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Research Article

Similarities and Differences between Clavicular Bacterial Osteomyelitis and Nonbacterial Osteitis: Comparisons of 327 Reported Cases

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Background. Currently, both clavicular bacterial osteomyelitis (BO) and nonbacterial osteitis (NBO) remain not well understood owing to their much lower incidences. This study is aimed at summarizing similarities and differences between clavicular BO and NBO based on comparisons of literature-reported cases. *Methods*. We searched the PubMed and Embase databases to identify English published literature between January 1st, 1980, and December 31st, 2018. Inclusion criteria were studies evaluating clinical features, diagnosis, and treatment of clavicular BO and NBO, with eligible data for synthesis analysis. *Results*. Altogether, 129 studies with 327 patients were included. Compared with BO, clavicular NBO favored females ($P < 0.001$) and age below 20 years ($P < 0.001$) and mostly presented in a chronic phase (disease term exceeding 2 months) ($P < 0.001$). Although local pain and swelling were the top two symptoms for both disorders, fever, erythema, and a sinus tract were more frequently found in BO patients ($P < 0.01$). Although they both favored the medial side, lesions in the clavicular lateral side mostly occurred in BO patients ($P = 0.002$). However, no significant differences were identified regarding the serological levels of white blood cell count ($P = 0.06$), erythrocyte sedimentation rate ($P = 0.27$), or C-reactive protein ($P = 0.33$) between BO and NBO patients before therapy. Overall, the BO patients achieved a statistically higher cure rate than that of the NBO patients ($P = 0.018$). *Conclusions*. Females, age below 20 years, and a long duration of clavicular pain and swelling may imply NBO. While the occurrence of a sinus tract and lesions in the lateral side may be clues of BO, inflammatory biomarkers revealed limited values for differential diagnosis. BO patients could achieve a better efficacy than the NBO patients based on current evidence.

1. Introduction

Clavicular inflammatory disorders can be classified as bacterial osteomyelitis (BO) and nonbacterial osteitis (NBO) according to different etiologies. Clavicular BO, caused by pathogen invasions via contiguous, perioperative, and hematogenous routes [1–4], contains infectious osteomyelitis (OM) and septic arthritis (SA) of the joints surrounding the clavicle. Infectious OM, which refers to inflammation-related osteonecrosis, osteolysis, and/or new bone formation with or without surrounding soft tissue involvement [5], primarily affects bones in the lower extremity, such as the tibia, femur, and metatarsal bones [6, 7], while SA usually leads to joint cartilage damage, host inflammation, and tissue ischemia following pathogen invasion, with the knee joint as the most frequently involved site [8]. However, clavicular BO remains seldom reported because of its much lower prevalence [9].

NBO, different from BO, acted as an autoinflammatory bone disorder not related to infectious disease, which is

characterized by activation of the innate immune system in the absence of high-titer autoantibodies without the involvement of the autoreactive lymphocytes (at least initially) [10]. In 1972, Giedion et al. [11] first described this disorder, known as chronic recurrent multifocal osteomyelitis (CRMO). Nowadays, aside from CRMO, NBO has become a broad concept disorder, including synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome, condensing osteitis, and even hyperostosis [12]. Despite its wide concept, up till now, the number of studies reporting clavicular NBO is also quite limited, which likewise associates with the much lower prevalence [13].

Due to their much lower prevalences, currently, both clavicular BO and NBO are still not well understood. In a previous review [14], we summarized clinical characteristics and treatment strategy of clavicular OM based on literature-reported cases; however, as mentioned in the study, both BO and NBO cases were included as a whole for analysis, resulting in a higher risk of heterogeneity. Although the two disorders share similarities, they also possess differences.

It is very important to distinguish clavicular BO and NBO patients as being able to do this can help clinicians avoid unnecessary diagnostic procedures, antibiotic therapies, and even surgeries. However, to the best of our knowledge, up till now, only one German study [9], based on a nationwide survey, reported similarities and differences between BO and NBO in pediatric patients. However, this study analyzed the whole-body bones. Currently, there still lacks such an analysis to differentiate BO and NBO of the clavicle. Therefore, this study is aimed at summarizing similarities and differences of clinical characteristics, diagnosis, and treatment between clavicular BO and NBO.

