test for high sensitivity Troponin-I (hsTnI) and NT-proBNP on the admission day and 24 hours postoperatively. NT-proBNP and hsTnI were measured by electrochemiluminescence immunoassay on a Dimension Vista 500 (Siemens Healthcare Diagnostics, Deerfield, Illinois, US). The normal value of hsTnI was defined as less than 34.2 ng/mL in males and 15.6 ng/mL in females [16]. The same postoperative protocol was applied to all patients, with early ambulation as soon as possible. Intermittent pneumatic pump was applied to all patients. Blood transfusion was considered when hemoglobin (Hb) was less than 8 g/dL or the patients had anemic symptoms (dyspnea, tachypnea, and hypoxemia). Controlled weight bearing ambulation on the injured leg with gait aid was allowed regarding the operation performed. Partial weight bearing was used for DHS, PFNA, and cementless BHR and then progress to full weight bearing after 6 weeks postoperatively. The patients who underwent cemented BHR were allowed postoperative full weight bearing with gait aid. Postoperative outcome and complications were followed for 6 months.

2.3. Data Collection. Demographic and perioperative data, including age, gender, body mass index, fracture type and side, comorbid disease, ASA physical status, operation, intraoperative blood loss, and postoperative length of stay (PLOS) were recorded. Age and comorbid diseases were then calculated into Charlson comorbid index (CCI). Preoperative laboratory values, including hemoglobin (Hb), glomerular infiltration rate (GFR), and serum albumin, were collected. Postoperative complications were classified into cardiac and noncardiac complications. Cardiac complication was defined as any of cardiovascular adverse events such as myocardial infarction (MI), congestive heart failure (CHF), or new-onset cardiac arrhythmia in the patients without underlying cardiac arrhythmia or uncontrolled cardiac arrhythmia in the patients with pre-existing cardiac arrhythmia, unstable angina, or death from cardiac complication. CHF was then classified as heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Noncardiac complication was defined as any of noncardiovascular adverse events, such as pressure ulcer, infection, delirium, pulmonary complication, acute renal failure (ARF), deep vein thrombosis (DVT), pulmonary embolism (PE), or death from noncardiac complication. The primary outcome was the in-hospital cardiac complication, and the secondary outcomes were in-hospital noncardiac events as mentioned above.

2.4. Statistical Analysis. Normally distributed continuous data were shown as mean ± standard deviation (SD) and compared using student's t test. Nonnormally distributed continuous data were shown as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. The categorical variables were presented as number of cases with proportion and compared with Chi-square or Fisher's exact test, as appropriate. A p value<0.05 was considered statistically significant. The efficacy of the serum cardiac biomarkers

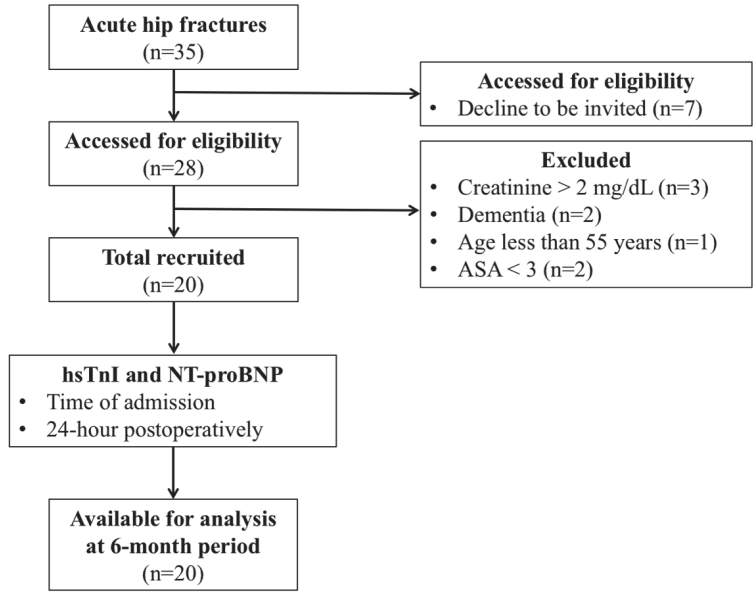


Figure 1: Flow diagram of this study.

for predicting the in-hospital cardiac complication and the cut-off reference level for NT-proBNP were assessed by the Receiver-Operator Characteristic (ROC) curve analysis. The difference between the risk factors for cardiac complication was assessed by the relative risk (R.R.) and their 95% confidence interval (CI). Statistical analysis was performed using the SPSS for Windows v15.0 (SPSS Inc., Chicago, IL, USA) software.

3. Results

A total of 20 acute hip fracture patients were included in this study (Figure 1). Table 1 demonstrated the baseline characteristic data of the study population. The mean patients' age was 79 years (range: 55-90 years) and 14 (70%) of them were females. The fractures were classified as femoral neck fractures in 9 patients (45%) and intertrochanteric fractures in 11 patients (55%). Patients who had femoral neck fractures were treated with either cemented (n=5) or cementless (n=4) bipolar hip replacements. Patients with unstable intertrochanteric fractures (n=9) were treated with PFNA, and those who had stable intertrochanteric fractures (n=2) were treated with DHS. The most common comorbid disease was hypertension (70%), and the pre-existing ischemic heart disease was found in 4 patients (20%). The mean CCI was 4.6 ± 1.4. The mean time from fracture to surgery was 2.3 days (range: 1-6 days).

Postoperative complications during the 6-month followup period was shown in Table 2. The incidences of overall cardiac and noncardiac complications during admission (in-hospital period) were all significantly higher compared to the other periods during the 6-month followup after discharge (p=<0.0001, 0.033, and 0.009, respectively). During the perioperative period, cardiac complications occurred in 5 patients (1 preoperative HFpEF, 1 preoperative unstable angina, 1 postoperative HFpEF on day 2, 1 postoperative AF with RVR on day 3, and 1 postoperative AF and RVR with HFrEF). Noncardiac complications occurred in 7 patients (1 with combined ARF, UTI, and delirium, 1 had ARF and delirium, 1 ARF and DVT, 1 DVT, 1 PE, and 2 UTI),

Table 1: Characteristics of study population.

Patients' characteristics	Value
Age, year □	79 ± 8
Male gender ◆	6 (30)
Body mass index, kg/m^2 □	21.1 ± 3.7
Femoral neck fracture: Intertrochanteric fracture	9 : 11
Injury on right side ◆	9 (45)
ASA physical status grade 3 : 4	15 : 5
Comorbid diseases ◆	
Diabetes	4 (20)
Hypertension	14 (70)
COPD	4 (20)
Ischemic heart disease	4 (20)
Atrial fibrillation	3 (15)
History of stroke	4 (20)
History of malignancy	2 (10)
Charlson comorbidity index □	4.6 ± 1.4
Preoperative laboratory investigations □	
Hemoglobin, g/dL	10.8 ± 2.0
GFR, mL/minute/1.73 m^2	65.4 ± 24.3
Albumin, g/L	32.3 ± 4.2
The time from fracture to surgery, day □	2.3 ± 1.5
Intraoperative blood loss, mL □	284 ± 282

□: values presented as mean ± standard deviation.
◆: values presents as number of cases with those condition (percentage).
COPD: chronic obstructive pulmonary disease.
GFR: glomerular infiltration rate.

Table 2: In-hospital complications and postoperative complications after discharge during 6-month followup period.

Complications	In-hospital	0-3 months	4-6 months	*p*-value
Overall ◆	12	2	0	**<0.0001∗**
Cardiac complications ◆				
Total	5	1	0	**0.033∗**
CHF	3	1	0	0.647
Cardiac arrhythmia	2	0	0	
Unstable angina	1	0	0	
Non-cardiac complications ◆				
Total	7	1	1	**0.009**
Infection	3	1	1	0.536
Renal	3	0	0	
VTE	3	0	0	
Delirium	2	0	0	

◆: no. of patients having that complication; ∗: significant difference with $p<0.05$.
CHF: congestive heart failure; VTE: venous thromboembolism.

Table 3: Comparison of the serum level of cardiac biomarkers between the patients who had and did not have either cardiac and noncardiac complications, at the time on admission and 24 hours postoperatively.

	Total (n=20)	Cardiac complication		*p*-value	Non-cardiac complication		*p*-value
		Yes (n=5)	No (n=15)		Yes (n=7)	No (n=13)	
hsTnI, ng/mL ⌘							
On admission	8.6 (5.2, 22.0)	99.5 ± 112.9	5.5 (5.0, 10.6)	**0.006∗**	8.4 (5.5, 154.4)	9.5 (5.0, 20.0)	0.843
Postoperative 24 hr	10.3 (8.2, 23.8)	28.6 (17.0, 461,3)	9.4 (7.9, 12.8)	**0.013∗**	9.0 (6.9, 99.0)	10.5 (9.2, 21.4)	0.501
NT-proBNP, pg/mL ⌘							
On admission	356 (214, 1643)	2299 ± 2629	281 (208, 802)	0.239	311 (132, 456)	781 (231, 1923)	0.362
Postoperative 24 hr	644 (389, 1830)	2266 ± 1677	586 (310, 943)	0.061	586 (516, 1937)	821 (318, 1661)	0.905

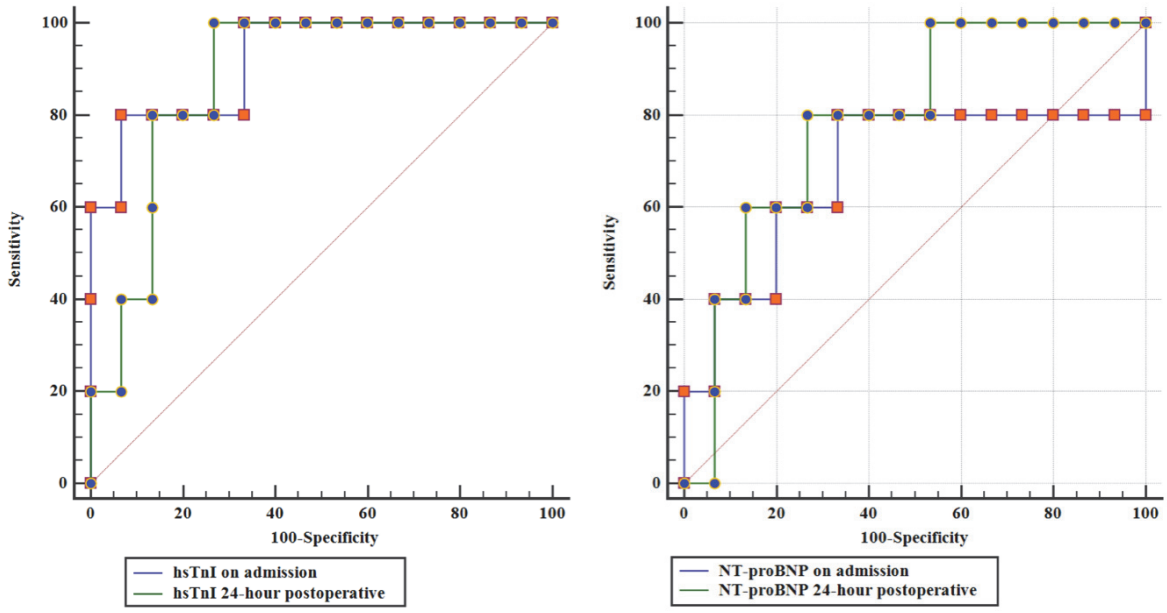
hsTnI: high sensitivity troponin I; NT-proBNP: N-terminal fragment of pro-B-type natriuretic peptide.
⌘: normally distributed value presented as mean standard deviation, and abnormally distributed value presented as median (interquartile range).
∗: significant difference with $p < 0.05$.

respectively. All patients had survived during the 6-month followup period.

Table 3 presented the comparison of the serum level of hsTnI and NT-proBNP, at the time of admission and 24 hours postoperatively, between the patients who had and did not have cardiac or noncardiac complications. Regarding the cardiac complication, the mean hsTnI levels in the patients having cardiac complication were significantly greater than those in the patients not having cardiac complication at both the time on admission (99.5 ng/mL vs 5.5 ng/mL, p=0.006) and 24 hours postoperatively (28.6 ng/mL vs 9.4 ng/mL, p=0.013). The mean NT-proBNP levels in the patients having cardiac complication were greater than those in the patients who not having cardiac complication at both time points, but they did not reach the statistical significance (on admission: 2299 pg/mL vs 281 pg/mL, p=0.239, and 24 hours postoperatively: 2266 pg/mL vs 586 pg/mL, p=0.061).

Regarding the noncardiac complication, the mean serum hsTnI levels in the patients who had noncardiac complication did not significantly differ from those in the patients who did not have noncardiac complication at both time on admission (8.4 ng/mL vs 9.5 ng/mL, p=0.843) and 24 hours postoperatively (9.0 ng/mL vs 10.5 ng/mL, p=0.501). Also, there was no significant difference between the mean NT-proBNP levels in the patients who had and did not have noncardiac complication at both time on admission (331 pg/mL vs 781 pg/mL, p=0.362) and 24 hours postoperatively (586 pg/mL vs 821 pg/mL, p=0.905) (Table 3).

Figure 2 illustrated the ROC analysis on using serum cardiac markers for predicting in-hospital cardiac complication. Figure 2(a) revealed that using the serum hsTnI test, at both the time on admission and 24 hours postoperatively, had significant association for predicting this complication (p<0.0001 both) with very good accuracy. The area under the curve (AUC) of hsTnI at the time on admission and 24 hours postoperatively was 0.920 (95% CI: 0.709-0.993) and 0.880 (95% CI: 0.658-0.981), respectively. However, the NT-proBNP test was significantly associated with the prediction of this complication only with those at 24 hours postoperatively (p=0.013) (p value from using the NT-proBNP test at the time on admission = 0.334). The AUC of NT-proBNP at the time on admission and 24 hours postoperatively were 0.680 (95%CI: 0.437-0.867) and 0.787 (95%CI: 0.549-0.935). With the cut-off level for the NT-proBNP at 24 hours postoperatively as 821 pg/mL, this would result in a sensitivity of 80%, and a specificity of 73% (Figure 2(b)).



(a) (b)

Figure 2: ROC analysis of using (a) hsTnI and (b) NT-proBNP, at the time on admission and 24 hours postoperatively, for predicting the in-hospital cardiac complication.

The correlation between the patients' characteristics and in-hospital postoperative complication was shown in Table 4. Regarding the in-hospital cardiac complication, the significant factors that were associated with this complication were ASA status grade 4 (p=0.005), preoperative Hb level (p=0.014), GFR (p=0.039), and the abnormal high serum hsTnI level at the time on admission (p=0.005) and at 24 hours postoperatively (p=0.014). The patients who had abnormal high serum hsTnI level, at the time of admission or 24 hours postoperatively, had 12 and 6 times greater risk for developing the in-hospital cardiac complication compared to those who had normal serum hsTnI level. Additionally, some factors, such as age, CCI, and serum albumin level, also showed a tendency toward cardiac complication, but these did not reach a significant effect (p=0.083, 0.056, and 0.059, respectively). Concerning the in-hospital noncardiac complication, the significant factors associated with this complication were the time from fracture to surgery (p=0.005), ASA status grade 4 (p=0.031), and postoperative length of stay (PLOS) (p=0.034) (Table 4).

4. Discussion

Perioperative cardiac injury (PCI) is common among the hip fracture patients, especially in those who are ageing population and having multiple comorbid diseases. Early PCI diagnosis is important and beneficial for risk stratification and appropriate management in for each individual patient. Recently, several studies have demonstrated a significant correlation between the increase of serum cardiac biomarkers level and the poor outcome after noncardiac surgery. However, only few studies have demonstrated the association between the abnormal rise of cardiac biomarkers and the perioperative complication after hip fracture [14, 15]. This study aimed to assess and compare the efficacy of two cardiac biomarkers, hsTnI and NT-proBNP, for predicting the in-hospital, 3-month, and 6-month postoperative complication after HF.

