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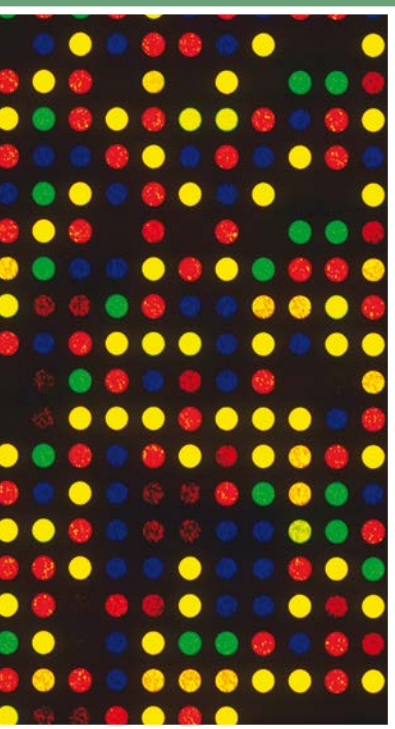
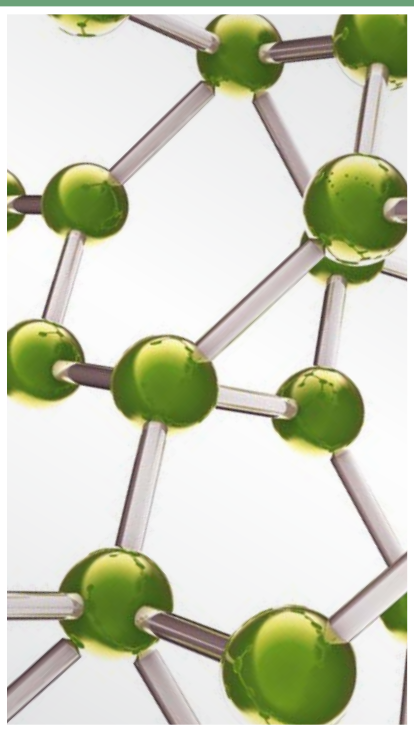
Korean Medicine in General Practice: Current Status, Challenges, and Vision in Clinical Evidence

Guest Editors: Tae-Hun Kim, Christopher Zaslawski, Sunoh Kwon, and Jung Won Kang



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Editorial Board

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Editorial

Korean Medicine in General Practice: Current Status, Challenges, and Vision in Clinical Evidence

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Research mirrors the reality of clinical practice in a society. Korean medicine (KM) shares many medical theories, principles, and interventions with other Traditional Eastern Asian Medicines (TEAM) which is due to Korea's interaction over the last two millennia with its geographical neighbors. Korean medicine however has developed specific clinical approaches and characteristics which can be observed when studying Korean medicine practitioners. These distinctive features and characteristics of Korean medicine have arisen due to the unique medical environment and resources shaped by the geological, cultural, and economic forces of ancient and modern Korea. We believe that the unique features of KM have evolved not only through the influence of the larger TEAM regional activity but also through the influence of local regional KM practices.

Since modern biomedicine has become the mainstream medicine in Korea, legislation and regulation have restricted KM practice to classical medical theory and its associated diagnostic framework and traditional treatment approaches. This has meant that KM doctors have been prohibited to use newly developed and conventional diagnostic imaging tools such as computed tomography and ultrasonography as part of their practice. Furthermore, the position of KM doctors continues to be threatened by biomedical doctors using acupuncture-related interventions and phytomedical products which had been previously regarded as the exclusive domain of KM doctors. Considering these circumstances, what can KM doctors do to remedy this situation and prepare for a better future? Research is one solution to advance the position of KM. By undertaking rigorous clinical studies, vague diagnostic concepts and poor clinical practices will wane, and an evidence-based KM approach to clinical practice will arise. This is surely a situation which all parties in the healthcare sector support.

In this special issue, you can examine current KM practice through clinical studies about new understanding of pattern identification (PI), cross-sectional surveys, evidence-based assessment of common KM interventions, and observational studies on the effect of KM on a variety of stubborn diseases.

PI, an important concept in the KM diagnostic framework, was examined from several perspectives. Patients with dyspepsia often express nongastrointestinal symptoms such as cold hands and feet which are important symptoms for the diagnosis of "spleen deficiency" in KM pattern identification. The study by K.-H. Bae et al. evaluated the responses from 6,444 patients and demonstrated a close association between dyspepsia and cold hypersensitivity of hands and feet. In another study, W. Jung et al. reported different clinical outcomes of acute stage stroke patients in accord with the result of PI. This suggests that PI can be a potential tool for predicting the prognosis of some specific diseases. The development of validated and reliable diagnostic questionnaires for PI is an active research area in KM. H. Kim et al. reported the results of a validation study for the "Phlegm Pattern Questionnaire." Identifying appropriate methods for developing such instruments and establishing models for the statistical

analysis will be helpful to improve the diagnostic accuracy for this emerging area of PI questionnaires. Another interesting study by M. M. Ko and H. Kim reanalyzed the coincidence rate of PI for stroke patients as determined by KM doctors and current stroke questionnaires suggesting a new analytic model for lowering misclassification probability. While it is acknowledged that studies like these are preliminary they are valuable for obtaining a better understanding of PI in KM.

From a therapeutic perspective, KM doctors display similar but different treatment approaches compared to practitioners from other countries. Pharmacoacupuncture, a technique that involves acupuncture-point injection with a single herb extract or herbal formula derivatives, is routinely administered as an acupuncture-related intervention by KM doctors. J. Park et al. conducted a systematic review of randomized controlled trials and assessed the clinical evidence of pharmacoacupuncture for a variety of conditions. Another interesting study by K.-J. Yun et al. analyzed the characteristics of the patients who attended a tertiary KM hospital and concluded that spinal diseases were the most frequent cause for hospital visits. U-code, a component of the KCD (the Korean version of International Classification of Disease), has been used as a specific diagnostic code system for KM doctors. Y.-S. Lee et al. redistributed U-codes into related KCD codes and estimated that the total burden of diseases in Korea, of which 2012 were KM treatments, were included. The authors found that when KM was included in the calculation for burden of disease, musculoskeletal disorders showed by far the most growth.

As with practice of alternative and complementary medicine in other countries, good results from clinical practice with KM for stubborn diseases are often reported, even in conditions where conventional medicines treatment strategies are not yet available. T. Park and S. Lee reported improved clinical outcomes (especially for recurrence) for urinary bladder cancer using complex KM interventions. J. Lee et al. using a retrospective observational approach assessed the effectiveness of the herbal decoction, Shihogye-jitang, for 54 drug resistant epileptic children and found meaningful seizure reduction. While these studies do not provide conclusive evidence for the use of KM for these conditions, they do highlight the need for more rigorous clinical trials in the future.

We hope this special issue will be helpful for both researchers and TEAM practitioners who want to comprehend and know more about the current clinical status of KM in general practice.

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Research Article

Clinical Experiences of Korean Medicine Treatment against Urinary Bladder Cancer in General Practice

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Urinary bladder cancer (UBC) is one of the most common cancers, with 1 out of every 26 men and 1 out of every 80 women worldwide developing the disease during their lifetime. Moreover, it is a disease that predominantly affects the elderly and is becoming a major health problem as the elderly population continues to rapidly increase. In spite of the rapid development of medical science, the 5-year survival rate has remained around 75% since the 1990s, and the FDA has approved no new drugs for UBC over the last 10 years. In addition, most patients experience frequent recurrence and poor quality of life after diagnosis. Therefore, in order to solve unmet needs by alternative methods, we present our clinical cases of UBC where we observed outstanding results including regression and recurrence prevention exclusively through Traditional Korean Medicine such as (1) herbal therapy, (2) acupuncture, (3) pharmacopuncture and needle-embedding therapy, (4) moxibustion, and (5) cupping therapy. From our experience, it appears that multimodal strategies for synergistic efficiency are more effective than single Korean Medicine treatment. We hope this will encourage investigation of the efficacy of Korean Medicine treatment in clinical trials for UBC patients.