2. Methods

2.1. Literature Search, Definition, and Inclusion and Exclusion Criteria. A systematic literature search was conducted in the PubMed and Embase databases by two independent authors, to identify English studies reporting clavicular BO and NBO, published between January 1st, 1980, and December 31st, 2018. Terms used for the search were "clavicle," "clavicular," "osteomyelitis," "osteitis," and "hyperostosis." Clavicular BO refers to infectious OM and septic arthritis of the surrounding joints, such as acromioclavicular and sternoclavicular joints, while clavicular NBO includes CRMO, SAPHO syndrome, condensing osteitis, and hyperostosis. The disease phase is defined as the duration from the onset of symptoms to clinical diagnosis, with the acute phase shorter than 2 months and the chronic phase longer than 2 months. Inclusion criteria of the present study were human studies evaluating clinical characteristics, diagnosis, and treatment of either clavicular BO or NBO or both, with eligible data (described in Section 2.3) for synthesis analysis. Case report/series, letter to the editor article, and conference paper were also screened only if they satisfied the inclusion criteria. Exclusion criteria included non-English published literature and studies without clavicular BO or NBO or without available data for pooled analysis. In addition, other study types (e.g., systematic reviews and meta-analyses) and research fields (e.g., radiology and flap surgery) were also excluded.

2.2. Study Identification and Data Extraction. Two authors independently screened titles of the identified studies initially, and unrelated ones were excluded. Subsequently, abstracts that were potentially relevant to the topic were reviewed. If studies appeared to be potentially applicable, full texts were reviewed for further evaluation of whether the studies satisfied all the inclusion criteria. Three authors participated in the extraction of the effective data from all eligible studies independently. Disagreement about eligibility and harvested data was resolved by discussion, and if necessary, the corresponding author's opinion was consulted to make the final decision.

2.3. Data Collection. Eligible data collected from included studies were the disorder type; sex; age and disease phase; clinical symptom and duration; pathogen culture results of the BO patients; body side and site; serological levels of white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) before therapy; treatment strategy; and efficacy.

2.4. Statistical Analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA). Distributions of the continuous variables were evaluated for normality using the Kolmogorov-Smirnov test. Then, the data were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. For normally distributed data, Student's t-test was used to compare differences between the two groups. Otherwise, the Mann-Whitney U test was applied. Dichotomous variables were expressed as percentages with events and totals. The chi-squared test was used to compare differences of rates between the two groups. A statistically significant difference was defined as a P value ≤ 0.05.

3. Results

3.1. Study Identification and Constitutions of Clavicular BO and NBO. Altogether, 928 reports were found initially; after removing the duplicates and applying the inclusion criteria, we finally included 129 studies of 327 patients [1–4, 12, 15–138] (Figure 1). Of the eligible 327 cases, 171 patients were classified as BO, with 39 caused by *Mycobacterium tuberculosis*. Among the 156 NBO cases, 66 were reported as condensing osteitis, 61 as CRMO, 21 as SAPHO syndrome, and the remaining 8 as sternocostoclavicular hyperostosis.

3.2. Clinical Characteristics of Clavicular BO vs. NBO

3.2.1. Sex Ratio and Age at Diagnosis. As shown in Table 1, a significant difference was identified regarding the female-to-male ratio between clavicular BO and NBO (1.01 vs. 3.08, $P < 0.001$), suggesting that clavicular NBO favored females. Additionally, the median age of NBO patients at diagnosis was significantly younger than that of the BO patients (13 years vs. 36 years, $P < 0.001$). The percentage of the NBO