Our study showed that the PCI, as shown by the abnormal rise of serum hsTnI level, was common as an incidence of 30% (n=6) in the HF patients and it could be detected as early as at the time of admission (Table 3), which was comparable to the previous studies [14, 15]. These results could imply that the HF itself and the poor physical condition of the HF patients are the major initiate factors for the PCI and should be responsible for the cardiac complication in preoperative period [17]. Also, the HF surgery could be the second factor that further stimulates the PCI resulting in the postoperative cardiac complication. The findings of this study also demonstrated that the abnormal rise of serum hsTnI, at either time of admission or 24-hours postoperatively, was significantly associated with the in-hospital cardiac complication and, therefore, was useful as one of the significant predictive factors for the in-hospital cardiac complication, the same as the other clinical predictive factors (ASA grade 4, Hb, and GFR). The results of the present study were comparative with those of previous studies that serum cardiac troponin test in elderly hip fracture has prognostic significance for postoperative mortality and morbidity [15, 18, 19]. However, none of these patients died during the 6-month postoperative period, so we could not find any association with the abnormal rising test and postoperative mortality. This may be explained by the facts that our study was a prospective study with strict protocol on perioperative management and early detection of those complications. As

Table 4: The relationship between patients' characteristics and in-hospital complications.

	Cardiac complication				Non-cardiac related complication			
	Yes (n=5)	No (n=15)	*p*-value	RR (95% C.I.)	Yes (n=7)	No (n=13)	*p*-value	RR (95% C.I.)
Age, year	84 ± 3	77 ± 9	0.083		78 ± 10	79 ± 7	0.803	
Male gender	1 (20)	5 (33)	1	0.58 (0.08-4.19)	2 (29)	4 (31)	1	0.93 (0.22-3.87)
BMI, kg/m2	20.1 ± 4.3	21.4 ± 3.6	0.499		21.7 ± 4.6	20.8 ± 3.3	0.615	
Intertrochanteric fracture	3 (60)	8 (53)	1	1.23 (0.26-5.82)	4 (57)	7 (54)	1	1.06 (0.47-2.40)
Injury on right side	3 (60)	6 (40)	0.617	1.83 (0.39-8.70)	3 (43)	6 (46)	1	0.93 (0.33-2.62)
Time from fracture to surgery, day	2.8 ± 1.9	2.1 ± 1.3	0.352		3.4 ± 1.9	1.6 ± 0.7	**0.005**∗	
ASA grade 4	4 (80)	1 (7)	**0.005**∗	12 (1.72-83.8)	4 (57)	1 (8)	**0.031**∗	7.43 (1.02-54.3)
Comorbid disease								
DM	1 (20)	3 (20)	1.000	1.00 (0.15-6.67)	1 (14)	3 (23)	1.000	0.62 (0.08-4.90)
Hypertension	3 (60)	11 (73)	0.613	0.64 (0.14-2.91)	4 (57)	10 (77)	0.613	0.73 (0.37-1.51)
IHD	2 (40)	2 (13)	0.249	2.67 (0.65-10.97)	1 (14)	3 (23)	1.000	0.62 (0.08-4.90)
AF	2 (40)	1 (7)	0.140	3.78 (1.03-13.89)	1 (14)	2 (15)	1.000	0.93 (0.10-8.53)
COPD	1 (20)	3 (20)	1.000	1.00 (0.15-6.67)	1 (14)	3 (23)	1.000	0.62 (0.08-4.90)
Stroke	0 (0)	4 (27)	0.530	0.31 (0.02-4.68)	1 (14)	3 (23)	1.000	0.62 (0.08-4.90)
Malignancy	1 (20)	1 (7)	0.447	2.25 (0.44-11.52)	1 (14)	1 (8)	1.000	1.86 (0.14-25.4)
CCI	5.6 ± 1.3	4.2 ± 1.3	0.056		4.3 ± 1.6	4.7 ± 1.4	0.559	
Hemoglobin, g/dL	8.9 ± 1.8	11.4 ± 1.7	**0.014**∗		10.8 ± 2.6	10.7 ± 1.7	0.955	
GFR, mL/minute/1.73m^2	46.3 ± 19.3	71.7 ± 22.8	**0.039**∗		55.8 ± 29.7	70.5 ± 20.3	0.204	
Albumin, g/L	29.3 ± 4.0	33.3 ± 3.9	0.059		32.6 ± 3.3	32.2 ± 4.8	0.838	
Intraoperative blood loss, mL	450 ± 499	228 ± 154	0.383	1.64 (0.53-5.09)	200 (150, 338)	300 (50, 363)	0.968	
PLOS, day	10 (3, 15)	4 (3, 5)	0.172		7 (4, 10)	3 (3, 5)	**0.034**∗	
Positive hsTnI with normal cut-off reference level								
On admission	4 (80)	1 (7)	**0.005**∗	12.0 (1.7-83.8)	2 (29)	3 (23)	1.000	1.24 (0.27-5.75)
Postoperative 24 hour	4 (80)	2 (13)	**0.014**∗	6.0 (1.54-23.4)	2 (29)	4 (31)	1.000	0.93 (0.22-3.87)
Positive NT-proBNP with cut-off level as 821 pg/mL								
On admission	3 (60)	3 (20)	0.131	3.0 (0.87-10.36)	1 (14)	5 (38)	0.354	0.37 (0.05-2.59)
Postoperative 24 hour	4 (80)	4 (27)	0.109	3.0 (1.16-7.73)	2 (29)	6 (46)	0.642	0.62 (0.17-2.29)

BMI: body mass index; ASA: American Society of Anesthesiologist; DM: diabetes milletus; IHD: ischemic heart disease; AF: atrial fibrillation.
COPD: chronic obstructive pulmonary disease; CCI: Charlson comorbidity index; PLOS: postoperative length of stay; GFR: glomerular infiltration rate.
□: values presented as mean ± standard deviation. ◆: values presented as number of cases (percentage); ■: values presented as median (interquartile range).
∗: significant difference with $p<0.05$

a result, our results on mortality and morbidity, especially from cardiac complication, may be better than those previous reports.

Regarding the NT-proBNP test for PCI diagnosis, the results of this study showed that the mean serum NT-proBNP level was also increased, the same as the hsTnI, but nonsignificantly in the patients who had in-hospital cardiac complication compared to those who did not have (Table 3). This might be explained by the small sample size of the present study. However, these findings were comparable to the previous studies that the prognostic information from the NT-proBNP was not as strong as those from the high sensitive cardiac troponin test [20]. Moreover, an increase of the NT-proBNP might be found in those who had a transient myocardial ischemia [21] or who received considerable infusion of intravenous fluid [22], and these could result in a lower diagnostic accuracy and the need of a high cut-off reference value [23–25]. This study also showed that the prognostic value of the NT-proBNP might be better in postoperative period (p=0.061) compared to the preoperative use (p=0.239) (Table 3), and this finding was comparable to the previous studies that recommended the use of NT-proBNP in the postoperative period and outpatients clinic setting [26].

The results from this study also demonstrated that in-hospital noncardiac complication was significantly associated with some factors as the time from fracture to surgery (p=0.005), ASA grade 4 (p=0.031), and postoperative length of stay (p=0.034). These findings were comparable with the previous studies on hip fracture [2, 3, 12, 15, 23, 27] and, therefore, highlighted the importance of the preoperative risk stratification and proper management on these high surgical risk patients.

This study also had some limitations. First, the study population was relatively small due to the nature of our prospective study and included only high-risk HF patients. Therefore, this may not detect other significantly clinical outcomes, such as the effect of serum cardiac biomarkers on postoperative mortality. Second, we excluded the patients who had creatinine $\geq$ 2 mg/dl to avoid the false positive value of abnormal rising test from very poor renal function. Thus, our results might not be applied to the patients with pre-existing severe renal disease. Lastly, the baseline serum cardiac biomarkers level before HF was not available in this study which would result in a selection bias and affected the outcome. Therefore, further prospective studies with larger study population are required for better clarification.

5. Conclusion

Our study showed that in-hospital cardiac complication in high-risk HF patients was significantly associated and predictable with the abnormal rise of serum hsTnI level, which is the same as the other significant predictive factors such as low preoperative Hb level, poor renal function, and poor physical status. We recommend using hsTnI for risk stratification during the perioperative period of HF surgery on high surgical risk patients.

Data Availability

Technical appendix, statistical code, and dataset are available from the corresponding authors at noratep28@gmail.com.

Conflicts of Interest

All of the authors declare that they have no conflicts of interest.

Authors' Contributions

Paphon Sa-ngasoongsong, M.D., and Noratep Kulachote, M.D., were the main researchers who designed and performed this study and prepared the manuscript. Sorawut Thamyongkit, M.D., was the orthopaedic trauma surgeon who assisted in data collection and manuscript preparation. Kitchai Luksameearunothai, M.D., was the orthopaedic trauma surgeon who assisted in data collection. Tachapong Ngamukos, M.D., was the senior cardiologist consultant who assisted in research process. Chanyut Suphachatwong, M.D., was the senior orthopaedic consultant who assisted in research process.

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References

[1] J. E. Kenzora, R. E. McCarthy, J. D. Lowell, and C. B. Sledge, "Hip fracture mortality. Relation to age, treatment, preoperative illness, time of surgery, and complications," *Clinical Orthopaedics and Related Research*, vol. 186, pp. 45–56, 1984.

[2] B. Nkanang, M. Parker, E. Parker, and R. Griffiths, "Perioperative mortality for patients with a hip fracture," *Injury*, vol. 48, no. 10, pp. 2180–2183, 2017.

[3] P. Carpintero, J. R. Caeiro, R. Carpintero, A. Morales, S. Silva, and M. Mesa, "Complications of hip fractures: A review," *World Journal of Orthopedics*, vol. 5, no. 4, pp. 402–411, 2014.

[4] S. Gombar, A. K. Khanna, and K. K. Gombar, "Corrosion in the Aestiva®/5 anaesthesia delivery system: is it time to modify the design?" *Acta Anaesthesiologica Scandinavica*, vol. 51, no. 7, pp. 957-958, 2007.

[5] D. T. Mangano, W. S. Browner, M. Hollenberg, J. Li, and I. M. Tateo, "Long-term Cardiac Prognosis Following Noncardiac Surgery," *Journal of the American Medical Association*, vol. 268, no. 2, pp. 233–239, 1992.

[6] P. Hietala, M. Strandberg, N. Strandberg, E. Gullichsen, and K. E. J. Airaksinen, "Perioperative myocardial infarctions are common and often unrecognized in patients undergoing hip fracture surgery," *Journal of Trauma and Acute Care Surgery*, vol. 74, no. 4, pp. 1087–1091, 2013.

[7] A. A. Fisher, E. N. Southcott, S. L. Goh et al., "Elevated serum cardiac troponin I in older patients with hip fracture:

Incidence and prognostic significance," *Archives of Orthopaedic and Trauma Surgery*, vol. 128, no. 10, pp. 1073–1079, 2008.

[8] J.-H. Choi, D. K. Cho, Y.-B. Song et al., "Preoperative NT-proBNP and CRP predict perioperative major cardiovascular events in non-cardiac surgery," *Heart*, vol. 96, no. 1, pp. 56–62, 2010.

[9] R. N. Rodseth, B. M. Biccard, Y. Le Manach et al., "The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: A systematic review and individual patient data meta-analysis," *Journal of the American College of Cardiology*, vol. 63, no. 2, pp. 170–180, 2014.

[10] B. Stojcevski, V. Celic, S. Navarin et al., "The use of discharge haemoglobin and NT-proBNP to improve short and long-term outcome prediction in patients with acute heart failure," *European Heart Journal: Acute Cardiovascular Care*, vol. 6, no. 8, pp. 676–684, 2016.

[11] C. P. Chong, W. J. van Gaal, J. E. Ryan, L. M. Burrell, J. Savige, and W. K. Lim, "Troponin I and NT-proBNP (N-terminal pro-Brain Natriuretic Peptide) do not predict 6-month mortality in frail older patients undergoing orthopedic surgery," *Journal of the American Medical Directors Association*, vol. 11, no. 6, pp. 415–420, 2010.

[12] S. Farzi, T. Stojakovic, T. Marko et al., "Role of N-terminal pro B-type natriuretic peptide in identifying patients at high risk for adverse outcome after emergent non-cardiac surgery," *British Journal of Anaesthesia*, vol. 110, no. 4, pp. 554–560, 2013.

[13] G. Karthikeyan, R. A. Moncur, O. Levine et al., "Is a Pre-Operative Brain Natriuretic Peptide or N-Terminal Pro-B-Type Natriuretic Peptide Measurement an Independent Predictor of Adverse Cardiovascular Outcomes Within 30 Days of Noncardiac Surgery?. A Systematic Review and Meta-Analysis of Observational Studies," *Journal of the American College of Cardiology*, vol. 54, no. 17, pp. 1599–1606, 2009.

[14] C. P. Chong, J. E. Ryan, W. J. Van Gaal et al., "Usefulness of N-terminal probrain natriuretic peptide to predict postoperative cardiac complications and long-term mortality after emergency lower limb orthopedic surgery," *American Journal of Cardiology*, vol. 106, no. 6, pp. 865–872, 2010.

[15] S. Dawson-Bowling, K. Chettiar, H. Cottam et al., "Troponin T as a predictive marker of morbidity in patients with fractured neck of femur," *Injury*, vol. 39, no. 7, pp. 775–780, 2008.

[16] A. Croce, P. Brunati, C. Colzani et al., "A Rational Adoption of the High Sensitive Assay for Cardiac Troponin I in Diagnostic Routine," *Disease Markers*, vol. 2017, pp. 1–11, 2017.

[17] J. J. W. Roche, R. T. Wenn, O. Sahota, and C. G. Moran, "Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study," *British Medical Journal*, vol. 331, no. 7529, pp. 1374–1376, 2005.

[18] A. Sandhu, S. Sanders, and S. A. Geraci, "Prognostic value of cardiac troponins in elderly patients with hip fracture - A systematic review," *Osteoporosis International*, vol. 24, no. 4, pp. 1145–1149, 2013.

[19] E. Spurrier, D. Wordsworth, S. Martin, R. Norris, and M. J. Parker, "Troponin T in hip fracture patients: Prognostic significance for mortality at one year," *Hip International*, vol. 21, no. 6, pp. 757–761, 2011.

[20] M. Weber, A. Luchner, S. Manfred et al., "Incremental value of high-sensitive troponin T in addition to the revised cardiac index for peri-operative risk stratification in non-cardiac surgery," *European Heart Journal*, vol. 34, no. 11, pp. 853–862, 2013.

[21] M. S. Sabatine, D. A. Morrow, J. A. De Lemos et al., "Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia," *Journal of the American College of Cardiology*, vol. 44, no. 10, pp. 1988–1995, 2004.

[22] M. Montagnana, G. Lippi, D. Regis et al., "Evaluation of cardiac involvement following major orthopedic surgery," *Clinical Chemistry and Laboratory Medicine*, vol. 44, no. 11, pp. 1340–1346, 2006.

[23] A. Oscarsson, M. Fredrikson, M. Sörliden, S. Anskär, and C. Eintrei, "N-terminal fragment of pro-B-type natriuretic peptide is a predictor of cardiac events in high-risk patients undergoing acute hip fracture surgery," *British Journal of Anaesthesia*, vol. 103, no. 2, pp. 206–212, 2009.

[24] H. Ushirozako, T. Ohishi, T. Fujita et al., "Does N-terminal Pro-brain Type Natriuretic Peptide Predict Cardiac Complications After Hip Fracture Surgery?" *Clinical Orthopaedics and Related Research*, vol. 475, no. 6, pp. 1730–1736, 2017.

[25] P. Nordling, T. Kiviniemi, M. Strandberg, N. Strandberg, and J. Airaksinen, "Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide," *BMJ Open*, vol. 6, no. 2, Article ID e009416, 2016.

[26] D. A. Morrow, J. A. De Lemos, M. A. Blazing et al., "Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease," *Journal of the American Medical Association*, vol. 294, no. 22, pp. 2866–2871, 2005.

[27] N. Simunovic, P. J. Devereaux, S. Sprague et al., "Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis," *Canadian Medical Association Journal*, vol. 182, no. 15, pp. 1609–1616, 2010.