1. Introduction

Urinary bladder cancer (UBC) is a common disease with more than 12 million new cases annually worldwide, which ranks ninth in worldwide cancer incidence [1]. UBC occurs most commonly in the elderly: the median age at diagnosis is 69 years for men and 71 years for women in the USA [2]. It is therefore likely that it will become a greater health problem as the ageing population increases globally [3]. Up to now, surgical resection of the tumor has been the best treatment, but about 70% of patients experience subsequent recurrence, often in different locations from the initial tumor [4]. After repeated resections, the tumor usually becomes more aggressive, and the patients will finally be obliged to receive radical cystectomy. For the remainder of their life, they must endure suffering without their urinary bladder [5].

Therefore, the remission of UBC without surgical resection and the prolongation of the relapse period are goals in the treatment of UBC. From our own clinical experiences from general practice with Korean Medicine (KM), we suggest here that KM could be beneficial in achieving those goals. The state of UBC can be interpreted according to the categories of "溺血" (hematuria), "血淋" (blood stranguria), and "癃閉" (obstruction of urine flow), as written in the books of Traditional Asian Medicine [6, 7]. In China, clinical practice guidelines on various cancers including UBC were recently published for the first time based on the integration of western medicine and Traditional Chinese Medicine (TCM) [7]. The use of TCM without western medicine is only offered to support patients who fail chemotherapy treatment or are in a state too poor to receive western treatment. However, the Korean medical system is different from China in this respect in that Korea has completely dualized Korean Medicine and western medicine [8]. Therefore, the spectrum of KM is broader than that of TCM and could be a potential option for curative treatments, for example, in patients awaiting surgical resection. In this paper, we introduce the multimodal treatments of KM and several outstanding UBC cases.

2. Methods for Korean Medicine against Bladder Cancer (KMBC)

2.1. Herbal Therapy. The KM textbook, Donguibogam, says that urine stored in the bladder can only be excreted through the "氣" (Qi) transformation [6]. In the body, fluid circulation is made by Qi, which is written as "水" (Water), with Qi deemed to be the parent of Water (the son). "肺" (the Lungs) are the major organ involved in controlling "水道" (Waterways) such as the vessels that deliver urine to the bladder. As such, urination problems related to the bladder can be handled with Qi in the Lungs. The shortage of Qi incapacitates the flow of the Waterways and can be improved by boosting the Qi in the Lungs. The herbal remedy, "生脈散" (Saeng-Maek-San, SMS), at "Internal Bodily Elements part I" in Donguibogam has been suggested to improve the shortage of Qi in the Lungs [6]. Based on this background, SMS composed of Liriopis Tuber (tuber of *Liriope platyphylla*, Liliaceae), Ginseng Radix (root of *Panax ginseng*), and Schisandrae Fructus (fruit of *Schisandra chinensis*) was selected as the major herbal decoction and prescribed to UBC patients. Depending on the status of the patients, herbs such as Astragali Radix (root of *Astragalus membranaceus*) and *Oldenlandia diffusa* were added in order to improve energy levels and increase the anticancer effects. The herbal remedies, "猪苓湯" (Jeoryengtang) or "八正散" (Paljeongsan), were also administered in some patients to manage lower urinary tract symptoms. In the case of hematuria, herbs such as Rehmanniae Radix (root of *Rehmannia glutinosa*), node of Lotus rhizome, and Typhae Pollen were added. The decoction was prepared from a mixture of chopped crude herbs which were extracted twice in water at 100°C for 4 hours. The quality of the herbs was tested according to the Korea Food & Drug Administration (K-FDA). Oral administration of 100 mL decoction was prescribed three times a day.

2.2. Acupuncture. The acupuncture treatment is also based on an acupuncture theory in Donguibogam. By stimulating acupoints using a needle, it helps Qi circulate harmoniously in the body through balancing of "陰" (Yin) and "陽" (Yang). The skin was cleaned with alcohol before each insertion. Acupuncture needles (stainless steel, single-use, sterile, and disposable, 0.25 × 30 mm length; DongBang Acupuncture, Inc., Korea) were inserted perpendicularly. The major acupoints are LI04, LR03, KI03, SP09, CV3, CV4, ST29, BL22, BL23, BL32, BL40, and BL52, the location of each based on the WHO standards. The acupoints BL65 and BL67 were also added in the case of urinary symptoms such as frequent and painful urination, and BL17, SP06, and SP10 were added in cases of hematuria dependent on the lower urinary tract symptoms. The acupuncture stimulation should make patients experience a dull or achy feeling known as the "得氣" (De Qi) sensation. The CV3 and CV4 locations anatomically adjacent to the bladder are given particular attention as a precaution to ensure no bladder puncture. It is recommended that the procedure for these points is undertaken after urination. The acupuncture treatments should be administered for at least 3 sessions per week lasting 20–25 minutes.

2.3. Pharmacopuncture and Needle-Embedding Therapy. Pharmacopuncture is a treatment injecting herbal medicine extracts into acupoints in order to enhance the mechanical and chemical effect of acupuncture and herbal medicine. "Herbs part VII" in Donguibogam says that *Nidus Vespae* is nontoxic and cures urination difficulties and stubborn abscesses, the latter through external use [6]. The *Nidus Vespae* pharmacopuncture solution was obtained by the guideline of the pharmacopuncture preparation at an extramural facility meeting Korean Good Manufacturing Practice (K-GMP) standards [9]. The final solution was stored at 4°C. The *Nidus Vespae* pharmacopuncture treatment was conducted using 30-gauge sterile disposable syringes (BD Ultra-Fine™ Needle, USA). After sterile skin preparation, the selected acupoints mentioned above were stimulated with a perpendicular, subcutaneous injection at a depth of 0.5 to 1.0 cm with 0.1 to 0.2 mL of the solution. The treatment can be given on twice-a-week basis for six months and a maintenance treatment may be given weekly. Embedding therapy is also referred to as medicinal thread inserting therapy in order to elongate the duration of stimulation on the acupoints. The harmless catgut threads were used (Miracu™, DongBang Acupuncture, Inc., Korea). The needle-embedding therapy was also performed on the several acupoints mentioned above depending on the status of the patients, which followed the general protocols [10]. It can be given once at two-week intervals for six sessions.

2.4. Moxibustion. Moxibustion has also the intention of stimulating Qi circulation by heating the acupoints through the burning of moxa made from dried mugwort (*Artemisia argyi*). The use of moxibustion can be divided into two methods, direct moxibustion and indirect moxibustion, depending, respectively, on whether moxa is in direct contact with the skin or not [11]. Direct moxibustion is seen to be more effective than the indirect method, but it causes skin burns. Patients with diabetes or edema should receive moxibustion only with careful monitoring by a KM doctor. Moxibustion points include the seven local acupoints of CV2, CV3, CV4, CV12, BL13, BL23, and BL28 affecting the anatomical bladder and the bladder meridian. The treatment should be conducted after sterilizing the skin surface at the acupoints and administered during at least 3 sessions per week. A dressing with povidone-iodine-containing local therapeutics can help to restore skin burns.

2.5. Cupping Therapy. The cupping therapy also helps Qi circulation through local suction created on the skin. It can be divided into two methods, wet-cupping and dry-cupping, depending, respectively, on whether a small quantity of blood was drawn out by vacuum or not [12]. The wet-cupping therapy is seen to be more effective than dry-cupping, but there is a risk of infection due to skin injuries. Correct sterilization is essential before the procedure is carried out, and only disposable cups must be used. Treatment points are located bilaterally at BL23, BL27, BL28, ST28, and ST29. We used 40 cc disposable cups (DongBang Acupuncture, Inc., Korea) and disposable caps for the autolancets. One or two cupping therapy sessions per week were recommended.