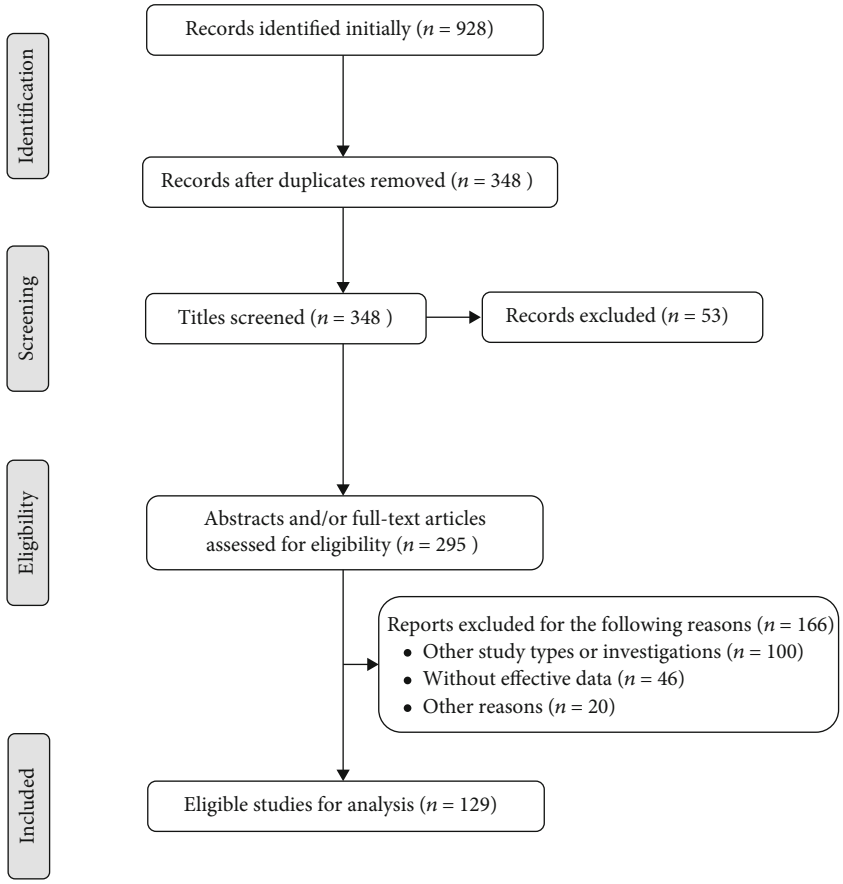

Figure 1: Flow diagram of the included studies in this review.

patients younger than 20 years at diagnosis was significantly higher than that of the BO patients (67.5% vs. 30.5%, $P < 0.001$), demonstrating that clavicular NBO was predominant in young people (Figure 2).

3.2.2. Disease Phase Ratio and Symptom Duration. Compared with the BO patients, the majority of the NBO patients were presented in a chronic phase (disease term ≥ 2 months) at diagnosis (91.4% vs. 55.1%, $P < 0.001$), with a significantly higher chronic-to-acute ratio of NBO than that of BO (10.6 vs. 1.2, $P < 0.001$). In addition, the median symptom duration of the NBO patients was twice longer than that of the BO patients (6 months vs. 3 months, $P < 0.001$) (Table 1).

3.2.3. Clinical Symptoms. Although the top two symptoms of both BO and NBO patients were local pain and swelling, the ratios of the two symptoms in the NBO patients were significantly higher than those of the BO patients ($P < 0.005$), while fever, erythema, and sinus tract were more frequently found in the BO patients ($P < 0.01$). However, no statistical difference was identified regarding the proportion of tenderness between BO and NBO patients ($P = 0.502$) (Table 1).

3.2.4. Pathogen Culture Outcomes of the BO Patients Included. The total positive rate of culture was 84.27% (123/146), with 109 and 14 patients having a monomicrobial and a multimicrobial infection, respectively. Figure 3 depicts the distributions of bacterial species, with *Staphylococcus aureus* (36.70%) as the most frequent type, followed by *Mycobacterium tuberculosis* (35.78%), *Pseudomonas aeruginosa* (5.50%), and *Streptococcus species* (5.50%), respectively.

3.2.5. Involved Side and Site Distributions. Both BO and NBO favored the right body side, with no statistical differences of side distributions between them. However, the percentage of the multifocal lesions in the clavicle of the BO patients was significantly higher than that of the NBO patients (17.9% vs. 7.5%, $P = 0.018$). As for the patients with a unifocal lesion, both BO and NBO favored the medial side. However, the percentage of lesions located on the medial side was statistically higher in the NBO patients (89.8% vs. 79.8%, $P = 0.044$). Conversely, BO favored the lateral side more than NBO (11.8% vs. 1.0%, $P = 0.002$).

3.3. Diagnosis of Clavicular BO vs. NBO

3.3.1. Serological Levels of Inflammatory Biomarkers before Therapy. As revealed in Table 2, no statistical differences were found regarding the serological levels of WBC ($P = 0.064$), ESR ($P = 0.272$), or CRP ($P = 0.330$) between BO and NBO patients prior to therapy. In the stratified analyses by disease phase, no statistical differences were identified for the levels of such biomarkers between the two disorders, neither in an acute phase nor in a chronic phase.