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Research Article

Can Clinical and Surgical Parameters Be Combined to Predict How Long It Will Take a Tibia Fracture to Heal? A Prospective Multicentre Observational Study: The FRACTING Study

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Background. Healing of tibia fractures occurs over a wide time range of months, with a number of risk factors contributing to prolonged healing. In this prospective, multicentre, observational study, we investigated the capability of FRACTING (tibia FRACTure prediction healING days) score, calculated soon after tibia fracture treatment, to predict healing time. *Methods*. The study included 363 patients. Information on patient health, fracture morphology, and surgical treatment adopted were combined to calculate the FRACTING score. Fractures were considered healed when the patient was able to fully weight-bear without pain. *Results*. 319 fractures (88%) healed within 12 months from treatment. Forty-four fractures healed after 12 months or underwent a second surgery. FRACTING score positively correlated with days to healing: $r = 0.63$ ($p < 0.0001$). Average score value was 7.3 ± 2.5; ROC analysis showed strong reliability of the score in separating patients healing before versus after 6 months: AUC = 0.823. *Conclusions*. This study shows that the FRACTING score can be employed both to predict months needed for fracture healing and to identify immediately after treatment patients at risk of prolonged healing. In patients with high score values, new pharmacological and nonpharmacological treatments to enhance osteogenesis could be tested selectively, which may finally result in reduced disability time and health cost savings.

1. Introduction

Over the past 50 years, orthopaedic surgery has defined, for the different skeletal sites and different fracture morphologies, guidelines to ensure a suitable mechanical environment to allow healing [1]. The treatment of tibia fractures has become almost solely surgical, using nails, plates, and screws and external fixation, to set the mechanical conditions (stability, contact, and alignment of the fracture fragments) for bone repair [2–4]. Following surgical treatment, patients have obtained significant benefits; limb function recovery is more rapid, and joint stiffness or local osteoporosis is rare.

Bone healing results from the activity of different cell populations at the fracture site [5, 6]; nowadays, orthopaedic research aims to stimulate bone callus formation by pharmacological [7], cellular [8], and biophysical means [9] in order to speed up fracture healing [10].

The tibia is the region with the highest incidence of fractures resulting from trauma [3]. The healing of a tibia fracture can occur over a very wide time range, from a

minimum of 2 months to a maximum of 6 months in most patients. Nevertheless, in a significant percentage of patients, healing may take place well beyond 6 months after the trauma or may require one or more surgical procedures, with significant associated health costs [11–13].

Although general and local conditions that may adversely affect fracture healing have been identified [14–18], the ability to early recognise fractures at risk of developing a nonunion is still left to the surgeon's experience.

In a previous retrospective study, we assessed clinical records of patients treated for tibia fractures to collect information on trauma characteristics, fracture treatment, patient's general conditions, and finally the time required for fracture healing. The data thus collected were analysed by logistic regression to identify those parameters that influenced time to fracture healing, and then they were combined in a score whose values increased as time to healing increased [19].

We conducted this prospective multicentre observational study to (i) investigate, in a large cohort of patients, if the score, calculated immediately after the treatment, could reliably predict the time to healing of a tibia fracture and (ii) determine the ability of the score to identify fractures at risk of nonunion, that is, healing after more than 6 months.

2. Materials and Methods

This prospective observational study mirrors the clinical practice for tibia fracture treatment throughout the country, "real world data." On this assumption, neither indication was given on how to treat the fracture nor the review on treatment appropriateness was performed.

From January 2010 to September 2012, patients who had suffered a tibia fracture were recruited in 41 Italian orthopaedic traumatology centres. Patient treatment was left to the choice of the trauma surgeon based on experience. All patients provided written, informed consent for the handling of personal data. The study was approved by the ethical committee of the coordinating centre: University of Ferrara, Italy.

Inclusion criteria were as follows: patients with posttraumatic fractures type 41-A and B, 42-A-B and C, 43-A and B according to AO classification [1]; fracture treatment within 3 days from trauma; and patient age > 18 years.

Exclusion criteria were as follows: fractures involving the tibia plateau and malleolar fractures, patients with autoimmune diseases or neoplasia, and patients who could not return to the treating centre for follow-up visits.

We selected a patient-centred end point to determine fracture healing: fully weight-bearing without pain. Within 12 months from trauma, the date at which the fracture healed was used to calculate days and months elapsed since treatment ("healing time"). We chose to follow patient for 12 months after treatment as a small percentage of fractures may slowly heal 6 months after the trauma [20–22].

Criteria for failure to heal included fractures not healed within 12 months from trauma and fractures that required surgical procedures not foreseen in the initial treatment plan.

2.1. Database. For each patient, surgical and clinical data were collected in dedicated software and used to calculate the score: FRACTING (FRACTure healING). Drop-down menu was used for descriptive variables. Required fields ensured complete and consistent data collection. The score was calculated adding all values shown in Table 1.

As ancillary information, on the day of healing, surgeons were asked to record on the database the presence of bone callus on tibia cortices in orthogonal radiographs; nevertheless no centralised review of the X-rays was performed.

2.2. Statistical Analysis. We conducted a power analysis to establish the number of patients required to demonstrate the correlation of the score with time to healing with a confidence interval of 0.10. Considering the correlation $r = 0.69$ observed in the retrospective study, we calculated a sample size of 301 patients.

In the descriptive analysis for continuous variables, mean values and standard deviations are reported. ANOVA analysis with post hoc Bonferroni test has been applied for comparison between multiple groups. The association between continuous variables was calculated by linear regression analysis and Pearson linear correlation coefficient. In order to determine the ability of the score to identify those who would not heal within 6 months posttrauma, contingency tests and receiver operating characteristic (ROC) analysis were used; specificity, sensitivity and positive predictive values were calculated. Data were analysed using SPSS 21.0 software [IBM, New York, USA].

3. Results

3.1. Study Cohort. 519 patients were screened, 38 did not meet the inclusion criteria, and 67 did not accept to be enrolled. Finally, 414 patients with tibia fracture entered into the database. Fifty-one patients (12%) did not return for follow-up visits. Overall 363 patients completed the study (Table 2) (Figure 1).

Twenty-one percent of fractures were open; in 3%, loss of bone tissue occurred. In 75% of fractures, both tibia and fibula were fractured. According to AO classification, 6% of fractures were type 41, 72% were type 42, and 22% were type 43. Table 3 reports the treatment performed in open or closed fractures.

Out of 363 patients, 319 (88%) healed within 12 months; 268 (74%) healed within 6 months and 51 (14%) between 6 and 12 months. Forty-four fractures (12%) were considered failure as they required either further surgery or more than 12 months to heal. Figure 2 shows the percentage of fractures healed at each month.

Fracture healing was achieved on average in 130 ± 54 days for all patients.

At healing, the presence of callus was reported for 311 fractures: in at least three cortices in 81% of patients, in two cortices in 15% of patients, and in one cortex only in 4% of patients.

At long-term follow-up (6 months from healing), 93% of fractures were reevaluated and their healing was confirmed;

Table 1: Parameters used for FRACTING score calculation.

Parameter	Values for score calculation	
Age increase	18–45	1
	46–60	2
	>60	3
Malnutrition	Yes	1
Diabetes	Yes	1
Smoking	Yes	1
Use of NSAIDs	Yes	1
Fracture exposure severity	Closed	1
	Open grade 1	2
	Open skin < 5 cm	3
	Open skin > 5 cm	4
Location: metaphysis or epiphysis	Yes	1
Synthesis device	Nail	1
	Plate	2
	External fixation	3
Unstable	Yes	1
Misalignment > 5°	Yes	1
Bone graft	Yes	1
Plate + diastasis	Yes	0.5
Angular stability plate	Yes	0.5
Plate + plaster cast	Yes	−0.5
Fracture of tibia alone	Yes	1
Loss of bone substance	Yes	1
Bone diastasis, >2 mm	Yes	1
Length of surgery, >120 minutes	Yes	1
Blood haemoglobin before treatment < 10 g/dl	Yes	1
Blood haemoglobin after treatment < 10 g/dl	Yes	1

NSAIDs: nonsteroidal anti-inflammatory drugs.

Table 2: Patients' characteristics.

Male/female	257/106
Age (yrs)	48 ± 17
Weight (Kg)	74 ± 13
Height (cm)	171 ± 8

Table 3: Treatment performed in open or closed fractures.

	No. of fractures treated	Open	Closed
External fixation	76	40	36
Nail	163	25	138
Plate & screws	124	12	112
Total	363	77 (21%)	286 (79%)

2 patients reported that the fracture, initially judged to be healed, had over time been treated again.

3.2. Healing Time and FRACTING Score. The values of the score ranged from 3 to 18, with a mean value of 7.3 ± 2.5, median 7.

The correlation of the score with healing time expressed in days is significant: $r = 0.63$; $p < 0.0001$ (Figure 3).

In traumatology practice, the patient follow-up interval after treatment is usually 30 days. Therefore, we grouped the fracture healing into five time intervals: ≤3, 4, 5, 6, and >6 months. The average score values by months after treatment are reported in Table 4.

In further analysis we evaluated for different score values the percentage of fractures healed at different time intervals from trauma (Figure 4).

Among the 363 fractures, 12% of fractures with score values ≤ 7 took more than 6 months to heal versus 43% of fractures with score values > 7 ($p < 0.0001$). We performed the ROC analysis to evaluate the ability of the score to predict fracture healing in more than 6 months (nonunion); the area under the curve (AUC) was 0.823 ± 0.033 ($p < 0.0001$). Data for the sensitivity, specificity, and positive predictive value for individual score values are shown in Table 5.

4. Discussion

To estimate healing time of a fracture immediately after its treatment is difficult, it is based on individual surgeon's

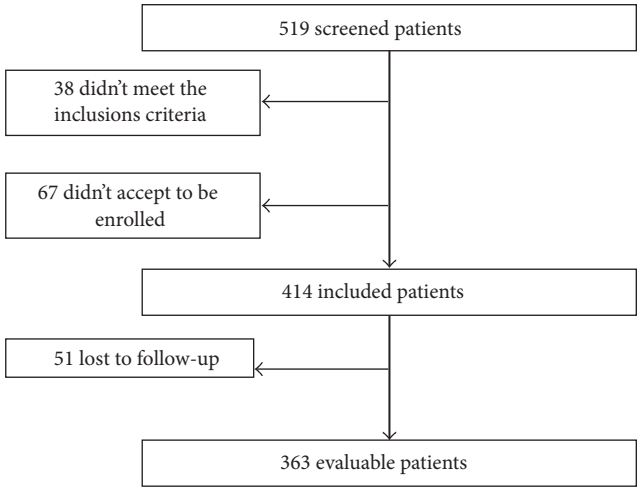

Figure 1: Flow diagram in which the eligible, screened, and included patients are illustrated.

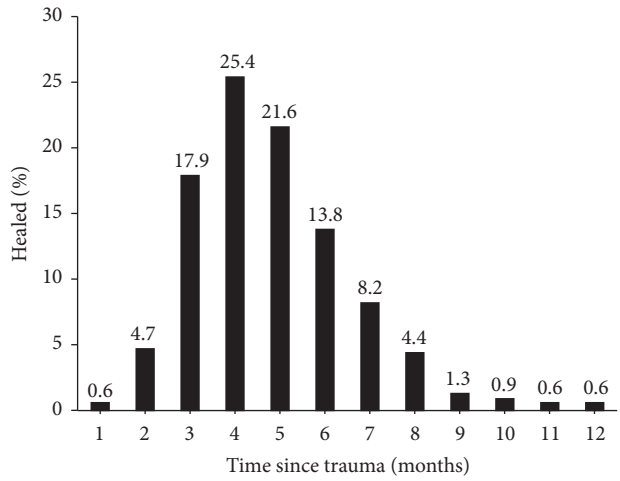

Figure 2: Percentage of fractures healed each month after treatment.

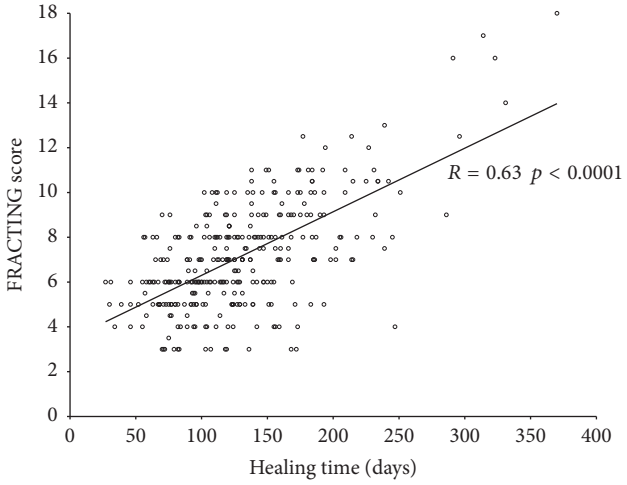

Figure 3: Linear correlation of the score value with fracture healing time in days.

experience, and it is made even more difficult as to date there is no accepted gold standard to determine the healing of a fracture [23, 24]. Several clinical studies have considered healing on both (i) radiographic criteria: presence of bone callus in at least three cortices on radiographs performed in the two projections, and (ii) clinical criteria: absence of tenderness at the fracture site, the absence of pain on application of pressure to the fracture site and during full weight-bearing [21, 22, 25].

In this observational study, we tested the ability of the FRACTING score to estimate immediately after fracture treatment how long it will take to heal. Here, fracture healing has been based exclusively on clinical criteria: full weight-bearing without pain. This patient-centred end point is relevant in clinical practice as it corresponds to the return to work and daily activities. As confirmation of reliability of the criteria for healing adopted, at 6-month follow-up, in 2 patients only, further treatment was required.

The FRACTING score is positively correlated with the healing time in days ($r = 0.63$; $p < 0.0001$). Furthermore, ANOVA test shows a significant association among score values and healing time in months (Table 4).

Within each score value (Figure 4), we observed fractures healing at different time periods, thus leaving a range of uncertainty that can be explained by individual biology, patient's behaviour, and adherence to the orthopaedic surgeon indications until healing. Nevertheless, it is noteworthy that while for scores ≤5, 12% of fractures healed after 6 months from trauma, for scores >9, the percentage increased to 61% ($p < 0.0001$).

The ROC analysis shows good reliability of the FRACTING score to assess the risk of nonunion (AUC = 0.823). In clinical practice, an effective threshold might be selected for a score value of 8 that shows a sensitivity of 63% with specificity of 81%, and a positive predictive value of 53% that shows that the fracture heals in more than 6 months (Table 3).

To our knowledge this is the first attempt to prospectively validate a score to predict fracture healing time. The results of this study cannot be extended to skeletal segments other than the tibia. However, our work suggests that the same approach can be adopted to develop specific scores for fractures located in different bones.

The major strength stems from the population studied that represents real world data. FRACTING score is associated with fracture healing time and able to accurately identify fractures at risk of nonunion.

Limitations include the exclusive use of clinical criteria for definition of fracture healing, although only 2 patients experienced fracture retreatment at follow-up.

5. Conclusions

FRACTING score might be used for selecting patients in whom the efficacy of therapeutic interventions to enhance fracture healing is assessed, such as cell therapy, growth factors, drugs, or physical stimuli. Furthermore, patients with high scores may benefit from customised treatment protocols by planning closer surveillance and specific rehabilitation

Table 4: Average score values in different fracture healing months.

Healing months	≤3	4	5	6	>6
No. of fractures	74	81	69	44	51
Avg score (st.dev.)	4.97 (2.00)	6.33 (2.14)	6.86 (2.20)	7.42 (2.56)	8.71 (1.84)
ANOVA: $p < 0.0001$					
Post hoc analysis among scores: p value					
Healing months	≤3	4	5	6	>6
≤3	1				
4	0.0379	1			
5	0.0007	0.6341	1		
6	0.0001	0.0401	0.5711	1	
>6	0.0001	0.0001	0.0001	0.0038	1

Table 5: Sensitivity, specificity, and predictive value of the score to identify fracture healing in more than 6 months.