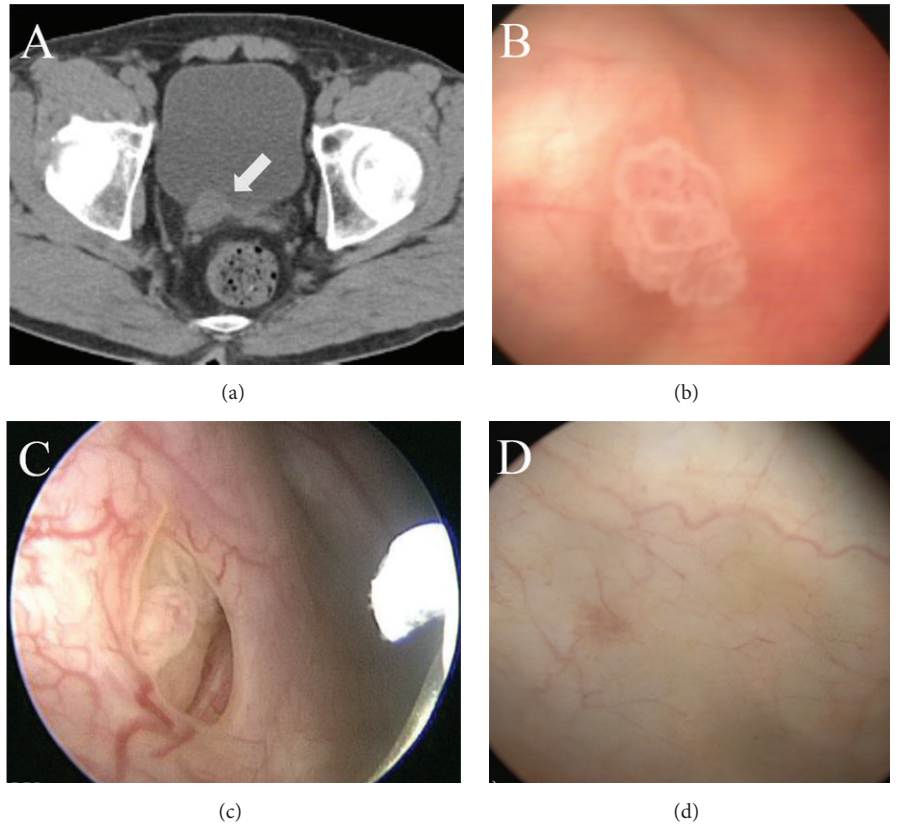

Figure 1: From the upper left, CT scans (a) showed the papillary urothelial carcinoma at the distal right ureter and initial cystoscopy (b) found another mass in the urinary bladder (May 2015). After treating solely with the Korean Medicine treatment, follow-up cystoscopy (c and d) in June and August 2015, respectively, demonstrated its complete remission.

3. UBC Cases

3.1. UBC Regression Waiting for Surgical Resection. The cases are as follows:

(1) A 59-year-old Asian man who presented with hematuria was identified with two masses at the distal right ureter and bladder by CT scans and cystoscopy in May 2015 (Figures 1(a) and 1(b)). Surgical resection was planned for one month later. Whilst waiting for the operation, he received the KMBC treatment for 38 days. Ureteroneocystostomy was performed in June 2015 and papillary urothelial carcinoma was pathologically confirmed with invasion into subepithelial connective tissue (pT1) and high grade (Gr 2). However, the other mass in the bladder, which had been scheduled to be removed transurethrally, could not be found (Figure 1(c)). Any UBC has not been found up to the last follow-up (October 2015).

(2) A 37-year-old Asian man was diagnosed with papillary urothelial carcinoma in June 2013. Multiple masses occurred at the anterior and posterior wall in his bladder in January 2015. Transurethral resection of the bladder tumor (TURBT) was recommended, but he delayed it because he was afraid of the frequent recurrence of UBC in spite of resection. The KMBC treatment was started from January 2015. After the KMBC treatment alone, cystoscopy was carried out in June 2015, revealing that the smaller masses had disappeared and the bigger masses had decreased as compared with the previous 5 months.

3.2. Frequently Recurrent pT2NxM0 Stage. A 71-year-old Asian woman with a past medical history of hypertension and diabetes who presented with urinary frequency and nocturia was diagnosed with urothelial carcinoma with pT1 in May 2013. TURBT was performed, followed by Bacillus Calmette-Guérin (BCG) vaccine treatment. Thereafter, she received TURBT three times against the recurrent UBC in August 2013, November 2013, and March 2014. Finally, the pathological T2 stage and high grade (Gr 3) were confirmed with invasion into subepithelial connective tissue and muscularis propria, micropapillary component (50%), and lymphovascular invasion was present. Cystectomy was therefore recommended for her due to disease progression. After considering the quality of life she would have without a bladder for the rest of her life, she decided to start KMBC treatment from March 2014. After the KMBC treatment alone, cystoscopy was carried out every 3 months, and no recurrent UBC was found up to the last follow-up (September 2015). Her period of disease-free survival (DFS) is over 18 months, which is exceptionally long when compared with her past frequency of recurrence every 3 months and muscle invasion.

3.3. Adenocarcinoma with pT1N0M0 Stage. A 58-year-old Asian woman who had been working as a painter in a shipbuilding yard for several years presented with hematuria. She received TURBT and was diagnosed with adenocarcinoma with pT1N0M0 in March 2011. Unfortunately, her UBC recurred 4 months later and TURBT was performed revealing the same diagnosis, adenocarcinoma with pT1 stage. In order to prevent tumor recurrence, she decided to start the KMBC treatments from October 2011. After the KMBC treatment alone, cystoscopy was carried out every 3 months, and no recurrent UBC has been found up to the last follow-up (November 2014). Her DFS is over 3 years, which is very long considering that her UBC is an adenocarcinoma that recurred in 4 months with poor prognosis compared with urothelial carcinoma.

3.4. Frequently Recurrent pTaN0M0 Stage. The cases are as follows:

(1) A 53-year-old Asian man with past nonspecific medical history presented with urinary frequency, urgency, and nocturia. He received TURBT and was diagnosed with papillary urothelial carcinoma with pTa and low grade (Gr 1) in January 2010. This was followed with BCG vaccine treatment. However, he received TURBT eight times against the recurrence of his UBC up until October 2014. Eventually, the pathological grade increased to Gr 2 and his UBC relapsed three times during the last 6 months. After growing tired of the frequently recurrent tumor, he decided to start the KMBC treatment from October 2014. After the KMBC treatment alone, cystoscopy was carried out every 3 months and no recurrent UBC has been found up to the last follow-up (September 2015). His DFS is around 12 months, which is long compared with his past frequent recurrence in 6-month intervals. Additionally, other urinary symptoms such as painful and frequent urination were improved after KMBC treatment.

(2) A 39-year-old Asian man with past nonspecific medical history presented with hematuria and after receiving TURBT was diagnosed with papillary urothelial carcinoma with pTa and Gr 2 in April 2013. Thereafter, he received TURBT twice against recurrent UBC in January 2014 and May 2014. His disease progressed with the number ($4 \leftarrow 1$) and the region of UBC broadened and expanded to the whole bladder. Due to fear of a frequently recurrent tumor, he decided to start the KMBC treatment from June 2014. After the KMBC treatment only, cystoscopy was carried out every 3 months and did not reveal any recurrent UBC up to the last follow-up (October 2015). His DFS is around 17 months, which is long compared with his past frequent recurrence and disease progression.

4. Discussions

Cancer is a very complex disease, characterized by sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, induction of angiogenesis, and the activation of invasion and metastasis [13, 14]. Besides the cancer cells themselves, aspects of the tumor microenvironment such as stroma or immune cells have also been found to play a key role in tumorigenesis [14]. For these reasons, the western treatment strategy of focusing and targeting only the cancer cells could have lots of limitations [15]. Therefore, a multitarget therapeutic approach is a relevant strategy for addressing the biological complexity of cancer development and one that could possibly be realized with botanicals through synergistic interaction or multifactorial effects between various compounds present in herbal extracts [16, 17]. Recently, a complex herbal formula from KM designed to holistically modulate a person's physiological/pathological networks could act as a blueprint for a new generation of medicine based on integrated network-based medicine [18].