Table 1: Similarities and differences of clinical characteristics between clavicular BO and NBO.

Items	Clavicular BO	Clavicular NBO	Statistics	*P* values
Included cases	171	156	—	—
Sex ratio (female/male)	1.0 (76/75)	3.1 (114/37)	20.493	<0.001
Age at diagnosis (year)	36 (14, 53)	13 (10, 32)	- 5.842	<0.001
Percentage of patients below 20 years	30.5 (46/151)	67.5 (102/151)	41.553	<0.001
Disease phase ratio (chronic/acute)	1.2 (76/62)	10.6 (117/11)	44.026	<0.001
Symptom duration (month)	3 (0.55, 7.0)	6 (3.0, 22.5)	- 4.134	<0.001
Clinical symptoms	97/78/40/29/34/24	118/96/15/2/1/16	66.850	<0.001
Pain	32.1 (97/302)	47.6 (118/248)	13.672	<0.001
Swelling	25.8 (78/302)	38.7 (96/248)	10.448	0.001
Fever	13.2 (40/302)	6.0 (15/248)	7.836	0.005
Erythema	9.6 (29/302)	0.8 (2/248)	19.810	<0.001
Sinus	11.3 (34/302)	0.4 (1/248)	26.928	<0.001
Tenderness	8.0 (24/302)	6.5 (16/248)	0.452	0.502
Body side distribution (left/right/bilateral)	53/79/5	52/67/7	0.871	0.647
Left	38.7 (53/137)	41.3 (52/126)	0.183	0.669
Right	57.7 (79/137)	53.2 (67/126)	0.536	0.464
Bilateral	3.6 (5/137)	5.5 (7/126)	0.548	0.459
Multifocal lesions in clavicle	17.9 (26/145)	7.5 (8/106)	5.638	0.018
Unifocal distribution (medial/middle/lateral)	95/10/14	88/9/1	9.645	0.008
Medial (including SC joint)	79.8 (95/119)	89.8 (88/98)	4.038	0.044
Middle	8.4 (10/119)	9.2 (9/98)	0.041	0.840
Lateral (including AC joint)	11.8 (14/119)	1.0 (1/98)	9.642	0.002

BO: bacterial osteomyelitis; NBO: nonbacterial osteitis; SC: sternoclavicular; AC: acromioclavicular. Continuous variables are presented as the median with interquartile range. Dichotomous variables are expressed as percentages and events with totals.