Score	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
3	100	5	27
4	98	12	28
5	94	28	31
6	94	50	38
7	80	65	43
8	63	81	53
9	53	90	65
10	43	97	82
11	20	100	94
12	16	100	100

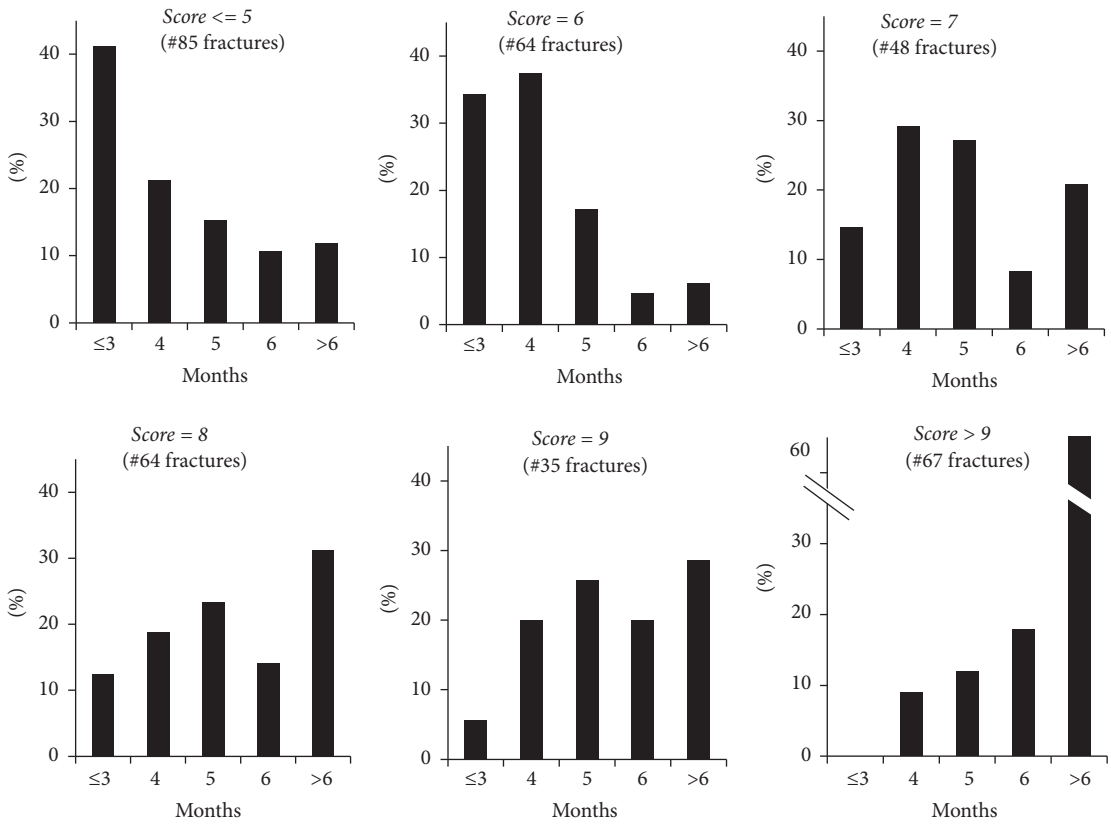

Figure 4: Healing time of fractures grouped by score values.

that might limit the occurrence of nonunions, thus leading to significant cost savings [12, 13].

Disclosure

Level of evidence is prognostic, investigating the effect of FRACTING score on the outcome of a disease, Level I.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] M. E. Müller, P. Koch, S. Nazarian, and J. Schatzker, *The Comprehensive Classification of Fractures of Long Bones*, Springer, Berlin, Germany, 1990.

[2] C. S. Keller, "The principles of the treatment of tibial shaft fractures. A review of 10,146 cases from the literature," *Orthopedics*, vol. 6, no. 8, pp. 993–1006, 1983.

[3] M. Bhandari, G. H. Guyatt, M. F. Swiontkowski et al., "Surgeons' preferences for the operative treatment of fractures of the tibial shaft: An international survey," *The Journal of Bone & Joint Surgery*, vol. 83, no. 11, pp. 1746–1752, 2001.

[4] L. E. Claes, C. A. Heigele, C. Neidlinger-Wilke et al., "Effects of mechanical factors on the fracture healing process," *Clinical Orthopaedics and Related Research*, no. 355, pp. S132–S147, 1998.

[5] R. Marsell and T. A. Einhorn, "The biology of fracture healing," *Injury*, vol. 42, no. 6, pp. 551–555, 2011.

[6] K. D. Hankenson, G. Zimmerman, and R. Marcucio, "Biological perspectives of delayed fracture healing," *Injury*, vol. 45, no. 2, pp. S8–S15, 2014.

[7] D. M. Fisher, J. M.-L. Wong, C. Crowley, and W. S. Khan, "Preclinical and clinical studies on the use of growth factors for bone repair: A systematic review," *Current Stem Cell Research & Therapy*, vol. 8, no. 3, pp. 260–268, 2013.

[8] K. L. Sinclair, R. Mafi, P. Mafi, and W. Khan, "Mesenchymal stem cells and growth factors used for bone formation, fracture healing and non-unions- A systematic review," *Current Stem Cell Research & Therapy*, 2016.

[9] R. K. Aaron and M. E. Bolander, *Physical Regulation of Skeletal Repair. American Academy of Orthopaedic Surgeons Research Symposia*, Chicago, 2005.

[10] W. M. Novicoff, A. Manaswi, M. V. Hogan, S. M. Brubaker, W. M. Mihalko, and K. J. Saleh, "Critical analysis of the evidence for current technologies in bone-healing and repair," *The Journal of Bone & Joint Surgery*, vol. 90, no. 1, pp. 85–91, 2008.

[11] E. Antonova, T. K. Le, R. Burge, and J. Mershon, "Tibia shaft fractures: costly burden of nonunions," *BMC Musculoskeletal Disorders*, vol. 14, article 42, 2013.

[12] L. A. Mills and A. H. R. W. Simpson, "The relative incidence of fracture non-union in the Scottish population (5.17 million): A 5-year epidemiological study," *BMJ Open*, vol. 3, no. 2, Article ID 002276, 2013.

[13] Z. Dahabreh, G. M. Calori, N. K. Kanakaris, V. S. Nikolaou, and P. V. Giannoudis, "A cost analysis of treatment of tibial fracture nonunion by bone grafting or bone morphogenetic protein-7," *International Orthopaedics*, vol. 33, no. 5, pp. 1407–1414, 2009.

[14] M. S. Gaston and A. H. R. W. Simpson, "Inhibition of fracture healing," *Journal of Bone and Joint Surgery Series: B*, vol. 89, no. 12, pp. 1553–1560, 2007.

[15] L. Audigé, D. Griffin, M. Bhandari, J. Kellam, and T. P. Rüedi, "Path analysis of factors for delayed healing and nonunion in 416 operatively treated tibial shaft fractures," *Clinical Orthopaedics and Related Research*, no. 438, pp. 221–232, 2005.

[16] G. M. Calori, W. Albisetti, A. Agus, S. Iori, and L. Tagliabue, "Risk factors contributing to fracture non-unions," in *Injury*, vol. 38, pp. S11–S18, 2007.

[17] M. Bhandari, P. Tornetta III, S. Sprague et al., "Predictors of reoperation following operative management of fractures of the tibial shaft," *Journal of Orthopaedic Trauma*, vol. 17, no. 5, pp. 353–361, 2003.

[18] K. Fong, V. Truong, C. J. Foote et al., "Predictors of nonunion and reoperation in patients with fractures of the tibia: An observational study," *BMC Musculoskeletal Disorders*, vol. 14, article no. 103, 2013.

[19] L. Massari, F. Falez, V. Lorusso et al., "Can a combination of different risk factors be correlated with leg fracture healing time?" *Journal of Orthopaedics and Traumatology*, vol. 14, no. 1, pp. 51–57, 2013.

[20] P. Joveniaux, X. Ohl, A. Harisboure et al., "Distal tibia fractures: Management and complications of 101 cases," *International Orthopaedics*, vol. 34, no. 4, pp. 583–588, 2010.

[21] H. T. Aro, S. Govender, A. D. Patel et al., "Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation," *The Journal of Bone & Joint Surgery*, vol. 93, no. 9, pp. 801–808, 2011.

[22] T. Lyon, W. Scheele, M. Bhandari et al., "Efficacy and safety of recombinant human bone morphogenetic protein-2/calcium phosphate matrix for closed tibial diaphyseal fracture a double-blind randomized controlled phase-ii/iii trial," *The Journal of Bone & Joint Surgery*, vol. 95, no. 23, pp. 2088–2096, 2013.

[23] B. G. Dijkman, J. W. Busse, S. D. Walter, and M. Bhandari, "The impact of clinical data on the evaluation of tibial fracture healing," *Trials*, vol. 12, article no. 237, 2011.

[24] D. B. Whelan, M. Bhandari, D. Stephen et al., "Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation," *The Journal of Trauma and Acute Care Surgery*, vol. 68, no. 3, pp. 629–632, 2010.

[25] S. Govender, C. Csimma, H. K. Genant et al., "Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures a prospective, controlled, randomized study of four hundred and fifty patients," *The Journal of Bone & Joint Surgery A*, vol. 84, no. 12, pp. 2123–2134, 2002.

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Research Article

Patient-Specific Surgical Implants Made of 3D Printed PEEK: Material, Technology, and Scope of Surgical Application

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Additive manufacturing (AM) is rapidly gaining acceptance in the healthcare sector. Three-dimensional (3D) virtual surgical planning, fabrication of anatomical models, and patient-specific implants (PSI) are well-established processes in the surgical fields. Polyetheretherketone (PEEK) has been used, mainly in the reconstructive surgeries as a reliable alternative to other alloplastic materials for the fabrication of PSI. Recently, it has become possible to fabricate PEEK PSI with Fused Filament Fabrication (FFF) technology. 3D printing of PEEK using FFF allows construction of almost any complex design geometry, which cannot be manufactured using other technologies. In this study, we fabricated various PEEK PSI by FFF 3D printer in an effort to check the feasibility of manufacturing PEEK with 3D printing. Based on these preliminary results, PEEK can be successfully used as an appropriate biomaterial to reconstruct the surgical defects in a "biomimetic" design.

1. Introduction

Reconstructive surgeries can be extremely challenging even to the most experienced surgeon especially due to complex anatomy, sensitivity of the involved systems, and uniqueness of each defect [1]. The need to reconstruct the defect in the best possible way along with time minimization for the surgical procedure is of crucial importance to surgeons for improving patient outcomes and well-being [2]. Patient-specific implant (PSI) can be an effective solution in this situation designed to fit precisely in the anatomical defects or malformations. The need to fabricate the PSI has led to many innovations and technological advancements in the field of medicine [3, 4].

The technologies, such as additive manufacturing (AM) also known as rapid prototyping (RP) or three-dimensional (3D) printing, are robustly growing and have positively influenced the biomedical sector over the last decade allowing the surgeons and researchers to utilize them in manufacturing objects [5, 6].

With its introduction in the late 1980s, along with a paradigm shift from the old mass production system of medical implants to customized implant production system, AM has attained a significant place in medical implant manufacturing industry [7]. Several organizations worldwide are manufacturing PSI using various AM technologies with computational tomography (CT) scan data [8]. Recently, the US Food and Drug Administration (FDA) increased their approval of 3D printed implants under the 510k (premarket notification) approval system. This will allow the healthcare providers to use the parts manufactured by AM in routine and for complex surgical procedures [2, 9].

AM works by building a model from the ground up, depositing the material in a layer-by-layer manner using digitally controlled and operated material laying tools [10]. AM is thus fundamentally different from traditional formative

or subtractive manufacturing in that it is the closest to the "bottom up" manufacturing where we can build a structure into its designed shape using a "layer-by-layer" approach. This layer-by-layer manufacturing allows an unprecedented freedom in manufacturing complex, composite, and hybrid structures with precision and control that cannot be made through traditional manufacturing routes [11, 12].

Good initial image capture is imperative for creating accurate 3D printed models. The recent strides in imaging modalities have made it possible to create patient-specific anatomical models with greater precision. In addition, advances in segmentation software have made it increasingly easy to automatically or semiautomatically extract the surface of structures of interest from 3D medical imaging data [13, 14].

With all these advances, AM has emerged as a mainstream manufacturing technology in medicine for the fabrication of anatomical models, surgical implants, surgical guides, external aids, and biomanufacturing [15–25]. Various studies have been published suggesting the use of AM in 3D printing of cells, blood vessels, vascular networks, bones, ears, windpipes, and dental prosthetics including a jaw bone, and in future, even in corneas [26]. Surgeons can now fabricate 3D printed hand-holdable models (called biomodels) for the surgical task that can be used to educate the patient, plan the surgical approach, and act as an intraoperative surgical guide. These 3D printed medical models are being extensively used in orthopedic, cardiac, dental, and craniomaxillofacial surgeries with a potential to optimize patient treatment [27–31].

Currently, there are several technologies for AM like stereolithography (SLA), photopolymer jetting, selective laser sintering (SLS), electron beam melting (EBM), direct metal laser sintering (DMLS), and fused deposition modelling (FDM), which is also known as fused filament fabrication (FFF) [32, 33]. These technologies have emerged as a valuable tool for surgeons in reproducing anatomical objects as 3D physical models and are being used in the reconstruction of PSI [34].

Various alloplastic materials, such as metals, ceramics, polymers, and composites, are fabricated by AM technologies and are used in reconstructive and orthopedic surgeries. Due to their abundant availability, there are no concerns about the donor site morbidity, which is a huge disadvantage for autologous grafts [35].

Metallic implants including gold, tantalum, stainless steel, shape memory alloy, titanium alloy, and cobalt chromium alloy have been widely used in the hospitals either as permanent prostheses such as knee and hip prosthesis, cranial prosthesis, and dental implants or as temporary implants such as plates, pins, screws, and rods for the fixation of bone fractures. These implants have favorable mechanical strength and excellent friction-resistance and are the most preferred alloplastic material in AM for the manufacturing of orthopedic implants [36, 37]. However, their high strength and elastic modulus do not match to the normal human bone tissues and thus can cause a stress shielding effect leading to prosthetic loosening. In addition, the strong X-ray absorption of metals with respect to the surrounding tissues usually results in streak artifacts in the CT scan images. Further, as many metals are magnetic resonance imaging (MRI) incompatible, the possibility of examining the patient with MRI is limited. The long-term presence of metals *in vivo* can also trigger hypersensitivity reaction and initiate osteolysis [38]. These limitations also led to the exploration of ceramics as an alternative biomaterial.

Among ceramics, metallic oxides, calcium phosphate, and glass ceramics are commonly used. These materials exhibit favorable toxicity profile, good biocompatibility, and bioactivity. However, their low fracture toughness and ductility along with high modulus of elasticity and brittleness make them unacceptable for load-bearing applications [39].

Due to an array of limitations observed with metallic and ceramic biomaterials, more recently the use of polymers as a viable alternative is being explored. A large number of polymers, such as ultrahigh molecular weight polyethylene (UHMWPE), polymethyl methacrylate (PMMA), polylactide (PLA), polyglycolide (PGA), and polyhydroxybutyrate (PHB), are also widely used in various biomedical applications. However, only a limited number of polymers have been used for bone replacement purposes because they tend to be too flexible, and too weak for orthopedic and load-bearing implants applications [40].

Among the various alloplastic materials, polyetheretherketone (PEEK) has emerged as an attractive option for the PSI. PEEK is a semicrystalline linear polycyclic aromatic thermoplastic belonging to a family of linear aromatic polymers containing ether and ketone linkages [38].

PEEK was first developed by a group of English scientists in 1978 [41]. In the 1980s, PEEK was used as aircraft and turbine blades and, by the late 1990s, PEEK was used to replace metal implant components, especially in orthopedic and trauma specialities. PEEK has since been used in a wide range of applications owing to its excellent combination of high-temperature performance, chemical resistance, fatigue resistance, lightweight, high yield strength, stiffness, and durability [38].

Although manufacturing and 3D printing of PEEK polymer have been widely investigated in different industries, its use in the medical field is challenging due to its physical properties [42, 43].

In this article, we present the preliminary results and technical aspects on the material extrusion (FFF, 3D printing) based fabrication process of PEEK parts with a focus on PSI for surgical applications.

2. Materials and Methods

2.1. PEEK Filament. For the printing process, Apium PEEK 450 Natural 1.75 mm filament produced from medical grade PEEK granules was used (Supplier: Apium Additive Technologies GmbH, Karlsruhe, Germany; Manufacturer: Evonik Industries AG, Germany). This filament is a semicrystalline polymer with density of 1.30 g/cm^3 and tensile strength of 97 MPa (Figure 1). With excellent chemical resistance, it is a perfect combination of strength, toughness, and stiffness. Additionally, it is very tolerant to gamma radiation, is extremely stable against hydrolysis, and is suitable for sterilization.

Table 1: Performance specifications of the FFF 3D printer.