In the KMBC treatments, the main herbal remedy is SMS (生脈散), literally meaning to encourage (生) the energy (脈) in our body, which is interpreted as the ability to enhance immune function. Scientifically, it has been proven to increase tumor necrosis factor- (TNF-) α and interleukin- (IL-) 6 levels with immunological activity enhancement in thymocytes and splenocytes as well as boost the phagocytic activity of macrophages [19, 20]. Several studies on the direct effect against UBC have suggested that a homogeneous polysaccharide from *Panax ginseng* displayed potent antiproliferative and antimetastatic activities in human bladder T24 cells, and Rg3 ginsenoside inhibited the proliferation of EJ (human bladder transitional cell carcinoma cells) by inducing apoptosis [21, 22]. Additionally, treatment with *Liriope platyphylla* significantly inhibited proliferation of MCF-7 (breast carcinoma cells) and Huh-7 (hepatic carcinoma cells) by inducing apoptosis and autophagy pathways [23]. DT-13, a saponin monomer from *Liriope platyphylla*, showed antiangiogenic effects mediated by reductions in vascular endothelial growth factor (VEGF), C-C chemokine receptor type 5 (CCR5), and hypoxia-inducible factor 1α (HIF-1α) [24]. Schizandrin B, one of the main dibenzocyclooctadiene lignans present in Schisandrae Fructus, was also shown to have an anticancer effect by blocking the invasion and migration of lung adenocarcinoma A549 cells through downregulation of expression of HIF-1, VEGF, and matrix metalloproteinase (MMP) [25]. A crude extract from *Schisandra chinensis* has a remarkable reversal effect on multidrug resistance in cancer cells by inhibiting the function and expression of P-glycoprotein and protein kinase C [26].

Externally applied onto the acupoints, *Nidus Vespae* is experimentally proven to increase TNF-α and IL-6 secretion of monocytes and the IgG production of B cells and promote the phagocytosis of tumor cells by monocytes, effects similar to the SMS herbal remedy [27]. Propolis (bee glue), a bee-metabolized resinous mixture of *Nidus Vespae*, has been used as a healing agent since ancient times because of various biological effects, which were validated to be antimicrobial, antioxidant, anti-inflammatory, antidiabetic, dermatoprotective, antiallergic, laxative, immunomodulatory, and anticancer [28, 29]. Recently, it has been suggested as a potential source of adjuvant drugs for bladder cancer

treatment because of the cytotoxicity in human superficial bladder cancer cells, antiangiogenic effects in rat bladder cancer, and chemopreventive effects against bladder chemical carcinogenesis [30–32]. Therefore, our outstanding clinical cases showing UBC regression or recurrence prevention are successful examples of a multitarget therapeutic strategy, both internally and externally, which exhibits the synergistic efficiency of multiextract combinations used presently in KM.

In Donguibogam, "積聚" (Jeok-Chi) was described as a tangible disease with hardness, which is quite similar to tumors [6]. It was seen to mostly develop from the stagnation of Qi, which is interpreted as localized hypoxic conditions with diminished local blood circulation that promotes inflammation and tumor growth [33, 34]. Qi stagnation has also been recorded as being improved by the stimulation of acupoints on the meridian in the body, because the meridian system in Traditional Asian Medicine is a path of Qi [6, 15]. Traditionally, acupuncture, moxibustion, and cupping therapy have been used to stimulate the acupoints on the meridian for Qi flow.

With the progress of research, acupuncture has become recognized and practiced as adjuvant treatment for cancer patients in treating various symptoms in western countries because of its modulatory effects on the nervous, endocrine, and immune systems [35, 36]. In addition to this, it can provide a beneficial effect in anticancer treatment by promoting IL-2, T cell subtypes, and natural killer cells in lung cancer patients [37, 38]. Recently, the anticancer mechanism in acupuncture has been explained to be a result of purinergic signaling involved in diseases of the lower urinary tract including UBC [39]. Treatment of bladder cancer with adenosine 5′-triphosphate (ATP) was confirmed to be effective via P2X5 and P2X7 ion channel receptors in animal models and human cell lines, and it also improved the systemic symptoms associated with advanced malignancy [40]. In light of this, the mechanical deformation of the acupoints on the skin by acupuncture, moxibustion, and cupping therapy in the KMBC treatments induces the release of large amounts of ATP from keratinocytes, fibroblasts, and other cell types in skin, which is beneficial for the inhibition of UBC as well as the symptoms of the lower urinary tract [41, 42].

The acupoints selected in KMBC treatments are commonly known to affect the micturition center and parasympathetic innervation to the urinary system [43, 44]. These places around the navel, sacrum, and legs are organized segmentally with the bladder, which is innervated peripherally by the sympathetic nerves originating at T11-L2, as well as the parasympathetic and somatic nerves originating at S2–S4. Several clinical studies have verified that stimulation on these acupoints alleviates pain, urinary symptoms, and quality of life in patients with an overactive bladder or chronic prostatitis/chronic pelvic pain syndrome (category IIIB) [45, 46]. In our UBC cases, these improvements were also observed, though urinary complaints such as frequency, urgency, and nocturia could not be evaluated by an official symptom assessment tool.

In conclusion, our clinical experiences in general practice suggest that multimodal strategies based on KM could be a safe and effective treatment in managing UBC. They seem to be a good alternative in preventing the recurrence of UBC after surgical resection given that approximately 70% of UBC patients go into relapse despite adjuvant BCG or chemotherapy. In particular, the first two cases suggest that KMBC treatment can be used as a neoadjuvant treatment or an alternative in inoperable status. Large, well-designed randomized clinical trials are necessary for this conclusion because the clinical evidence from our study is insufficient. However, it should be considered that multimodal KM treatments in general practice make it difficult to be standardized and blinded in clinical trials.

Competing Interests

The authors declare that they have no competing interests.

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Research Article

Cold Hypersensitivity in the Hands and Feet May Be Associated with Functional Dyspepsia: Results of a Multicenter Survey Study

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Aim. To investigate whether dyspepsia symptoms differ depending on the presence or absence of cold hypersensitivity in the hands and feet (CHHF). *Methods*. In all, 6044 patients were recruited and provided with a questionnaire about CHHF and dyspepsia. Based on their responses, subjects were divided into a CHHF group (persons who noted cold sensations; $n = 1209$) and a non-CHHF group (persons who noted warm or intermediate sensations; $n = 1744$). The groups were compared in terms of their usual digestion status, using chi-square tests and logistic regression analyses to calculate the propensity score and odds ratios (ORs). We analyzed the participants' responses to questions on dyspepsia symptoms. *Results*. After matching, chi-square tests indicated that the CHHF group had higher frequencies of the following symptoms: bad digestion, poor appetite, discomfort in the upper abdomen, motion sickness, epigastric burning, postprandial fullness, nausea, and bloating. Additionally, CHHF was associated with an increased OR for dyspepsia (bad digestion, vomiting, motion sickness, epigastric burning, postprandial fullness, nausea, epigastric pain, and bloating) compared with the non-CHHF group. *Conclusion*. This study confirmed that CHHF patients have elevated frequencies of most dyspepsia symptoms.

1. Introduction

In traditional Korean medicine, pattern identification is important to both understanding the patient's status and writing a prescription. There are several methods of pattern identification, including 8-principle pattern identification, constitutional pattern identification, and visceral pattern identification [1, 2]. The 8-principle system includes the following factors: yin and yang, exterior and interior, cold and heat, and deficiency and excess. Cold and heat is an important factor for revealing the patient's status. In Korean medicine, cold and heat do not refer to the patient's body temperature alone but instead are an inclusive concept that incorporates the patient's subjective feeling of warmth and chill, as well as fevers diagnosed by a doctor (4 examinations). Cold and heat is a phenomenon that appears when functional activities decline or increase due to diseases or constitution.

Because cold and heat pattern identification is diagnosed based on both the patient's symptoms and 4 examinations by a doctor of Korean medicine, objective evidence is necessarily insufficient for diagnosis. Further, evidence on the effects of cold and heat status on the body also remains uncertain. To resolve these issues, recent studies have attempted to provide objective standards for cold and heat, including the development of a cold pattern questionnaire by Ryu et al. [3] and a study in which Song et al. [4] investigated the dependence of Korean medicine prescriptions on cold and heat disposition in knee osteoarthritis. However, studies of cold and heat and the effects of their status on the body have been performed rarely to date. The rarity of such studies may be explained by the absence of verified diagnostic tools for cold and heat pattern identification; there is considerable uncertainty when conducting a study of cold and heat

with relatively broad inclusion criteria and an open-ended definition of the pattern.