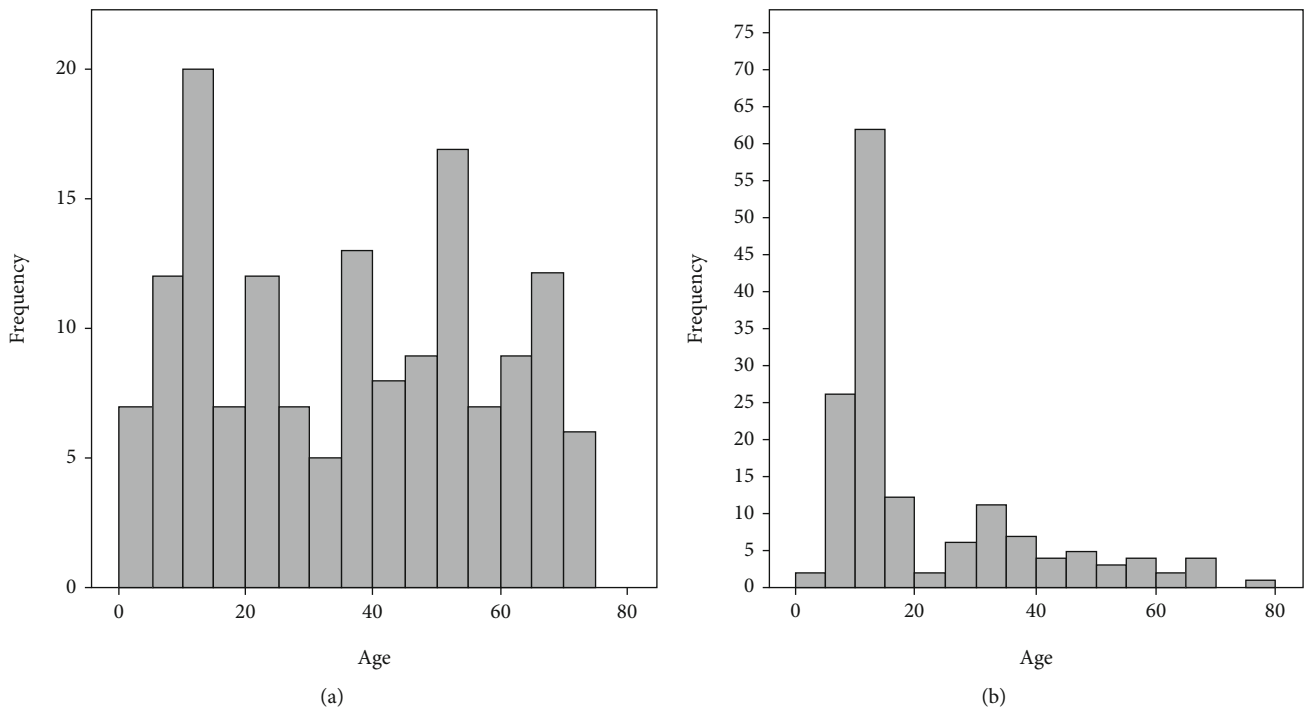

Figure 2: Age distributions of the included clavicular BO (a) and NBO (b) patients.

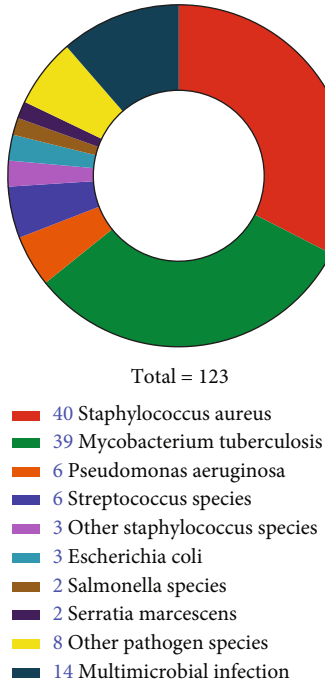

Figure 3: Distributions of pathogen culture outcomes of the BO patients included.

3.4. Treatment and Efficacy of Clavicular BO vs. NBO

3.4.1. Cure Rate of Clavicular BO vs. NBO. Although outcomes revealed no statistical differences regarding the cure rates following surgery or nonsurgery between the BO and NBO patients, the overall cure rate of the BO patients was significantly higher than the NBO patients (89.5% vs. 76.8%, $P = 0.018$), implying probably better efficacy of the BO patients (Table 3).

3.4.2. Cure Rate of Surgery vs. Nonsurgery for Clavicular BO and NBO. As shown in Table 3, no significant differences were observed in the cure rates after surgical and nonsurgical interventions, neither in BO patients (92.5% vs. 86.0%, $P = 0.234$) nor in NBO patients (81.8% vs. 75.9%, $P = 0.668$).

4. Discussion

Outcomes of this study demonstrated that both similarities and differences have been found between clavicular BO and NBO. Based on the synthesis analysis, we concluded that females, people younger than 20 years, and long duration (over 2 months) of clavicular pain and swelling may imply NBO, while a local sinus tract and lesions in the lateral side of the clavicle may be clues of BO. However, serological levels of WBC, ESR, and CRP had limited values for differential diagnosis. Despite treatment strategies, BO patients might achieve better efficacy than NBO patients. Our findings can be summarized with the following primary three aspects.

First, we summarized similarities and differences of clinical characteristics between clavicular BO and NBO. Initially, we noticed that compared with BO, NBO favored females and people below 20 years, which were in accordance with previous studies [9, 13, 139–141]. In addition, we also noted that the proportion of NBO patients in a chronic phase at diagnosis was significantly higher than that of the BO patients, implying that NBO may be subtler than BO in most cases. Therefore, it is reasonable to understand why the median symptom duration of the NBO patients was longer than BO patients. In addition to the disease type, symptom duration is also influenced by other factors, such as its severity, host immune status, and medical interventions.