Parameter	Performance specifications
Print bed volume (w, d, h)	155 × 155 × 155 mm
Print volume (w, d, h)	140 × 135 × 148 mm
x/y resolutions	Product resolution: 0.5 mm, machine resolution: 0.0125 mm
z resolution	Product resolution: 0.1 mm, machine resolution: 0.05 mm
Reproducibility	0.1 mm
Minimum layer thickness	0.1 mm
Maximum layer thickness	0.3 mm

Figure 1: Medical grade PEEK filament. https://apiumtec.com/de/new-peek-printing.

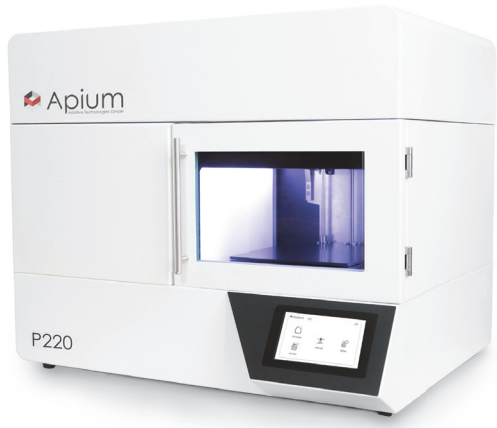

Figure 2: PEEK FFF 3D printer (Model P220).

2.2. PEEK FFF 3D Printer. The FFF 3D printer used in our study was a prototype of the Apium P220 (Figure 2), based on the FFF technology (Apium Additive Technologies GmbH, Karlsruhe, Germany). The printer uses Apium Controlling Software (ACS) with 65 adjustable parameters utilizing Standard Tessellation Language (STL) format files.

The performance and technical specifications of the FFF 3D printer are mentioned in Tables 1 and 2.

Table 2: Technical specifications of the FFF 3D printer.

Parameter	Technical specifications
Number of extruders	1
Nozzle diameter	0.4 mm
Filament diameter	1.75 mm
Print head temperature	Up to 520°C
Print bed temperature	Up to 160°C
Size (w, d, h)	590 × 620 × 680 mm
Slicing software compatible	slic3r and Simplify3D

2.3. FFF 3D Printing Process. FFF starts with a 3D computer-aided design (CAD) model of the implant, exported as an STL file from a CAD modelling software program. The STL file is sliced by the computer slicing software into horizontal layers that are as high as the layers in the 3D printer machine. A rod-shaped filament is supplied to the machine through a feeding tube. The molten thermoplastic material is extruded through one nozzle (diameter 0.4 mm, computer controlled) and deposited layer-by-layer following a specific laydown pattern. The nozzle follows a raster pattern in the X, Y plane and forms a layer. Later, a layer deposition is finished, the working bed in the Z direction is lowered, and the new layer is extruded. With complex anatomical geometries, support structures are incorporated and the 3D object including support structures is printed layer-by-layer fusing the layers together. A special fixative (DimaFix, DIMA 3D, Valladolid, Spain) spray was applied to the "cold" print bed for adhesion before printing. The entire chamber was enclosed so that recommended bed temperature of about 100°C and print temperature of about 400°C can be achieved.

2.4. Digital Data Acquisition and Preparation. For the anatomical data modelling, the representative models of the patient's anatomical data were constructed based on radiological raw data of the patient obtained in a Digital Imaging and Communications in Medicine (DICOM) format from CT scan data. In DICOM format, the data was presented in a series of slices through the patient's anatomy, with slice thickness between 0.3 and 0.6 mm depending on the anatomical region. A medical modelling software program (Mimics; Materialise, Leuven, Belgium) was used to compile the DICOM data into axial, sagittal, and coronal planes. Following this, threshold selection was done, in which the inbuilt

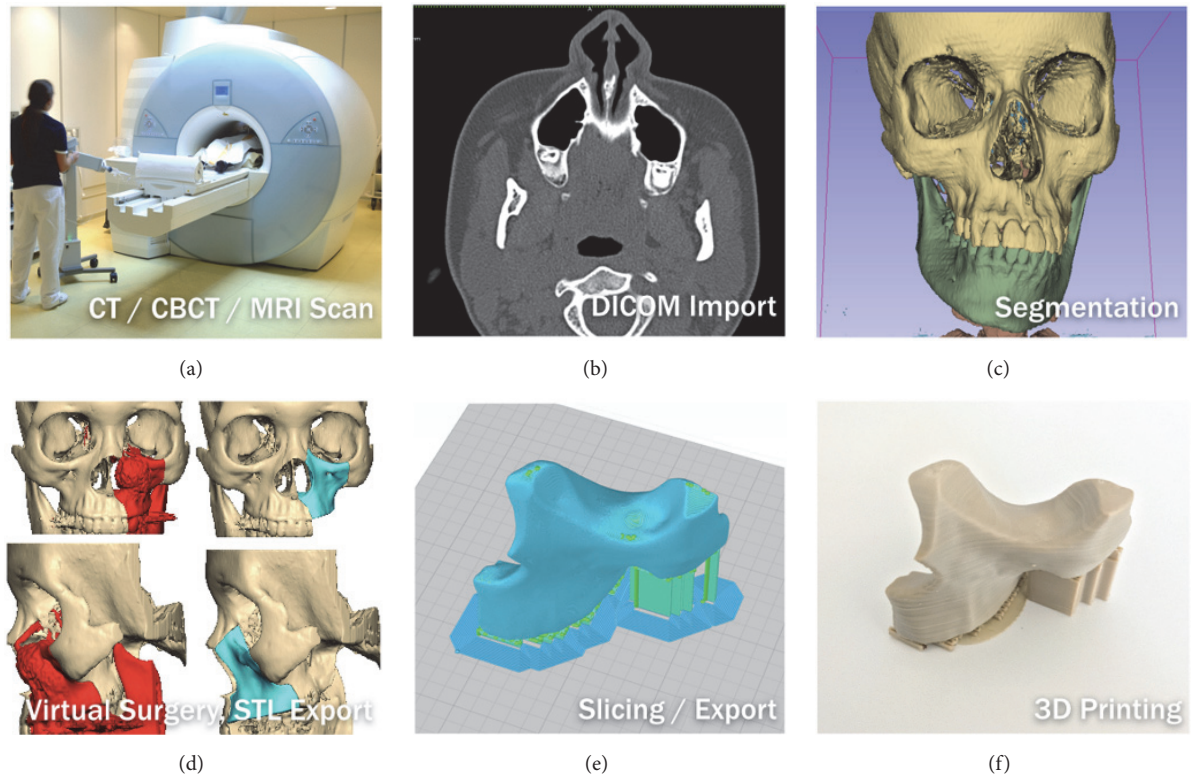

Figure 3: Workflow to generate a 3D model. *Thieringer FM*.

Figure 4: 3D printed PEEK osteosynthesis plates. *Thieringer FM et al. AMPA 2017*.

greyscales for bone are selected to mark a particular anatomical tissue type. Using segmentation, a virtual 3D model of the anatomical region was thus created. The 3D virtual model created in Mimics was exported to 3-Matic (Materialise, Leuven, Belgium) for further processing, design, and construction of PSI. The final data sets were converted and exported as an STL file and sent to the 3D printer, which finally fabricated the PSI by FFF. The overall sequential process is displayed in Figure 3.

3. Results and Discussion

3.1. Results. During this preliminary evaluation, five different PEEK structures were fabricated as follows.

(i) Osteosynthesis plate (Figure 4)

(ii) Cranioplasty PSI for repair of defects in the cranial vault (Figure 5)

(iii) Lightweight midface-zygomatic bone PSI with support structures for immediate replacement (Figure 6)

(iv) Small fragment PSI osteosynthesis plates (Figure 7)

(v) Prosthetic implant for scaphoid bone replacement (Figure 8)

The fabrication results showed that the 3D printed PEEK PSI were of a smooth finish without any irregularities. No black-specks formation nor discoloration (improper crystallization) was detected in the test parts. All of the 3D printed parts passed a certified sterilization test without any deformation. Thus, these preliminary tests confirm the possibility of fabricating 3D printed PEEK in the desired way (extrusion through nozzle) by FFF.

4. Discussion

Over the past few years, PEEK has attracted a great deal of interest from material scientists and orthopedists. It is suitable for load-bearing implants because of its favorable biomechanical properties, radiolucency, MRI compatibility, and chemical inertness [44, 45]. PEEK has primarily been used in spine surgery for interbody fusion cages. PEEK has also been used in combination with other materials such as reinforced carbon fiber (CF/PEEK), for fracture fixation and prosthesis (e.g., artificial hip joints) [46–49]. Various studies conducted

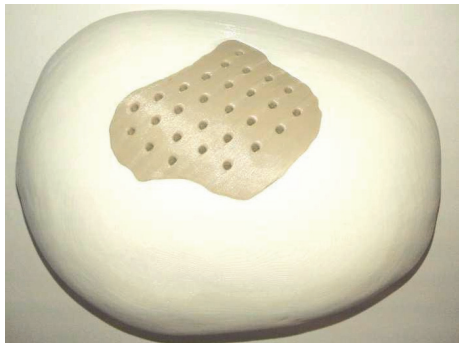

Figure 5: 3D printed PEEK cranioplasty PSI for repair of defects in the cranial vault. *Thieringer FM et al. AMPA 2017*.

Figure 6: Lightweight midface-zygomatic bone PSI with support structures for immediate replacement. *Thieringer FM et al. AMPA 2017*.

with PEEK in reconstruction of complex maxillofacial defects and calvarial defects have also shown excellent postoperative esthetic and functional results without any complications [41, 50–52]. Hence, PEEK is a suitable biomaterial and an appropriate alloplastic material for reconstructive and orthopedic surgeries.

Until now, PEEK medical implants can only be manufactured by traditional subtractive manufacturing methods, with the use of Computer Numerical Controlled (CNC) machine. This technique usually starts with a blank block of PEEK material that is slowly shaped into the final part. The computer controls the tools needed for fabrication of the part by controlling the lathes, mills routers, and grinders used in the process. Furthermore, additional postprocessing work needs to be done after fabrication. This technique is time consuming resulting in substantial waste generation and is far more expensive than AM [53]. Additionally, as mentioned earlier the use of PEEK polymer in 3D printing is challenging due to its physical properties [42, 43].

Technological advances have recently provided techniques such as 3D printing of PEEK using FFF, which can create various CAD forms. FFF, being a low-cost technique with a short start-up time, provides a major advantage over other manufacturing techniques. In this technique, the PEEK polymer material in the solid state is thermally brought to a flow regime and then solidified through a thermal gradient. As rheology and heat transfer characteristics are two important properties of FFF thermoplastic materials, the interplay

Figure 7: PSI small fragment osteosynthesis plates. *With permission of Apium GmbH*.

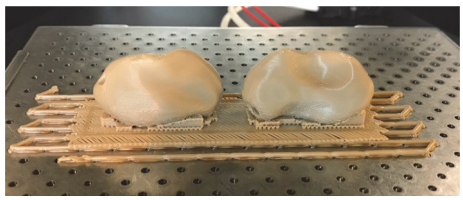

Figure 8: Prosthetic implant for scaphoid bone replacement (green body), patent pending (EP15195745.1 PCT).

between cooling rate and material flow behavior needs to be fully moderated in this technique in order to create parts with an appreciable high dimensional accuracy [54].

With the introduction of CAD and computer-aided manufacturing (CAM) techniques in surgery, it is now possible to fabricate implants in various forms and designs with biocompatible materials. The 3D printed PSI are used in a wide range of applications in the medical field. Our research focused on the surgical fields in which PEEK is already being used and fabricated either by milling or by injection molding techniques. However, as these manufacturing techniques are expensive and material-consuming, with the introduction of FFF 3D PEEK printers, fabrication of PSI is conceivable, providing substantial benefits to the surgical fields.

Osseous integration of PEEK depends on the surface composition, surface energy, surface roughness, and topography [55]. With the standard production techniques, the surface structure of PEEK is inert and smooth [38]. However, with FFF 3D printing, PEEK surface properties can be modified and fabricated to yield either rough or smooth surfaces.

Osteosynthesis materials made out of PEEK are already being used in hand and trauma surgeries especially for treating distal radius fractures. With FFF, 3D printed PEEK patient-specific plates (Figure 7) can be produced in a short period at a very low cost. This plays an important role in general trauma and orthopedic surgeries as 3D printed PEEK PSI can be readily available for use within 24 hours after admission in the hospital. As a proof of concept, we also test printed a standard osteosynthesis plate (Figure 4) and a scaphoid bone replacement prosthesis (Figure 8).

Until now, the reconstructive surgeries for congenital and acquired defects of the skull and facial regions are reconstructed with standard manufactured PEEK implants [56]. However, with FFF, 3D printing of these PSI is now

possible (Figures 5 and 6) and defects can be easily treated in a short period of time with this low-cost and in-house printing facility at the hospitals [57]. Our results, thus, suggest that FFF has the ability to manufacture complex implant structures with unlimited geometries that could not have been possible with traditional milling techniques.

Conversely, manufacturing PEEK by FFF itself is quite complex and various parameters interactions have to be considered. Formation of black-specks can potentially develop in the printed parts or at the regions of the printer where the melt exits, such as the nozzle as well as areas around the nozzle. These deformations suggest uncontrollable thermodynamically driven changes within the melt. Possible sources of black-specks in FFF 3D printed PEEK are (1) degradation of the molten filament at the joint of the heat-break and nozzle, (2) degradation of the melted filament inside the nozzle shaft, (3) poorly designed nozzle tip-area such that the melt collects at the exposed surface and then degrades, (4) irregular thermal loading of the melt by the heating elements, (5) melt degradation due to presence of foreign particles interfacing with the melt, (6) prolonged residency of a melt-batch in the nozzle shaft/barrel, and (7) too high processing temperature. Therefore, one of the critical factors for 3D printing of PEEK by FFF is continuous maintenance of high temperature for material extrusion.

With the introduction of an all metal hot-end extruder in the printer used in our study, it is possible to attain uniform temperatures up to 540°C, and the enclosed chamber provides an efficient heat management for continuous printing. The bed temperature and the print temperature of the printer are maintained high enough to provide a good thermal control over the entire build chamber leading to good layer bonding and thereby prevents "specking" in PEEK parts. This was evident from the various structures created during the present study where such black-specks were not observed [53].

The preliminary findings from our study suggest that anatomically complex PSI can be printed using an FFF 3D printer. The authors strongly believe that FFF has a huge potential and can provide various advantages such as less wastage of material, cost-effectiveness, low investment on machine, easy operator training, faster in-house implant production, and a better personalized patient care approach. All these factors have a potential effect in reducing the financial burden on the overall healthcare sector.

4.1. Study Limitation. Along with a requirement of support structures in complex geometries, another important aspect that needs to be addressed is the effect of anisotropy on FFF 3D printed parts. In FFF, a mechanical adhesion (not chemical) is created within the layers of the polymer and, thus, the printed objects have different mechanical properties based on the direction of mechanical stress applied on them. This means that along a particular line deposition pattern, the part will be stronger in the direction of the deposited line and relatively less strong along the axes that are primarily composed of interfiber bonding regions, namely, the two spatial axes orthogonal to the line axis.

As in many spinal and craniomaxillofacial applications, the mechanical stresses are essentially directed along a specific axis and an anisotropic response from the implant can be advantageous, and future experiments to address this behavior are needed. Further, the part testing needs to be done according to International Organization for Standardization (ISO)/American Society for Testing and Materials (ASTM) standards to make FFF 3D printed PEEK usability beyond PSI.

5. Conclusion

Personalized medicine is poised to revolutionize the modern practice of medicine where "one size does not fit all" and implants must be tailored to individual patient's needs, which are the ultimate goal. The refinement of imaging technologies, coupled with the capabilities to fabricate PSI, has given rise to a proliferation of alternatives to traditional off-the-shelf implants. With the availability of inexpensive compact desktop 3D printers, the surgeons in near future can manufacture medically certified 3D PSI in their own hospitals. This would have a major advantage for surgical planning, thereby reducing an enormous amount of time compared with the off-site implant production by third-party providers leading to a more cost-effective healthcare management. Although few regulations specifically targeting AM for medical devices currently exist, regulation by the FDA and other bodies is expected to increase in the coming years making the approval and manufacturing of new device classes at companies or at hospitals a lengthy process.

From the requirement of clinical trial data, pre- and postmarketing approvals, vigilance reporting timelines, data transparency, and unique device identification (UDI), to name a few, various regulatory measures will be needed to be adhered to, so as to make the medical device available to the patients.