Therefore, we decided to conduct the present study using a narrower range of inclusion criteria and a more specific scope of research. First, rather than investigating the dual states of cold and heat, we limited our investigation to differences between cold and noncold individuals. Second, rather than recruiting subjects based on various symptoms of coldness, we specifically analyzed cold hypersensitivity in the hands and feet (CHHF), which is a representative cold symptom. CHHF is relatively common symptom in Korea and is more frequently observed in women than in men [5]. Patients with CHHF feel coldness both in cold places and at temperatures that are relatively warm. The prevalence rate of CHHF is somewhat uncertain because there is insufficient data to obtain an accurate estimate; however, 38.7% of women complained of coldness in a study by Kondo and Okamura [6]. Third, to investigate the effects of cold on body function, we specifically investigated differences in digestive function between the CHHF and non-CHHF groups via functional dyspepsia symptoms. Our decision to investigate digestive function was based on the relatively high prevalence rate of functional dyspepsia (8–30%) [7] and the "spleen and 4 extremities" theory of the *Huangdi Neijing* [2], which states that the limbs are connected to the spleen. This theory implies that digestive function affects the 4 limb extremities, meaning that the limbs are healthy when the digestive function is healthy and diseased when the digestive function is poor.

Previous studies have also reported that cold hypersensitivity and dyspepsia are correlated [8, 9]. However, those studies targeted limited subjects such as women or patients of a specific age group or involved an insufficient sample size. Thus, additional studies are necessary to clearly demonstrate this relationship. With these considerations in mind, we hypothesized that individuals with CHHF would have a poorer digestion status than those without CHHF. Accordingly, we investigated differences in digestion status among persons with and without CHHF by analyzing responses to a questionnaire.

2. Methods

2.1. Data Collection. This cross-sectional study was conducted between November 2006 and August 2014. All of the questionnaire data, including CHHF and dyspepsia status, were compiled from the Korean Medicine Data Center (KDC) of the Korea Institute of Oriental Medicine (KIOM) [10]. Using this resource, we collected questionnaire data on 6044 adults (19 years old or older) who were admitted to 13 traditional Korean medicine hospitals and 11 traditional Korean medicine clinics. To isolate our analysis from any effects of organic dyspepsia, we excluded data on patients diagnosed with chronic gastritis, gastroduodenal ulcers, esophagitis, fatty liver, hepatitis, or digestive tract tumors. After applying these exclusions, 3558 individuals remained. Among them, patients were excluded who showed unclear symptoms for classification into the CHHF group or non-CHHF group. The remaining 2953 individuals were selected as the final study subjects, including 1209 persons in the CHHF group and 1744 persons in the non-CHHF group (Figure 1). This study was approved by the Institutional Review Board of KIOM (I-0910/02-001).

2.2. Cold Hypersensitivity in the Hands and Feet. Those who responded "cold" to the question "are your hands cold or warm?" and those who responded "cold" to the question "are your feet cold or warm?" were classified as the CHHF group. Those who responded "warm" or "normal" to the both of these questions were classified as the non-CHHF group. We excluded those who stated that they were cold in response to only 1 of these 2 questions because the presence of CHHF symptoms appeared to be unclear. For similar reasons, we excluded those who stated that they were unsure in response to either question.

2.3. Questionnaire on Digestion. The questionnaire included 9 items that refer to common complaints in Korea and were derived from descriptions in the Rome II classification [11]. In addition to these 9 items, the questionnaire included items on 3 topics that are needed to apply pattern identification in Korean medicine: digestion status ("how is your digestion?"), motion sickness, and exhaustion when hungry. The definition for each symptom was based on the description presented in Rome II [12]. The subjects were asked to answer the questionnaire based on their usual status within the past 6 months, which was chosen because the Glasgow Dyspepsia Severity Score [13] includes evaluations of symptoms during the latest 6 months and because the same symptom duration was presented in the most recent Rome III classification.

The details of each question were as follows. To the question "how is your digestion?" the subjects chose either "1. good" or "2. bad." To the question "how is your appetite?" and an item related to anorexia, the subjects chose "1. very good," "2. good," "3. average," or "4. not good." The criteria for these responses were as follows: "1. very good" refers to the desire to eat more foods despite satiety after meal; "2. good" refers to the case in which one feels hungry at mealtimes and wants to eat food; "3. average" refers to the case in which one eats meals at mealtimes but does not have a good appetite; and "4. not good" refers to the case in which one has no appetite at mealtimes and does not have a good sense of taste, even when eating. For the items on dyspepsia symptoms (discomfort in the upper abdomen, vomiting, motion sickness, exhaustion when hungry, belching, epigastric burning, postprandial fullness, nausea, epigastric pain, and abdominal bloating), respondents were asked to choose 1 of the following answers: "1. often," "2. sometimes," and "3. rarely." "1. often" refers to greater than or equal to 2 times per week, "2. sometimes" refers to greater than or equal to 3 times per month, and "3. rarely" refers to less than or equal to 2 times per month (Supplementary Table 1; see Supplementary Material available online at http://dx.doi.org/10.1155/2016/8948690).

2.4. Statistical Analysis. The statistical program SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The general characteristics of the subjects were matched using a propensity score consisting

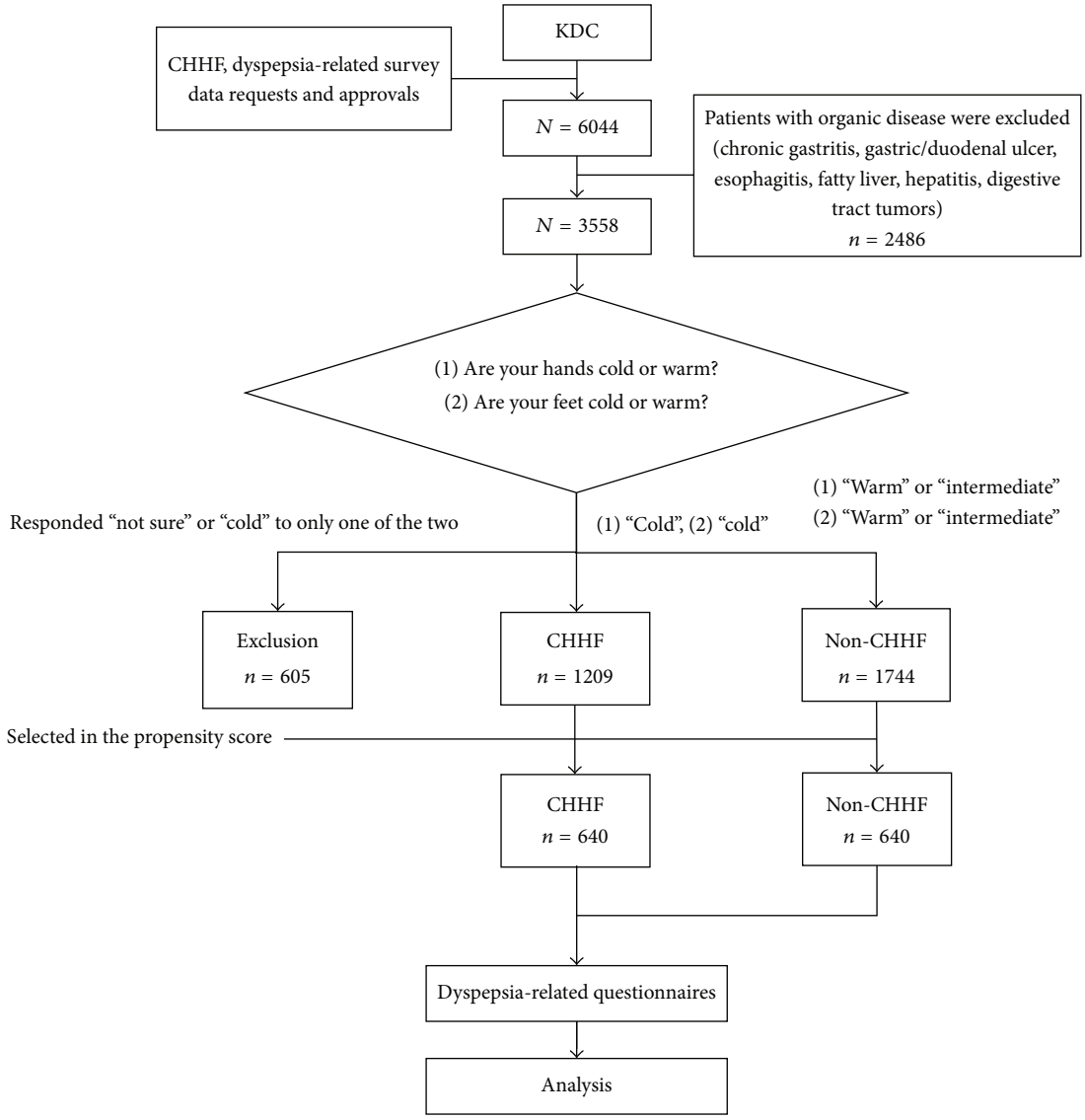

Figure 1: Flow chart of the study. KDC: Korean Medicine Data Center; CHHF: cold hypersensitivity in the hands and feet; non-CHHF: noncold hypersensitivity in the hands and feet.