Clinical symptom is an important clue for differentiating BO and NBO. Although local pain and swelling were the most frequently reported symptoms for both BO and NBO, it is unsuitable to be regarded as distinguishing indicators. Likewise, tenderness is also not helpful as both of their percentages were low. However, ratios of fever, erythema, and a sinus tract in the BO patients were significantly higher than those in the NBO patients. Of the above three symptoms, we believe a sinus tract was mostly clinically significant, as a sinus tract with communication to the bone or implant is one of the confirmatory criteria for diagnosis of bacterial osseous infection [142]. It is interesting that among the included studies, one case reported as SAPHO syndrome was also with a discharging sinus tract, with a pathogen culture outcome of *P. acnes* [41]. Therefore, a sinus tract implies BO in most cases but cannot completely rule out NBO, especially for the culture outcome of *P. acnes.* With regard to pathogen culture results of the BO patients, outcomes revealed that *Staphylococcus aureus* and *Pseudomonas aeruginosa* were more frequently detected, which was in accordance with our previous studies regarding extremity infectious OM [6, 143]. Aside from the two pathogens, *Mycobacterium tuberculosis* was also frequently found in BO patients; considering particularity of this bacteria, *Mycobacterium tuberculosis*-related clavicular BO should be further investigated.

Lesion location may be another important clue for distinguishing BO and NBO. Here, we failed to find any statistical difference of body side distribution between them, both of which favored the right side. However, the proportion of the multifocal lesions in the clavicle in BO patients was significantly higher than that of the NBO patients. Additionally, we noticed that the lesions were mostly located in the medial side in both BO and NBO patients, though a slightly higher percentage in the NBO patients, which should not be regarded as an effective indicator to differentiate the two diseases. In contrast, the percentage of the lesions on the lateral side of the BO patients was much higher than that in the NBO patients, which may be a clue of BO.

Second, we investigated potential values of serological WBC, ESR, and CRP for differential diagnosis of BO and NBO. Unfortunately, we failed to observe any significant differences between BO and NBO, neither in an acute phase nor in a chronic phase. Therefore, serological levels of WBC, ESR, or CRP may be inappropriate to distinguish the two disorders. Similarly, aside from the disease phase, many other factors may also affect serological levels of these biomarkers, such as bacteria species and virulence, host status, lesion number, and previous treatment. In addition to the above

Table 2: Serological levels of WBC, ESR, and CRP for differential diagnosis of clavicular BO and NBO.

Items	Clavicular BO	Clavicular NBO	Statistics	*P* values
Serological levels of inflammatory biomarkers before therapy (for overall patients)				
WBC ($\times 10^9$/L)	9.8 (8.45, 16.25)	9.25 (6.72, 12.37)	− 1.850	0.064
ESR (mm/1 h)	56 (35, 92)	49 (30, 77)	− 1.098	0.272
CRP (mg/L)	20 (8.25, 63.75)	20.1 (2.5, 38.5)	− 0.974	0.330
Serological levels of inflammatory biomarkers before therapy (for patients in acute phase at diagnosis)				
WBC ($\times 10^9$/L)	9.77 (7.30, 17.15)	9.95 (7.35, 11.65)	− 0.154	0.877
ESR (mm/1 h)	60 (39.5, 108)	36.5 (11.25, 67)	− 1.004	0.315
CRP (mg/L)	20.5 (6.32, 77.3)	41.85 (25.7, 58)	− 0.783	0.433
Serological levels of inflammatory biomarkers before therapy (for patients in chronic phase at diagnosis)				
WBC ($\times 10^9$/L)	9.6 (8.2, 14.2)	8.27 (6.65, 11.8)	− 1.692	0.091
ESR (mm/1 h)	55.5 (35, 78.25)	49 (30, 77)	− 0.616	0.538
CRP (mg/L)	26 (10.4, 147)	9 (2.5, 34)	− 1.622	0.105

BO: bacterial osteomyelitis; NBO: nonbacterial osteitis; WBC: white cell blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. Continuous variables are expressed as median with interquartile range.

Table 3: Treatment strategy and efficacy between clavicular BO and NBO.