Though this article presents only a small amount of the research done in the project to fabricate 3D printed PEEK PSI using FFF, it indeed opens up a huge scope for innovation and future development in the surgical applications.

6. Further Steps

Future development is planned to improve the mechanical properties, so some more tests with appropriate or additional knowledge on part orientation and equipment parameters will be done.

Within the framework of the cooperation of the institutions listed above, a medical version based on the P220 of this PEEK FFF printer (Figure 9), which has been introduced to the industrial market for some time, is currently undergoing the certification process for medical applications. The test specimens required for the certification were prepared, evaluated, and passed through other test methods (e.g., cleaning, sterilization).

Additionally, the integration of 3D printing is additionally examined from the medico-legal point of view in the clinical environment.

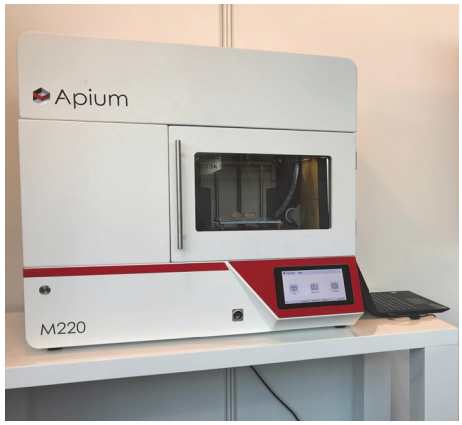

Figure 9: Medical version of the PEEK FFF printer (Model M220).

Conflicts of Interest

The authors received no specific grant from any funding agency in the public commercial or nonprofit sectors.

Authors' Contributions

Philipp Honigmann and Neha Sharma have equal contribution.

References

[1] J. Parthasarathy, "3D modeling, custom implants and its future perspectives in craniofacial surgery," *Annals of Maxillofacial Surgery*, vol. 4, no. 1, pp. 9–18, 2014.

[2] M. Mohammed, I. Gibson, S. K. Malyala, and A. P. Fitzpatrick, "Customised design and development of patient specific 3D printed whole mandible implant," in *SFF Symp: Proceedings of the 27th Annual International Solid Freeform Fabrication Symposium*, pp. 1708–1717, Laboratory for Freeform Fabrication and University of Texas, Austin, Tex, USA, 2016.

[3] F. Rengier, A. Mehndiratta, H. von Tengg-Kobligk et al., "3D printing based on imaging data: review of medical applications," *International Journal for Computer Assisted Radiology and Surgery*, vol. 5, no. 4, pp. 335–341, 2010.

[4] M. P. Chae, W. M. Rozen, P. G. McMenamin, M. W. Findlay, R. T. Spychal, and D. J. Hunter-Smith, "Emerging applications of bedside 3d printing in plastic surgery," *Frontiers in Surgery*, vol. 2, p. 25, 2015.

[5] K. C. Wong, "3D-printed patient-specific applications in orthopedics," *Orthopedic Research and Reviews*, vol. 8, pp. 57–66, 2016.

[6] M. Attaran, "The rise of 3-D printing: The advantages of additive manufacturing over traditional manufacturing," *Business Horizons*, vol. 60, no. 5, pp. 677–688, 2017.

[7] M. C. H. Chua and C.-K. Chui, "Optimization of Patient-Specific Design of Medical Implants for Manufacturing," in *Proceedings of the 13th Global Conference on Sustainable Manufacturing, GCSM 2015*, pp. 402–406, Viet Nam, September 2015.

[8] M. Navarro, A. Michiardi, O. Castaño, and J. A. Planell, "Biomaterials in orthopaedics," *Journal of the Royal Society Interface*, vol. 5, no. 27, pp. 1137–1158, 2008.

[9] FDA, 3D Printing of Medical Devices. 2017, Available from: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/3DPrintingofMedicalDevices/default.htm.

[10] M. McGurk, A. A. Amis, P. Potamianos, and N. M. Goodger, "Rapid prototyping techniques for anatomical modelling in medicine," *Annals of the Royal College of Surgeons of England*, vol. 79, pp. 169–174, 1997.

[11] A. Bandyopadhyay and S. Bose, *Additive Manufacturing*, CRC Press, Florida, Fla, USA, 2015.

[12] I. Gibson, D. W. Rosen, and B. Stucker, *Additive Manufacturing Technologies: Rapid Prototyping to Direct Digital Manufacturing*, Springer, Berlin, German, 2010.

[13] P. A. Lioufas, M. R. Quayle, J. C. Leong, and P. G. McMenamin, "3D printed models of cleft palate pathology for surgical education," *Plastic and Reconstructive Surgery - Global Open*, vol. 4, no. 9, p. e1029, 2016.

[14] E. Vezzetti, D. Speranza, F. Marcolin, and G. Fracastoro, "Diagnosing cleft lip pathology in 3D ultrasound: A landmarking-based approach," *Image Analysis and Stereology*, vol. 35, no. 1, pp. 53–65, 2015.

[15] M. Javaid and A. Haleem, "Additive manufacturing applications in medical cases: a literature based review," *Alexandria Journal of Medicine*, 2017.

[16] S. Mazzoni, A. Bianchi, G. Schiariti, G. Badiali, and C. Marchetti, "Computer-aided design and computer-aided manufacturing cutting guides and customized titanium plates are useful in upper maxilla waferless repositioning," *Journal of Oral and Maxillofacial Surgery*, vol. 73, no. 4, pp. 701–707, 2015.

[17] R. Schwarzkopf, M. Brodsky, G. A. Garcia, and A. H. Gomoll, "Surgical and Functional Outcomes in Patients Undergoing Total Knee Replacement With Patient-Specific Implants Compared With "Off-the-Shelf" Implants," *Orthopaedic Journal of Sports Medicine*, vol. 3, no. 7, 2015.

[18] R. S. Gil, A. M. Roig, C. A. Obispo, A. Morla, C. M. Pagès, and J. L. Perez, "Surgical planning and microvascular reconstruction of the mandible with a fibular flap using computer-aided design, rapid prototype modelling, and precontoured titanium reconstruction plates: A prospective study," *British Journal of Oral and Maxillofacial Surgery*, vol. 53, no. 1, pp. 49–53, 2015.

[19] C. Wilasrusmee, J. Suvikrom, J. Suthakorn et al., "Three-dimensional aortic aneurysm model and endovascular repair: An educational tool for surgical trainees," *International Journal of Angiology*, vol. 17, no. 3, pp. 129–133, 2008.

[20] S. Han, Z. Wang, Q. Hu, and W. Han, "Combined use of an anterolateral thigh flap and rapid prototype modeling to reconstruct maxillary oncologic resections and midface defects," *The Journal of Craniofacial Surgery*, vol. 25, no. 4, pp. 1147–1149, 2014.

[21] M. Rana, C. H. Chui, M. Wagner, R. Zimmerer, M. Rana, and N. Gellrich, "Increasing the accuracy of orbital reconstruction with selective laser-melted patient-specific implants combined with intraoperative navigation," *Journal of Oral and Maxillofacial Surgery*, vol. 73, no. 6, pp. 1113–1118, 2015.

[22] F. P. W. Melchelsab, M. A. N. Domingosc, T. J. Kleina, J. Maldaab, P. J. Bartoloc, and D. W. Hutmacher, "Additive manufacturing of tissues and organs," *Progress in Polymer Science*, vol. 37, no. 8, pp. 1079–1104, 2012.

[23] J. Tuomi, K.-S. Paloheimo, J. Vehviläinen et al., "A novel classification and online platform for planning and documentation of medical applications of additive manufacturing," *Surgical Innovation*, vol. 21, no. 6, pp. 553–559, 2014.

[24] P. Honigmann, F. Thieringer, R. Steiger, M. Haefeli, R. Schumacher, and J. Henning, "A Simple 3-Dimensional Printed Aid

for a Corrective Palmar Opening Wedge Osteotomy of the Distal Radius," *Journal of Hand Surgery*, vol. 41, no. 3, pp. 464–469, 2016.

[25] M. Haefeli, D. J. Schaefer, R. Schumacher, M. Müller-Gerbl, and P. Honigmann, "Titanium template for scaphoid reconstruction," *Journal of Hand Surgery (European Volume)*, vol. 40, no. 5, pp. 526–533, 2015.

[26] C. Schubert, M. C. Van Langeveld, and L. A. Donoso, "Innovations in 3D printing: a 3D overview from optics to organs," *British Journal of Ophthalmology*, vol. 98, no. 2, pp. 159–161, 2014.

[27] R. Kaye, T. Goldstein, D. Zeltsman, D. A. Grande, and L. P. Smith, "Three dimensional printing: A review on the utility within medicine and otolaryngology," *International Journal of Pediatric Otorhinolaryngology*, vol. 89, pp. 145–148, 2016.

[28] L. C. Hieu, N. Zlatov, J. Vander Sloten et al., "Medical rapid prototyping applications and methods," *Assembly Automation*, vol. 25, no. 4, pp. 284–292, 2005.

[29] B. Sanghera, S. Naique, Y. Papaharilaou, and A. Amis, "Preliminary study of rapid prototype medical models," *Rapid Prototyping Journal*, vol. 7, no. 5, pp. 275–284, 2001.

[30] M. Martorelli, S. Maietta, A. Gloria, R. De Santis, E. Pei, and A. Lanzotti, "Design and Analysis of 3D Customized Models of a Human Mandible," in *Proceedings of the 2nd CIRP Conference on Biomanufacturing, 2016*, pp. 199–202, UK, July 2015.

[31] J. Winder, R. S. Cooke, J. Gray, T. Fannin, and T. Fegan, "Medical rapid prototyping and 3D CT in the manufacture of custom made cranial titanium plates," *Journal of Medical Engineering & Technology*, vol. 23, no. 1, pp. 26–28, 1999.

[32] D. Hoang, D. Perrault, M. Stevanovic, and A. Ghiassi, "Surgical applications of three- dimensional printing: a review of the current literature how to get started," *Annals of Translational Medicine*, vol. 4, no. 23, p. 456, 2016.

[33] P. M. Dickens, R. Stangroom, M. Greul et al., "Conversion of RP models to investment castings," *Rapid Prototyping Journal*, vol. 1, no. 4, pp. 4–11, 1995.

[34] I. Zein, D. W. Hutmacher, K. C. Tan, and S. H. Teoh, "Fused deposition modeling of novel scaffold architectures for tissue engineering applications," *Biomaterials*, vol. 23, no. 4, pp. 1169–1185, 2002.

[35] D. Rohner, D. W. Hutmacher, T. K. Cheng, M. Oberholzer, and B. Hammer, "In vivo efficacy of bone-marrow-coated polycaprolactone scaffolds for the reconstruction of orbital defects in the pig," *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, vol. 66, no. 2, pp. 574–580, 2003.

[36] R. Adell, U. Lekholm, B. Rockler, and P. I. Branemark, "A 15-year study of osseointegrated implants in the treatment of the edentulous jaw," *International Journal of Oral Surgery*, vol. 10, no. 6, pp. 387–416, 1981.

[37] A. L. Jardini, M. A. Larosa, R. M. Filho et al., "Cranial reconstruction: 3D biomodel and custom-built implant created using additive manufacturing," *Journal of Cranio-Maxillo-Facial Surgery*, vol. 42, no. 8, pp. 1877–1884, 2014.

[38] R. Ma and T. Tang, "Current strategies to improve the bioactivity of PEEK," *International Journal of Molecular Sciences*, vol. 15, no. 4, pp. 5426–5445, 2014.

[39] T. Kokubo, H. Kim, and M. Kawashita, "Novel bioactive materials with different mechanical properties," *Biomaterials*, vol. 24, no. 13, pp. 2161–2175, 2003.

[40] S. Ramakrishna, J. Mayer, E. Wintermantel, and K. W. Leong, "Biomedical applications of polymer-composite materials: a review," *Composites Science and Technology*, vol. 61, no. 9, pp. 1189–1224, 2001.

[41] L. Eschbach, "Nonresorbable polymers in bone surgery," *Injury*, vol. 31, supplement 4, pp. D22–D27, 2000.

[42] M. Vaezi and S. Yang, "Extrusion-based additive manufacturing of PEEK for biomedical applications," *Virtual and Physical Prototyping*, vol. 10, no. 3, pp. 123–135, 2015.

[43] J. W. Stansbury and M. J. Idacavage, "3D printing with polymers: Challenges among expanding options and opportunities," *Dental Materials*, vol. 32, no. 1, pp. 54–64, 2016.

[44] S. M. Kurtz and J. N. Devine, "PEEK biomaterials in trauma, orthopedic, and spinal implants," *Biomaterials*, vol. 28, no. 32, pp. 4845–4869, 2007.

[45] S. Najeeb, Z. Khurshid, J. P. Matinlinna, F. Siddiqui, M. Z. Nassani, and K. Baroudi, "Nanomodified Peek Dental Implants: Bioactive Composites and Surface Modification - A Review," *International Journal of Dentistry*, vol. 2015, Article ID 381759, 2015.

[46] PEEK Film: Protecting batteries in heart pacemakers, *Kunststoffe International*, vol. 2, pp. 61, 2011.

[47] T. Jiya, T. Smit, J. Deddens, and M. Mullender, "Posterior lumbar interbody fusion using nonresorbable poly-ether-ether- ketone versus resorbable poly-l-lactide-co-d,l-lactide fusion devices: A prospective, randomized study to assess fusion and clinical outcome," *The Spine Journal*, vol. 34, no. 3, pp. 233–237, 2009.

[48] M. Jarman-Smith, "Evolving uses for implantable PEEK and PEEK based compounds," *Medical Device Technology*, vol. 19, no. 6, pp. 12–15, 2008.

[49] D. Williams, "Polyetheretherketone for long-term implantable devices," *Medical Device Technology*, vol. 19, pp. 10-11, 2008.

[50] P. Scolozzi, A. Martinez, and B. Jaques, "Complex orbito-fronto-temporal reconstruction using computer-designed PEEK implant," *The Journal of Craniofacial Surgery*, vol. 18, no. 1, pp. 224–228, 2007.

[51] M. M. Hanasono, N. Goel, and F. DeMonte, "Calvarial reconstruction with polyetheretherketone implants," *Annals of Plastic Surgery*, vol. 62, no. 6, pp. 653–655, 2009.

[52] M. M. Kim, K. D. O. Boahene, and P. J. Byrne, "Use of customized polyetheretherketone (PEEK) implants in the reconstruction of complex maxillofacial defects," *JAMA Facial Plastic Surgery*, vol. 11, no. 1, pp. 53–57, 2009.

[53] F. M. Thieringer, N. Sharma, A. Mootien, R. Schumacher, and P. Honigmann, "Patient specific implants from a 3D printer – an innovative manufacturing process for custom PEEK implants in cranio-maxillofacial surgery," *Industrializing Additive Manufacturing - Proceedings of Additive Manufacturing in Products and Applications*, pp. 308–315, 2017.

[54] L. Novakova-Marcincinova and I. Kuric, "Basic and advanced materials for fused deposition modeling rapid prototyping technology," *Journal of Manufacturing and Industrial Engineering*, vol. 11, no. 1, 2012.

[55] Z. Schwartz and B. D. Boyan, "Underlying mechanisms at the bone-biomaterial interface," *Journal of Cellular Biochemistry*, vol. 56, no. 3, pp. 340–347, 1994.

[56] C. Relvas, J. Reis, J. A. Potes, F. M. Fonseca, and J. A. Simões, "Rapid manufacturing system of orthopedic implants," *Revista Brasileira De Ortopedia*, vol. 44, no. 3, pp. 260–265, 2015.

[57] B. Msallem, F. Beiglboeck, P. Honigmann, C. Jaquiéry, and F. Thieringer, "Craniofacial reconstruction by a cost-efficient template-based process using 3d printing," *Plastic and Reconstructive Surgery - Global Open*, vol. 5, no. 11, p. e1582, 2017.