of sex, age, and BMI, with the matching process involving a minimum distance scoring method. Figure 2 shows the alteration in propensity score distribution between the matched CHHF and non-CHHF groups. These physical characteristics were presented as frequencies and percentages or means ± standard deviations. Between-group comparisons were performed using the chi-square test (for categorical variables) and the independent-samples t-test (for continuous variables). The chi-square test was used to analyze the frequencies and percentages of responses to digestion-related questions in the CHHF and non-CHHF groups. In addition, logistic regression was performed to calculate the odds ratios (ORs) for dyspepsia in the propensity-matched group as well as in the original groups. The OR was determined for each dyspepsia-related item in the CHHF group compared to the non-CHHF group. The statistical significance level was set at $P < 0.05$.

3. Results

3.1. Demographic Characteristics. The number of subjects in the original CHHF and non-CHHF groups was 1209 and 1744, respectively. The total study sample included more women ($n = 1958$; 66.3%) than men ($n = 995$; 33.7%). The female-to-male ratio was much higher in the CHHF group (983 women, 81.4%, versus 226 men, 18.7%) than in the total study sample. The mean ages in the CHHF and non-CHHF groups were 44.6 and 47.4 years, respectively. The mean height and weight in the non-CHHF group were 1.7 cm taller and 6.8 kg heavier, respectively, than the corresponding values in the CHHF group. The mean BMIs in the CHHF and non-CHHF groups were 22.0 and 24.1, respectively. The general characteristics were significantly different between CHHF and non-CHHF groups before matching (all $P < 0.001$). After propensity score matching, the total number

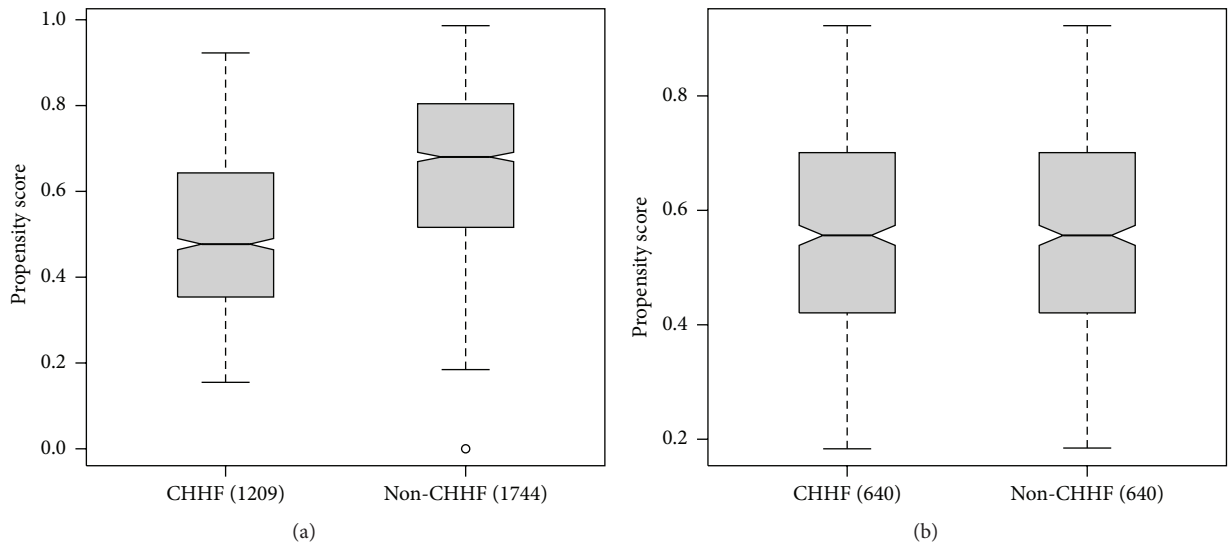

Figure 2: Comparison of the propensity score between the CHHF group and non-CHHF group before and after propensity matching. (a) Propensity score before matching; (b) propensity score after matching. CHHF: cold hypersensitivity in the hands and feet; non-CHHF: noncold hypersensitivity in the hands and feet.

Table 1: General characteristics of the study subjects.

Variable	Before matching			After matching		
	CHHF (n = 1209)	Non-CHHF (n = 1744)	P value	CHHF (n = 640)	Non-CHHF (n = 640)	P value
Sex						
Male	226 (18.7)	769 (44.1)	<0.001	168 (26.3)	173 (27)	0.752
Female	983 (81.3)	975 (55.9)		472 (73.8)	467 (73)	
Age (y)	44.6 ± 13.8	47.4 ± 14.8	<0.001	44.9 ± 14.8	45 ± 14.4	0.858
Height (cm)	161.3 ± 7.6	163.1 ± 8.8	<0.001	161.6 ± 8.1	161.2 ± 8.0	0.375
Weight (kg)	57.4 ± 8.8	64.2 ± 11.0	<0.001	59.8 ± 8.8	59.4 ± 9.1	0.447
BMI (kg/m^2)	22 ± 2.8	24.1 ± 3.2	<0.001	22.9 ± 2.8	22.8 ± 2.8	0.731

Results are presented as n (%) or mean ± standard deviation.
CHHF: cold hypersensitivity in the hands and feet; Non-CHHF: noncold hypersensitivity in the hands and feet; BMI: body mass index.

of patients in each group was 640, with no statistically significant differences in general characteristics between the groups (Table 1).

3.2. Chi-Square Tests of the Relationship between CHHF and Dyspepsia. Before matching, the CHHF group and non-CHHF group significantly differed ($P < 0.001$) in every dyspepsia item. A higher proportion of the CHHF group reported bad digestion and not good appetite compared to the non-CHHF group, and the frequency of all dyspepsia symptoms (discomfort in the upper abdomen, vomiting, motion sickness, exhaustion when hungry, belching, epigastric burning, postprandial fullness, nausea, epigastric pain, and bloating) was also higher.

After matching, significant differences were detected in digestion, postprandial fullness, bloating ($P < 0.001$), discomfort in the upper abdomen, motion sickness, epigastric burning, postprandial fullness, nausea, and appetite ($P < 0.05$). The frequency of dyspepsia symptoms was higher in the CHHF group compared to the non-CHHF group, while there was no statistically significant difference between the two groups in items of vomiting, exhaustion when hungry, belching, and epigastric pain (related to digestion) (Table 2).

3.3. The Odds Ratios for Dyspepsia according to CHHF Status. As can be seen in Table 3 and Supplementary Figure 1, ORs were used to investigate the differences in dyspepsia between the CHHF and non-CHHF groups. Before propensity matching, a significant between-group difference was observed for all items.

After matching analyses, bad digestion, motion sickness, postprandial fullness, bloating ($P < 0.001$), vomiting, epigastric burning, nausea, and epigastric pain ($P < 0.05$) significantly differed between the groups, and there was no significant difference for not good appetite, discomfort in the upper abdomen, exhaustion when hungry, and belching. The OR was highest for bad digestion (2.423) before matching and for bloating after matching (1.883) (Table 3).