Treatment strategy	Clavicular BO	Clavicular NBO	Statistics	*P* values
Surgery	92.5 (62/67)	81.8 (9/11)	1.102	0.294
Debridement	91.1 (41/45)	100 (3/3)		
Partial resection	93.8 (15/16)	50 (2/4)[#]		
Total/subtotal resection	100 (6/6)	100 (4/4)		
Nonsurgery	86.0 (49/57)	75.9 (44/58)	1.897	0.168
Overall cure rate	89.5 (111/124)	76.8 (53/69)	5.604	0.018
Statistics*	1.418	0.184		
P values*	0.234	0.668		

BO: bacterial osteomyelitis; NBO: nonbacterial osteitis. Dichotomous variables are expressed as percentages and events with totals. [#]No patients diagnosed with clavicular NBO received partial resection of the clavicle. Four patients with NBO received incisional/excisional biopsy. *Statistics and *P* values were for comparisons regarding cure rates between surgical and nonsurgical interventions in the BO and NBO patients, respectively.

factors, the limited sample size, especially for the patients in the acute phase, may also influence the outcomes. Here, we did not analyze the potential roles of imaging tests in the assisted diagnosis of BO and NBO because of the unavailability for pooling of such data. However, imaging tests, including conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy (BS), and whole-body MRI (WB-MRI), are another effective way to differentiate the two disorders in some selected patients [9].

Third, we compared the cure rates after surgical and nonsurgical interventions between BO and NBO. On the one hand, the overall cure rate of the BO patients (90%) was significantly higher than that of the NBO patients (77%), demonstrating probably better efficacy of BO patients. However, such a difference between BO and NBO may be just statistically different, as they both revealed fairly high response rates. Considering the very different nature of BO and NBO, the follow-up time is also an important factor that may affect the outcomes. Additionally, such a difference also should be interpreted with caution as currently, management of clavicular BO and NBO remains primarily empirical. Indications for surgery or nonsurgery still are a hot debate. Likewise, surgery or nonsurgery just to be one issue, disorder type, clinicians' experiences, patients' compliances, and surgical or nonsurgical strategies may also affect clinical efficacy. On the other hand, although surgically treated BO and NBO patients had slightly higher cure rates than their respective conservative treatment, no significant differences were found between surgery and nonsurgery, which is thought-provoking. Whether surgery remains essential and indications of surgery for both BO and NBO should be further investigated.

The present study also had limitations. Although this updated study categorized clavicular OM as BO and NBO, heterogeneity may be lower to some extent but cannot be eliminated absolutely. Although both OM and SA were included as BO, with CRMO, SAPHO syndrome, condensing osteitis, and hyperostosis recruited as NBO, comparisons between BO and NBO which are constituted of different disorder types may have biases. Therefore, in-depth or stratified analyses may be necessary. Additionally, although this study included all available cases reported between 1980 and 2018, the total number of eligible

patients was still limited, especially for the subtypes of NBO. Therefore, a larger sample size is warranted to obtain more accurate conclusions in the future. Moreover, publication bias might be another limitation as many of the patients diagnosed with BO/NBO may have never been reported or published.

5. Conclusions

In summary, this updated synthesis analysis with 327 cases suggested that females, people younger than 20 years, and a long duration of clavicular site pain and swelling may imply NBO. While the occurrence of a sinus tract and lesion in the clavicular lateral side may be important clues of BO. Serological levels of WBC, ESR, and CRP had limited differential diagnostic values. The overall cure rate of clavicular BO patients was higher than that of NBO patients. However, the current evidence did not support the belief that surgery could bring better efficacy than nonsurgery, neither in the BO patients nor in the NBO patients.

Abbreviations

BO: Bacterial osteomyelitis
NBO: Nonbacterial osteitis
OM: Osteomyelitis
SA: Septic arthritis
CRMO: Chronic recurrent multifocal osteomyelitis
SAPHO: Synovitis-acne-pustulosis-hyperostosis-osteitis
WBC: White blood cell count
ESR: Erythrocyte sedimentation rate
CRP: C-reactive protein
SPSS: Statistical Package for the Social Sciences
SD: Standard deviation
IQR: Interquartile range
CT: Computed tomography
MRI: Magnetic resonance imaging
BS: Bone scintigraphy
WB-MRI: Whole-body MRI.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

Nan Jiang and Ping Zhang contributed equally to this study. All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting of the article or critical revision of the manuscript for important intellectual content; and final approval of the version to be submitted.

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