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Research Article

Early Experience with Reduction of Unstable Pelvic Fracture Using a Computer-Aided Reduction Frame

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Purpose. The optimal closed reduction technique for unstable pelvic fractures remains controversial. The purpose of this study is to verify the effectiveness and report early experiences with the reduction of unstable pelvic fractures using a computer-aided pelvic reduction frame. *Methods*. From January 2015 to August 2016, a total of 10 patients with unilateral unstable pelvic fractures were included in this study. The surgical reduction procedure was based on the protocol of the computer-aided pelvic reduction frame that we proposed in a previous work. The quality of the reductions achieved using this system was evaluated with residual translational and rotational differences between the actual and virtual reduction positions of pelvis. The duration of the operation was recorded for quality control. *Results.* The mean times required to set up the frame, to complete the virtual surgery simulation, and to reduce the unstable pelvic fractures were 10.3, 20.9, and 7.5 min, respectively. The maximum residual translational and rotational displacements were less than 6.5 mm and 3.71 degrees, respectively. *Conclusions*. This computer-aided reduction frame can be a useful tool for the speedy and accurate reduction of unstable pelvic fractures. Further clinical studies should be conducted with larger patient samples to verify its safety and efficacy.

1. Introduction

Pelvic fractures, especially unstable pelvic fractures, are associated with massive hemorrhage and injury to important organs, and they can cause significant morbidity and mortality. Early reduction and fixation have the advantages of better pain relief, early mobilization, easier nursing care, and improved bleeding control [1–3], and they have come to be associated with lower morbidity, shorter ICU stays, fewer transfusions, and lower rates of complications such as in-hospital infection, thromboembolism, and pressure ulcers [1]. They may also be capable of preventing the long-term complications of posterior pelvic ring fracture, such as malunion, which eventually lead to differences in the lengths of the lower extremities and the resulting lower back pain.

However, the optimal early reduction technique for unstable pelvic fractures remains unclear. There are currently two types of reduction techniques, mainly classified as open and closed. Because extensive open surgery for pelvic fracture is usually associated with increased bleeding, increased risk of neurovascular injury, and the potential of a second hit to the hemodynamically unstable trauma patients, there has been a growing trend toward using different types of external fixators to reduce the unstable pelvic fracture and displacement through various types of lower extremity traction and intraoperative temporary stabilization, followed by definitive fixation of percutaneous iliosacral screws with or without additional anterior fixations. This is called a closed procedure.

The classic external fixator for the unstable pelvic fracture reduction is called the pelvic C-clamp. It was designed in the 1990s [4], and it is associated with several major intraoperative complications related to the superior gluteal artery and nerve. Since then, several types of external fixators have been designed to reduce the unstable pelvic fractures by

manipulating the anterior pelvic ring. Bellabarba et al. placed two Schanz screws to the anterior inferior iliac spine (AIIS) and used a single external fixation bar to secure them for use as levers to reduce the external rotation of the affected hemipelvis in lateral compression (LC) pelvic fractures [5]. This technique has been revised and verified in the following clinical and biomechanical studies [6–8]. Sellei et al. designed a special X-frame to try to provide more posterior pelvic compression for reduction manipulation [9]. Queipo-De-Llano et al. used a pretensed curved bar as a means to reduce unstable pelvic fractures by applying a simultaneous compression on the posterior and anterior rings [10].

With these tools, the reduction position of affected hemipelvis had to be maintained manually until definitive fixation was complete. To overcome this problem, Matta and Yerasimides [11] and Lefaivre et al. [12, 13] each designed another type of pelvic reduction frames to connect the intact and injured hemipelvis to the operating table to perform the reduction manipulations in a stepwise manner. Inspired by the configuration of the Starr pelvic reduction frame designed by Lefaivre et al. [12, 13], we developed a computer-aided reduction mechanism for unstable pelvic fractures. The hardware of the entire system is based on three remote center of motion (RCM) mechanisms articulated with each other, and the software incorporates the 3-dimensional (3D) reconstruction pelvic model based on the intraoperative CT data, matrix algorithms procedure, and several commercial computer-aided design (CAD) software packages, which are used to perform the virtual reduction operations. In our previous study [14], the precision of the entire system was established and verified, including the rotational and translational precision for different degrees of freedom. From January 2015 to August 2016, we used this system to treat 10 patients with unstable pelvic fractures. Here, we report the effectiveness and early experience with reduction of the unstable pelvic fractures using this computer-aided pelvic reduction frame.

As with the Starr pelvic reduction frame [12, 13], all the reduction manipulations of the displaced hemipelvis, including translational and rotational ones, are performed with the reference position of its intact counterpart, which has to be held securely to the operating table by the external frame. This can ensure that the reduction position by the reduction frame is equal to its simulated position calculated using CAD software. Thus, the indication of this system is limited to unilateral unstable pelvic fractures.

2. Materials and Methods

2.1. Patient Characteristics. The study was approved by the local ethics and institutional review committee and registered on the ISRCTN registry (registration number: ISRCTN38873803). Informed consent was obtained from all participants included in the study. From January 2015 to August 2016, a total of 10 patients admitted in our institution, including 7 males and 3 females with an average age of 41.5 years (range, 31 to 55 years), were selected and included in this clinical research. The mean Injury Severity Score was 29.5 (range, 17 to 53). The mean time from injury to surgery was 4.7 days (range, 4 h to 21 days). The indication of this pelvic reduction frame was the same as that of the Starr frame, which were the unilateral unstable pelvic fractures and displacements. The pelvic fractures were classified according to the Young-Burgess [15] and OTA classifications [16]. According to Young-Burgess classification, there were four LC II type fractures, four APC II type fractures, one APC III type fracture, and one VS type fracture. According to OTA classification, there were four 61-B1 fractures, four 61-B2 type fractures, and two 61-C1 type fractures.

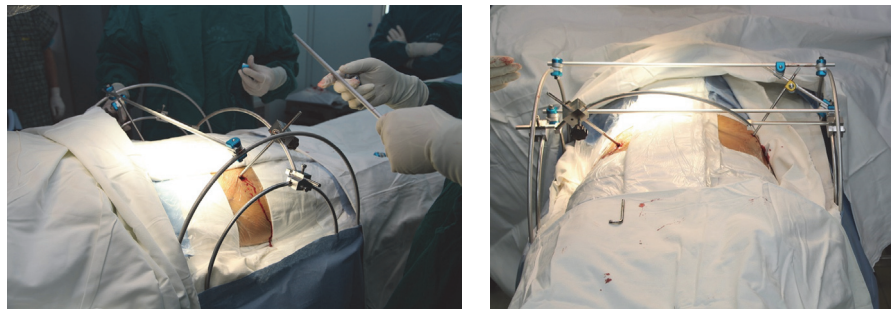
2.2. Surgical Procedure. The entire frame consists of two large side arc bars, which are used to secure the intact hemipelvis, and two smaller side arc bars, which are used to connect and hold the injured hemipelvis. The actual position of the injured hemipelvis is controlled by a Schanz screw, also called the end-effector of the system, which can slide on the anterior arc bar and rotate around the center of the anterior arc. The anterior arc bar connects the bilateral smaller side arc bars and can slide on them. When the anterior arc bar slides on the smaller bilateral side arc bars, the end-effector can rotate around the center of the smaller side arc bar in the lateral view.

During the reduction procedure, the patients were placed in supine position. The Schanz screws were connected with the larger side arc bars and placed in the intact hemipelvis. The end-effector Schanz screw was placed into the AIIS of the injured hemipelvis in the direction from AIIS to posterior superior iliac spine (PSIS), the so-called LC II screw (Figure 1).

After assembly of the entire frame and positioning the patient, the patient and frame were processed with the intraoperative CT scan. Then, based on the intraoperative CT scan data, several commercial CAD software packages will be used to reconstruct the 3D models of the pelvis and frame and calculate the reduction process. In general, the entire reduction process can be broken down into rotations and translations in three directions, rotations around the center of the anterior arc on the anterior arc bar in the LC II plane and the LC II screw in the plane vertical to LC II screw, movement along the side arc bars in the sagittal plane, and cephalic, caudal, and lateral translations. The reduction process of rotational displacements was presented in Figure 2.

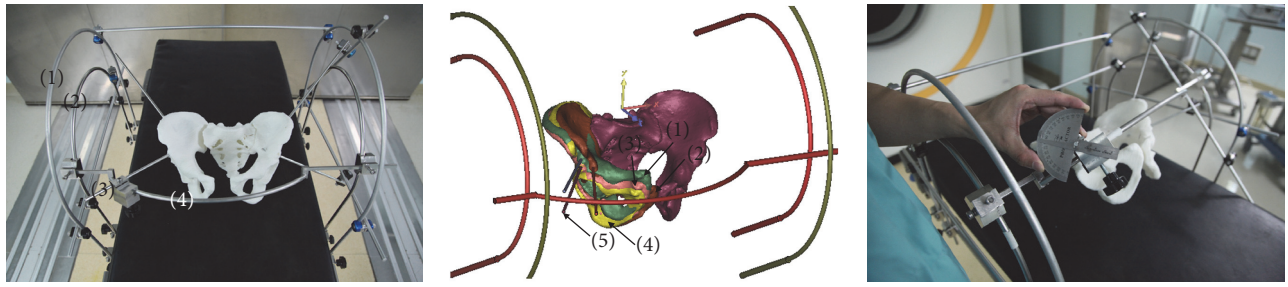
We then performed virtual reduction using CAD software. After each step in the reduction process and the virtual final reduction position was verified by the software, the actual reduction manipulations of the unstable pelvic fracture will be performed with the reduction frame according to the calculation results. The details of the reduction functions of the entire frame are described in our previous publication [14].

For evaluation of the reduction quality of the clinical application of the entire system, these series of patients underwent a second intraoperative CT scan after reduction with the frame. Based on this second intraoperative CT scan data, the 3D pelvic model at the anatomical reduction position can be reconstructed. The residual translational and rotational differences between the actual and virtual anatomical reduction positions were calculated with the



(a) (b)

Figure 1: The frame configurations and setup during the operation.



(a) (b) (c)

Figure 2: The frame configurations and reduction process were presented with the pelvic 3D printed and reconstruction models. (a) The frame configurations include two larger side arc bars (1), which are used for securing the intact hemipelvis, and two smaller side arc bars (2), which are used for connecting and holding the injured hemipelvis. The injured hemipelvis can be rotated or translated by the smaller side arc bars through the LC II screw (3) in a controlled manner. The rotations of hemipelvis can be performed around the center of the anterior arc on the anterior arc bar (4) in the LC II plane and the LC II screw in the plane vertical to LC II screw, and along the smaller side arc bars in the sagittal plane. (b) The reduction process of the rotational displacements of the injured hemipelvis can be explained by four hemipelves in four different virtual places. Hemipelves (1) and (2) are the hemipelves at displaced and reduction places, respectively. Hemipelves (3) and (4) are two intermediate places, which are rotated from hemipelves (1) and (2), respectively. The rotation degrees from hemipelvis (1) to (3) and hemipelvis (2) to (4) can be calculated by using the intersection degrees of their respective LC II screws in the sagittal and LC II planes, respectively. In this condition, there will be only one self-rotation around the LC II screw (5) with hemipelves (3) or (4), which are parallel to each other in space and can be calculated using the matrix transformation of 3D rotation around an arbitrary axis as follows: $\begin{bmatrix} n_x^2(1-\cos\theta)+\cos\theta & n_y n_x(1-\cos\theta)+n_z\sin\theta & n_x n_z(1-\cos\theta)-n_y\sin\theta \\ n_y n_x(1-\cos\theta)-n_z\sin\theta & n_y^2(1-\cos\theta)+\cos\theta & n_z n_x(1-\cos\theta)+n_x\sin\theta \\ n_z n_x(1-\cos\theta)+n_y\sin\theta & n_z n_y(1-\cos\theta)-n_x\sin\theta & n_z^2(1-\cos\theta)+\cos\theta \end{bmatrix}$. (c) During the operation, the self-rotation around the LC II screw could be completed with a specialized protractor.

matrix transformation between two positions using CAD software. They represent the reduction quality of this frame. Based on the translational and rotational residues, we fine-tuned the reduction position and took the inlet and outlet views using C-arm to confirm the results before definite fixation.

In addition, the operation time was also recorded for the quality control of this technique.

2.3. Statistical Analysis. Before fine-tuning, the residual translational and rotational differences between the actual and virtual anatomical reduction positions in each direction were computed and compared with zero using one-sample Student's t-test.

3. Results

Because the entire frame consisted of several RCM mechanisms, bars, and specialized connectors, the setup process was a time-consuming process before the beginning of the operation. The mean time required for setting up the frame, the virtual surgery simulation, and the reduction of the unstable pelvic fractures was 10.3 min (range, 7.7–12.1 min), 20.9 min (range, 18.1–22.5 min), and 7.5 min (range, 6.3–9.9 min), respectively. No complications, including the nerve or vascular injures, were reported during the operations performed on this series of patients.

The reduction results are shown in Table 1. As shown, the average residual translational displacements in each direction were slightly larger than the rotational ones, which might

Table 1: The translational and rotational residual displacements in each direction.

Type	Axis	Measurement (n = 10, mean ± SD)	|Max|	|Min|	T	P
Translational (mm)	X	2.43 ± 1.2	4.6	0.98	6.404	0.0001
	Y	2.15 ± 0.95	3.58	0.73	7.157	0.0001
	Z	2.57 ± 2.1	6.5	0.21	6.252	0.0001
Rotational (degrees)	X	1.63 ± 1.05	3.29	0.01	10.56	0.0001
	Y	1.55 ± 0.64	2.51	0.42	7.659	0.0001
	Z	1.48 ± 1.3	3.71	0.07	3.6	0.0057

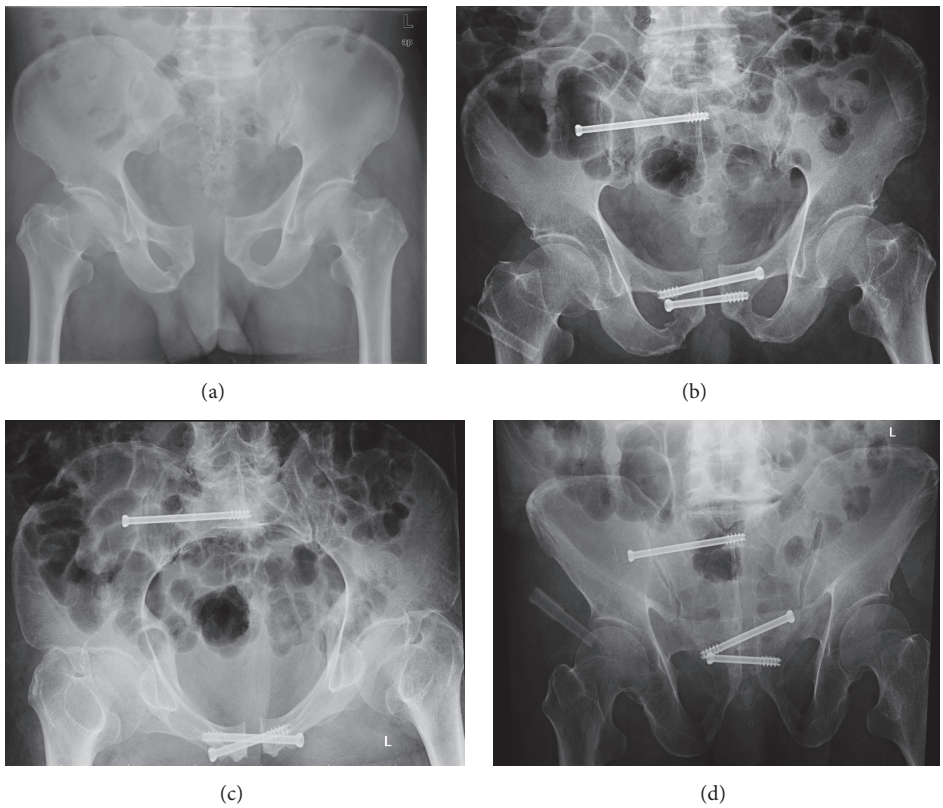


Figure 3: Case number 1. (a) Preoperative AP view radiograph; (b), (c), and (d) postoperative AP, inlet and outlet view radiographs.

indicate that the entire system could control the rotational displacements of the injured hemipelvis better than the translational displacements. The maximum residual translational displacement of the unstable pelvic fracture was less than 6.5 mm with an average value of 2.38 mm, and the maximum residual rotational displacement was less than 3.71 degrees with an average value of 1.55 degrees. These values indicate the accuracy of the whole system during the clinical applications. There were significant differences between the residual translational and rotational displacements and neutral position in each direction. However, the reduction position almost fulfilled the clinical requirements according to the previous published standards [17–19].

Figures 3 and 4 show two cases of clinical applications of the established frame and system.