For the OR of each response ("often" and "sometimes") for dyspepsia symptoms after matching, both responses

Table 2: Dyspepsia in the CHHF and non-CHHF groups before and after propensity matching.

Variable	Before matching			After matching		
	CHHF *n* (%)	Non-CHHF *n* (%)	*P* value	CHHF *n* (%)	Non-CHHF *n* (%)	*P* value
Digestion						
Good	814 (67.3)	1453 (83.3)	<0.001	440 (68.8)	513 (80.2)	<0.001
Bad	395 (32.7)	291 (16.7)		200 (31.3)	127 (19.8)	
Appetite						
Extremely good	74 (6.1)	131 (7.5)		43 (6.7)	45 (7.0)	
Good	608 (50.3)	1014 (58.1)	<0.001	319 (49.9)	366 (57.2)	0.045
Average	423 (35)	508 (29.1)		223 (34.9)	188 (29.4)	
Not good	103 (8.5)	91 (5.2)		54 (8.5)	41 (6.4)	
Discomfort in the upper abdomen						
Often	74 (6.1)	40 (2.3)		32 (5.0)	17 (2.7)	
Sometimes	441 (36.5)	410 (23.5)	<0.001	210 (32.8)	193 (30.2)	0.038
Rarely	694 (57.4)	1294 (74.2)		398 (62.2)	430 (67.2)	
Vomiting						
Often	5 (0.4)	5 (0.3)		3 (0.5)	3 (0.5)	
Sometimes	133 (11)	98 (5.6)	<0.001	67 (10.5)	45 (7.0)	0.094
Rarely	1071 (88.6)	1641 (94.1)		570 (89.1)	592 (92.5)	
Motion sickness						
Often	40 (3.3)	19 (1.1)		16 (2.5)	11 (1.7)	
Sometimes	327 (27)	292 (16.7)	<0.001	165 (25.8)	113 (17.7)	0.001
Rarely	842 (69.6)	1433 (82.2)		459 (71.7)	516 (80.6)	
Exhaustion when hungry						
Often	132 (10.9)	120 (6.9)		60 (9.4)	41 (6.4)	
Sometimes	524 (43.3)	617 (35.4)	<0.001	260 (40.6)	245 (38.3)	0.057
Rarely	553 (45.7)	1007 (57.7)		320 (50)	354 (55.3)	
Belching						
Often	135 (11.2)	125 (7.2)		70 (10.9)	53 (8.3)	
Sometimes	408 (33.7)	578 (33.1)	<0.001	217 (33.9)	224 (35.0)	0.272
Rarely	666 (55.1)	1041 (59.7)		353 (55.2)	363 (56.7)	
Epigastric burning						
Often	48 (4.0)	41 (2.4)		19 (3.0)	17 (2.7)	
Sometimes	354 (29.3)	396 (22.7)	<0.001	194 (30.3)	156 (24.4)	0.049
Rarely	807 (66.7)	1307 (74.9)		427 (66.7)	467 (73.0)	
Postprandial fullness						
Often	73 (6.0)	47 (2.7)		32 (5.0)	19 (3.0)	
Sometimes	326 (27.0)	285 (16.3)	<0.001	166 (25.9)	120 (18.8)	0.001
Rarely	810 (67.0)	1412 (81.0)		442 (69.1)	501 (78.3)	
Nausea						
Often	32 (3.6)	20 (1.6)		13 (2.8)	12 (2.6)	
Sometimes	228 (25.6)	187 (15.2)	<0.001	121 (25.7)	74 (16.2)	0.002
Rarely	631 (70.8)	1024 (83.2)		336 (71.5)	370 (81.1)	
Epigastric pain (related to digestion)						
Often	40 (3.3)	22 (1.3)		12 (1.9)	9 (1.4)	
Sometimes	250 (20.7)	223 (12.8)	<0.001	118 (18.4)	90 (14.1)	0.078
Rarely	919 (76.0)	1499 (86.0)		510 (79.7)	541 (84.5)	
Bloating						
Often	76 (6.3)	51 (2.9)		35 (5.5)	16 (2.5)	
Sometimes	422 (34.9)	419 (24)	<0.001	228 (35.6)	157 (24.5)	<0.001
Rarely	711 (58.8)	1274 (73.1)		377 (58.9)	467 (73.0)	

P values are calculated from chi-square tests of the CHHF versus non-CHHF groups.
CHHF: cold hypersensitivity in the hands and feet; Non-CHHF: noncold hypersensitivity in the hands and feet.
Sample questions: digestion: "how is your digestion?"; appetite: "how is your appetite?"; symptoms (discomfort in the upper abdomen, vomiting, motion sickness, exhaustion when hungry, belching, epigastric burning, postprandial fullness, nausea, epigastric pain, and bloating): "do you have any of the following symptoms?"

Table 3: The odds ratios and 95% confidence intervals for dyspepsia before and after propensity matching according to CHHF status.

Variable	Non-CHHF	Before matching		After matching	
		CHHF OR (95% CI)	*P* value	CHHF OR (95% CI)	*P* value
Digestion: bad	Ref	2.423 (2.036–2.884)	<0.001	1.836 (1.421–2.372)	<0.001
Appetite: not good	Ref	1.693 (1.264–2.268)	<0.001	1.349 (0.885–2.056)	0.165
Discomfort in the upper abdomen	Ref	2.134 (1.825–2.495)	<0.001	1.245 (0.990–1.566)	0.061
Vomiting	Ref	2.053 (1.572–2.680)	<0.001	1.515 (1.031–2.226)	0.035
Motion sickness	Ref	2.008 (1.689–2.389)	<0.001	1.641 (1.264–2.130)	<0.001
Exhaustion when hungry	Ref	1.621 (1.398–1.879)	<0.001	1.238 (0.994–1.542)	0.057
Belching	Ref	1.207 (1.041–1.400)	0.013	1.065 (0.854–1.329)	0.573
Epigastric burning	Ref	1.490 (1.268–1.751)	<0.001	1.347 (1.060–1.711)	0.015
Postprandial fullness	Ref	2.095 (1.769–2.481)	<0.001	1.615 (1.255–2.077)	<0.001
Nausea	Ref	2.038 (1.656–2.509)	<0.001	1.716 (1.260–2.336)	0.001
Epigastric pain	Ref	1.931 (1.598–2.332)	<0.001	1.393 (1.044–1.858)	0.024
Bloating	Ref	1.899 (1.625–2.219)	<0.001	1.883 (1.489–2.382)	<0.001

CHHF: cold hypersensitivity in the hands and feet; Non-CHHF: noncold hypersensitivity in the hands and feet; OR: odds ratio; CI: confidence interval; Ref: reference.
"Non-CHHF" was employed as the reference in every analysis.
Sample questions: digestion: "how is your digestion?"; appetite: "how is your appetite?"; symptoms (discomfort in the upper abdomen, vomiting, motion sickness, exhaustion when hungry, belching, epigastric burning, postprandial fullness, nausea, epigastric pain, and bloating): "do you have any of the following symptoms?" Symptoms are the sum of "often" and "sometimes" responses.

("often" and "sometimes") for bloating significantly differed between groups. There was a significant difference in either "often" or "sometimes" responses for discomfort in the upper abdomen, vomiting, motion sickness, exhaustion when hungry, epigastric burning, postprandial fullness, nausea, and epigastric pain, and there was no difference in belching (Supplementary Figure 1).

4. Discussion

We chose to investigate the relationship between CHHF (including various cold symptoms) and indigestion because of the "spleen and 4 extremities" theory that was described in Huangdi's classic text [2], which is one of the most famous works in oriental medicine. As stated in this theory, the spleen is included in the human digestive system and controls the passage of nutrition to the 4 limbs, and therefore symptoms in the 4 extremities are thought to relate to the function of the spleen. This theory is taken into consideration when prescribing acupuncture or herbal medicine in the clinic. Furthermore, because the prevalence of functional dyspepsia is high (8–30%), we expected that it would be relatively easy to investigate correlations between CHHF and dyspepsia [7].