4. Discussion

Regarding the closed reduction and percutaneous fixation of the unstable pelvic fractures, several methods and techniques have been proposed, including different patient positions, equipment for lower extremity traction, and stabilization of reduction positions of injured hemipelvis. Accurate reduction for the unstable pelvic fractures has been recognized as the cornerstone of safe placement of iliosacral screws, but no consensus has been reached regarding the optimal reduction technique.

Our previous study confirmed the accuracy of the system *in vitro*, which yielded maximum residual translational and rotational displacements less than 5 mm and 4 degrees, respectively; these values meet clinical requirements, and

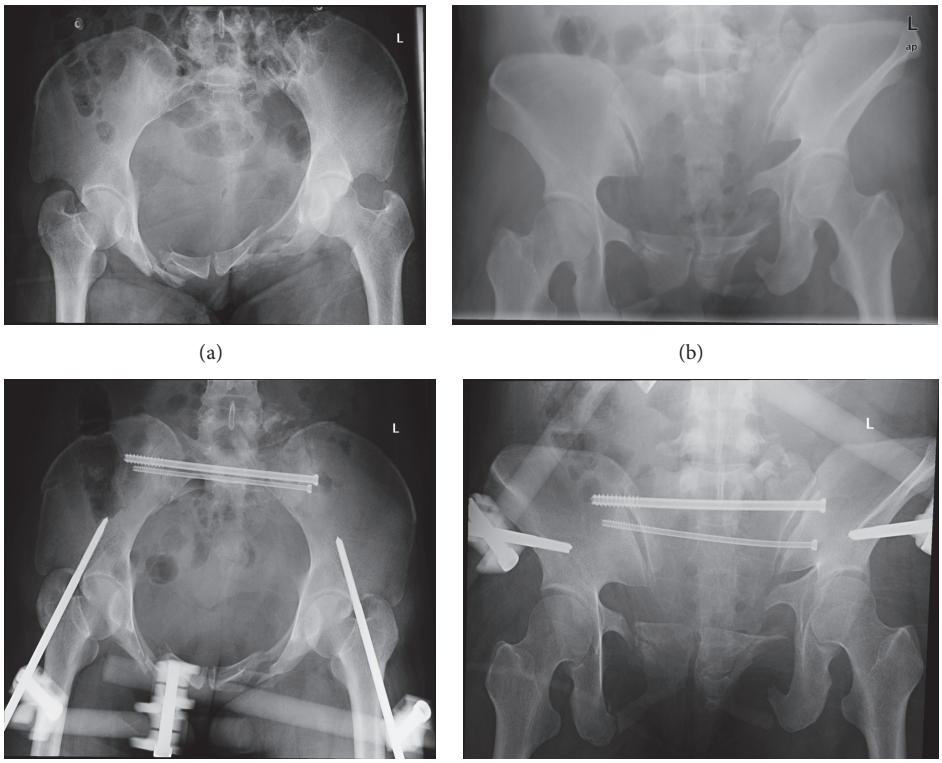


Figure 4: Case number 2. (a) and (b) Preoperative inlet and outlet view radiographs; (c) and (d) postoperative inlet and outlet view radiographs.

they can be classified as good according to Majeed [17] and excellent or nearly excellent according to Lindahl et al. [18] and Matta and Tornetta [19]. The present results indicate that the quality of rotational reduction was slightly better than that of the translational reductions. One possible reason for this might be that the entire system consisted of RCM mechanisms, the function of which was to hold the target in place and rotate it around the remote center of motion in a precise manner. However, the translational reduction is usually performed by lower extremity traction or moving the injured hemipelvis as a whole body controlled by the frame and Schanz screws, which inevitably produces uncontrolled errors.

The results of the present study show that, except for residual translation in the z-axis, the maximum residual translational displacement of the unstable pelvic fracture in the clinical applications was less than 4.6 mm, with an average value of 2.29 mm; and the maximum residual rotational displacement was less than 3.71 degrees, with an average value of 1.55 degrees. The residual rotational and translational displacements in each direction were greater than the corresponding values published in our previous study [14]. One reason for this may be the resistance from the elasticity of the soft tissue inside the pelvis. Another reason why residual translation in the z-axis was slightly greater than in other directions might be the design and manufacture of the frame, which was the same as that shown in our previous study [14]. Furthermore, the accuracy of the system could be improved with better configuration and manufacture of the frame, even though there is no standard or grading that can precisely quantify the residual rotational displacements of the hemipelvis in unstable pelvic fractures. Meanwhile, the elasticity of the soft tissue should be considered an important factor for better design, manufacturing, and experimentation in the next generation of reduction frames.

The time elapsed from injury to surgery is another important risk factor for the fracture reduction manipulation. It is easier for the close reduction manipulation of almost all suitable fractures in the initial phase of fractures. As time goes on, varying degrees of consolidation take place at the site of the fracture, increasing the difficulty of close reduction manipulations. Thus, the delayed unstable pelvic fractures with significant bony consolidation should be evaluated with caution beforehand to ensure the reduction quality of this technique.

The traditional reduction procedure for pelvic fractures is based primarily on stepwise manual maneuvers verified via intraoperative fluoroscopy. Most measurement methods used to verify traditional reduction results are also based on the 2D radiographs, which can only quantify the translational displacements and assess the quality of the rotational direction of the hemipelvis. A literature review by Mataliotakis and Giannoudis outlined the various measurement systems proposed by different authors [20]. The radiological evaluation

of pelvic translational displacement depend mainly on the pelvic AP view [18, 19, 21, 22], the outlet view [23], and the inlet view [22]. Many authors argue that the current radiographic measurement methods used for fractured pelvises lack standardization, well-accepted reliability, and validity [13, 21].

Using our system, the measurement method was based on a 3D reconstruction model of the pelvis, which could indicate the translational and rotational displacements at the same time through calculation of the transformation matrix between the displaced hemipelvis and the reduced hemipelvis. Although no intra- or interobserver reliability studies of this method have been performed, the software and the equation itself should not cause any intra- or interobserver differences. Such differences are related primarily to the accuracy of the manufacture of the frame.

Because no single software program could meet the needs of this study, different software packages with different functions were used to perform the calculations and simulations at various points in the process. Mimics software (Materialise, Haasrode, Belgium) was used to construct the 3D model of the pelvis. The Geomagic software (Research Triangle Park, NC, USA) was used to calculate the transformation matrix of the hemipelves between locations. The 3-Matic software (Materialise) was used to perform the visual simulation of the reduction processes. Although many export and import steps were involved in the processes, the spatial orientation and coordinates of the pelvic models used in these software packages were consistent, and they served as the basis of the calculations used in this study. Thus, the accuracy of the system might be minimally influenced by the repetitive manipulations of several types of software. The total time required for the virtual manipulation was approximately 20.9 min.

Several types of CAD software had to be used in this study to complete the anatomical reduction of the unstable pelvic fracture using the frame. There might be a learning curve required before untrained surgeons can use these software packages, almost all of which are professional computer graphics programs. As given above, we have been developing professional software to expedite the process.

Because the authors have encountered difficulties with the closed reduction of unstable pelvic fractures, the procedure reported in this study was designed and implemented step by step. It was informed by knowledge of applied computer software, computer graphics, physics, computer navigation, and radiologic imaging. Many computer-assisted or robotic surgeries to reduce long bone fractures have been reported. A study of computer-assisted fracture reduction for pelvic fractures was reported in 2002 [24]; however, this procedure was still a real-time virtual operation performed by the surgeons using a registration method based on the preoperative CT dataset. The advantage of the present study was the use of an intraoperative CT-based registration method, which greatly improved the accuracy of registration and the subsequent virtual operation.

The overdose radiation problem encountered in clinical orthopedic trauma practices was the impetus underlying the development of this system. We attempted to combine the techniques of intraoperative imaging and virtual surgery to facilitate the performance of anatomical closed reductions using minimally invasive pelvic surgery. We believe that with development of computer-assisted surgery techniques and orthopedic surgery robots, radiation exposure could be eliminated or mitigated in the future. The RCM mechanism that is predominantly used in medical surgery robotic systems was the prototype for the final pelvic reduction frame presented in this study. Our team has been developing a reduction robot for use with long bone fractures, and we have used it in tibial fracture reduction, and the results have been published in research journals [25–29]. The algorithm and mechanism of the present system could also be the basis for the further studies on the pelvic fracture reduction robot.

As the indication of this technique is limited to unilateral unstable pelvic fractures, the number of patients included in this study was relatively small. The advantages and disadvantages of this technique should be evaluated with a larger number of participating patients and a matched control group of the traditional ORIF treatment with long-term follow-up.

5. Conclusions

This computer-aided reduction frame can be a useful tool for the speedy and accurate reduction of unstable pelvic fractures. Further clinical studies should be conducted with larger patient samples to verify its safety and efficacy.

Disclosure

The authors declare that they have a Chinese invention patent named "A Pelvic Reduction Frame for Closed Reduction of Unstable Pelvic Fractures."

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jing-Xin Zhao and Li-Cheng Zhang have contributed equally to this work.

References

[1] M. J. Halawi, "Pelvic ring injuries: Surgical management and long-term outcomes," *Journal of Clinical Orthopaedics and Trauma*, vol. 7, no. 1, pp. 1–6, 2016.

[2] H. A. Vallier, B. A. Cureton, C. Ekstein, F. P. Oldenburg, and J. H. Wilber, "Early definitive stabilization of unstable pelvis and acetabulum fractures reduces morbidity.," *The Journal of Trauma and Acute Care Surgery*, vol. 69, no. 3, pp. 677–684, 2010.

[3] M. Tile, "Acute Pelvic Fractures: II. Principles of Management," *Journal of the American Academy of Orthopaedic Surgeons*, vol. 4, no. 3, pp. 152–161, 1996.

[4] P. F. Heini, J. Witt, and R. Ganz, "The pelvic C-clamp for the emergency treatment of unstable pelvic ring injuries. A report on clinical experience of 30 cases," *Injury*, vol. 27, suppl 1, pp. SA38–SA45, 1996.

[5] C. Bellabarba, W. M. Ricci, and B. R. Bolhofner, "Distraction external fixation in lateral compression pelvic fractures," *Journal of Orthopaedic Trauma*, vol. 14, no. 7, pp. 475–482, 2000.

[6] J. M. Vigdorchik, A. O. Esquivel, X. Jin, K. H. Yang, and R. Vaidya, "Anterior internal fixator versus a femoral distractor and external fixation for sacroiliac joint compression and single stance gait testing: a mechanical study in synthetic bone," *International Orthopaedics*, vol. 37, no. 7, pp. 1341–1346, 2013.

[7] H. C. Sagi and S. Papp, "Comparative radiographic and clinical outcome of two-hole and multi-hole symphyseal plating," *Journal of Orthopaedic Trauma*, vol. 22, no. 6, pp. 373–378, 2008.

[8] M. J. Gardner, D. Kendoff, S. Ostermeier et al., "Sacroiliac joint compression using an anterior pelvic compressor: A mechanical study in synthetic bone," *Journal of Orthopaedic Trauma*, vol. 21, no. 7, pp. 435–441, 2007.

[9] R. M. Sellei, P. Schandelmaier, P. Kobbe, M. Knobe, and H.-C. Pape, "Can a modified anterior external fixator provide posterior compression of AP compression type III pelvic injuries?" *Clinical Orthopaedics and Related Research*, vol. 471, no. 9, pp. 2862–2868, 2013.

[10] A. Queipo-De-Llano, A. Perez-Blanca, F. Ezquerro, and F. Luna-González, "Simultaneous anterior and posterior compression of the pelvic ring with external fixation using a pre-tensed curved bar: A biomechanical study," *Injury*, vol. 44, no. 12, pp. 1787–1792, 2013.

[11] J. M. Matta and J. G. Yerasimides, "Table-skeletal fixation as an adjunct to pelvic ring reduction," *Journal of Orthopaedic Trauma*, vol. 21, no. 9, pp. 647–656, 2007.

[12] K. A. Lefaivre, A. J. Starr, B. P. Barker, S. Overturf, and C. M. Reinert, "Early experience with reduction of displaced disruption of the pelvic ring using a pelvic reduction frame," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 91, no. 9, pp. 1201–1207, 2009.

[13] K. A. Lefaivre, A. J. Starr, and C. M. Reinert, "Reduction of displaced pelvic ring disruptions using a pelvic reduction frame," *Journal of Orthopaedic Trauma*, vol. 23, no. 4, pp. 299–308, 2009.

[14] L.-H. Zhang, J.-X. Zhao, Z. Zhao et al., "Computer-aided pelvic reduction frame for anatomical closed reduction of unstable pelvic fractures," *Journal of Orthopaedic Research*, vol. 34, no. 1, pp. 81–87, 2016.

[15] J. W. R. Young, A. R. Burgess, R. J. Brumback, and A. Poka, "Pelvic fractures: Value of plain radiography in early assessment and management," *Radiology*, vol. 160, no. 2, pp. 445–451, 1986.

[16] "Fracture and dislocation compendium. Orthopaedic Trauma Association Committee for Coding and Classification," *Journal of Orthopaedic Trauma*, vol. 10, no. Suppl 1, p. v-ix, 1-154, 1996.

[17] S. A. Majeed, "External fixation of the injured pelvis. The functional outcome," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 72, no. 4, pp. 612–614, 1990.

[18] J. Lindahl, E. Hirvensalo, O. Böstman, and S. Santavirta, "Failure of reduction with an external fixator in the management of injuries of the pelvic ring. Long-term evaluation of 110 patients," *The Journal of Bone & Joint Surgery (British Volume)*, vol. 81, no. 6, pp. 955–962, 1999.

[19] J. M. Matta and P. Tornetta, "Internal Fixation of Unstable Pelvic Ring Injuries," *Clinical Orthopaedics & Related Research*, vol. 329, pp. 129–140, 1996.

[20] G. I. Mataliotakis and P. V. Giannoudis, "Radiological measurements for postoperative evaluation of quality of reduction of unstable pelvic ring fractures: Advantages and limitations," *Injury*, vol. 42, no. 12, pp. 1395–1401, 2011.

[21] K. A. Lefaivre, P. A. Blachut, A. J. Starr, G. P. Slobogean, and P. J. O'Brien, "Radiographic displacement in pelvic ring disruption: Reliability of 3 previously described measurement techniques," *Journal of Orthopaedic Trauma*, vol. 28, no. 3, pp. 160–166, 2014.

[22] R. C. Henderson, "The long-term results of nonoperatively treated major pelvic disruptions," *Journal of Orthopaedic Trauma*, vol. 3, no. 1, pp. 41–47, 1989.

[23] J. Lindahl and E. Hirvensalo, "Outcome of operatively treated type-C injuries of the pelvic ring," *Acta Orthopaedica*, vol. 76, no. 5, pp. 667–678, 2005.

[24] T. Hüfner, T. Pohlemann, S. Tarte et al., "Computer-assisted fracture reduction of pelvic ring fractures: An in vitro study," *Clinical Orthopaedics and Related Research*, no. 399, pp. 231–239, 2002.

[25] H. Du, L. Hu, C. Li, C. He, L. Zhang, and P. Tang, "Preoperative trajectory planning for closed reduction of long-bone diaphyseal fracture using a computer-assisted reduction system," *The International Journal of Medical Robotics and Computer Assisted Surgery*, vol. 11, no. 1, pp. 58–66, 2015.

[26] T. Wang, C. Li, L. Hu et al., "A removable hybrid robot system for long bone fracture reduction," *Biomed Mater Eng*, vol. 24, no. 1, pp. 501–509, 2014.

[27] S. Luan, L. Sun, L. Hu et al., "Projective invariant biplanar registration of a compact modular orthopaedic robot," *Biomed Mater Eng*, vol. 24, no. 1, pp. 511–518, 2014.

[28] H. Du, L. Hu, C. Li et al., "Advancing computer-assisted orthopaedic surgery using a hexapod device for closed diaphyseal fracture reduction," *The International Journal of Medical Robotics and Computer Assisted Surgery*, vol. 11, no. 3, pp. 348–359, 2015.

[29] P. Tang, L. Hu, H. Du, M. Gong, and L. Zhang, "Novel 3D hexapod computer-assisted orthopaedic surgery system for closed diaphyseal fracture reduction," *The International Journal of Medical Robotics and Computer Assisted Surgery*, vol. 8, no. 1, pp. 17–24, 2012.