CHHF refers to a condition in which one experiences discomfort in daily living because of cold symptoms in the limbs. It is more inclusive than Raynaud's phenomenon and includes decreased temperature in the hands and feet, as well as the subjective sensation of cold. CHHF is suspected to induce spastic peripheral vasoconstriction, but no specific, certain cause has yet been identified. In Korea, CHHF is a relatively common symptom and occurs more often in women than in men [5]. The diagnosis and treatment of CHHF are a relatively active topic of research in Korea, including recent studies by Park et al. [14] and Hur et al. [5]. In another study of the relationship between CHHF and diseases, Tokunaga et al. [15] investigated "Hie," which refers to oversensitivity to coldness. Kondo and Okamura [6] also investigated the relationship between CHHF and the Cornell Medical Index (CMI).

Dyspepsia is a digestive function disorder that refers to the collective symptoms of the upper gastrointestinal tract. In general, the term "dyspepsia" denotes functional dyspepsia; in this study, we therefore excluded persons who had been diagnosed with chronic gastritis, gastroduodenal ulcers, esophagitis, fatty liver, hepatitis, and digestive tract tumors. Through these exclusions, we sought to remove as many cases of organic dyspepsia as was feasible. In Rome III [16], functional dyspepsia is defined as the presence of symptoms including postprandial satiety, early satiety, gastric pain, and epigastric burning without any organic disease. Although the Rome III definition is generally accepted, the diagnostic standard of Rome III has not been applied strictly to many cases in clinical practice, and therefore the diagnostic period of dyspepsia has remained somewhat controversial [17].

In the present study, the data were compiled from questionnaire responses that had been collected by KDC. Participants who noted having cold hands and feet were assigned to the CHHF group, while participants who had neither cold hands nor cold feet were assigned to the non-CHHF group. Between-group differences in indigestion were analyzed using the KDC digestion questionnaire. Several recent studies have used the KDC data, including those by Do et al. [18] study on the Sasang constitutional diagnostic method, Chae et al. [19] on the development of the Sasang constitution questionnaire, and Jang et al. [20] on metabolic syndrome.

The aim of this study was to verify whether there was a difference in functional dyspepsia frequency according to the presence of CHHF and, if so, which of the various digestion-related symptoms differed. In summary, patients with CHHF showed a high frequency of dyspepsia, with this tendency generally maintained after matching. Bloating in particular significantly differed between groups both before and after matching: the highest OR after matching was 1.883 and the responses "often" and "sometimes" were significantly more common in the CHHF group.

The general characteristics of subjects differed markedly depending on the presence of CHHF. In the CHHF group, the female-to-male ratio (81%) was much higher compared to the non-CHHF group (56%), and the mean age and BMI were higher in the non-CHHF group (47.4 years and 24 kg/m^2 versus 44.6 years and 22 kg/m^2, resp.). We concluded that these differences could harbor considerable bias in examining the relation between CHHF and dyspepsia. Therefore, the patients were matched in the CHHF group and non-CHHF group using the propensity score matching method (640 patients per matched group). There was no difference in sex, BMI, and age after matching. These differences in general characteristics confirmed that CHHF was influenced by sex and BMI, as in previous studies [5, 6].

This study suggests that there is a correlation between CHHF and functional dyspepsia. In the chi-squared test shown in Table 2, the CHHF group and non-CHHF group significantly differed in all items before matching and in digestion, appetite, discomfort in the upper abdomen, motion sickness, epigastric burning, postprandial fullness, nausea, and bloating after matching. There was no significant difference in vomiting, exhaustion when hungry, belching, or epigastric pain.

As shown in Table 3, the OR for the development of dyspepsia symptoms (bad digestion, not good appetite, and sum of "often" and "sometimes" for the occurrence of each symptom) was increased in every item before matching in the CHHF group, and a significantly increased OR was observed for bad digestion, vomiting, motion sickness, epigastric burning, postprandial fullness, nausea, epigastric pain, and bloating after matching. A significant OR was not observed for not good appetite, discomfort in the upper abdomen, exhaustion when hungry, or belching. These results revealed a slight difference in the items with significant differences according to the analysis method but generally supported a high frequency of dyspepsia in the CHHF group.

In this study, we observed a significant difference between the frequencies of indigestion in participants who did and did not have CHHF. Previously, Tokunaga et al. [15] found that symptom frequencies differed according to the presence of Hie (oversensitivity to coldness), and Nietert et al. [21] found that Raynaud's phenomenon was associated with undiagnosed vascular disease. Together with these earlier investigations, the present study provides evidence supporting the notion that the human disease state of "cold" can endanger human health.

However, this study has several limitations. First, it relied on a cross-sectional design and used qualitative and subjective indicators. Second, the KDC survey was provided to patients who had been admitted to a group of traditional Korean medicine clinics and hospitals in Korea, rather than to members of the general population. Third, survey respondents were assigned to the CHHF and non-CHHF groups based on the questionnaire answers, rather than a doctor's diagnostic findings. Fourth, although the questions on dyspepsia were for the most part based on the functional dyspepsia symptoms described in Rome II [12], a verified questionnaire on dyspepsia was not used. Additionally, the questions referring to digestion status were 2-point scales, questions referring to appetite were 4-point scales, and dyspepsia symptoms were 3-point scales. Therefore we could not sum the total scores for examination. Fifth, we also used self-reported survey responses to determine which patients had organic digestive diseases (and subsequently exclude the identified patients from our analysis). However, the presence or absence of organic disease was not verified based on doctors' examinations, such as endoscopic findings.

Therefore, we believe that a follow-up study is necessary to accurately define the relationship between CHHF and functional dyspepsia. Additional studies to delineate the mechanism between dyspepsia and CHHF are also needed. We hope that future studies will better reveal the precise correlation between these two symptoms and their underlying cause.

5. Conclusions

In this study, we were able to verify that patients with CHHF have more chronic (lasting more than 6 months) functional dyspepsia symptoms, especially bloating.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contribution

Kwang-Ho Bae conceived the study design and drafted the paper. Ki-Hyun Park and Jong-Hyang Yoo collected and analyzed the questionnaire data. Ju Ah Lee, Youngseop Lee, and Siwoo Lee helped with the previous study and reviewed the paper. All of the authors contributed critically to the final paper and approved the final version. Youngseop Lee and Siwoo Lee are equal contributors.

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Research Article

Translation of Korean Medicine Use to ICD-Codes Using National Health Insurance Service-National Sample Cohort

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Background. Korean medicine was incorporated into the Korean Classification of Diseases (KCD) 6 through the development of U codes (U20–U99). Studies of the burden of disease have used summary measures such as disability-adjusted life years. Although Korean medicine is included in the official health care system, studies of the burden of disease that include Korean medicine are lacking. *Methods*. A data-based approach was used with National Health Insurance Service-National Sample Cohort data for the year 2012. U code diagnoses for patients covered by National Health Insurance were collected. Using the main disease and subdisease codes, the proportion of U codes was redistributed into the related KCD 6 codes and visualized. U code and KCD code relevance was appraised prior to the analysis by consultation with medical professionals and from the beta draft version of the International Classification of Diseases-11 traditional medicine chapter. *Results*. This approach enabled redistribution of U codes into KCD 6 codes. Musculoskeletal diseases had the greatest increase in the burden of disease through this approach. *Conclusion*. This study provides a possible method of incorporating Korean medicine into burden of disease analyses through a data-based approach. Further studies should analyze potential yearly differences.

1. Introduction

Efforts towards standardization and globalization of heath care are occurring in different aspects of medicine and health policy [1]. Traditional medicine is included in this work; since the founding of the Division of Traditional Medicine in the World Health Organization in 1972, traditional medicine, based on the International Classification of Traditional Medicine (ICTM), is being included in the current updates to the International Statistical Classification of Diseases and Related Health Problems (ICD), currently in its 10th revised edition and in the progress of being updated to the 11th edition [2]. The Korean Classification of Diseases (KCD) also reflects these efforts. In 2010, the third edition of the Korean Classification of Diseases of Oriental Medicine (KCDOM3) was incorporated into the Korean modification of the ICD-10, or KCD 6, using U codes (U20–U99) [3]. In this aspect, KCD 6 was groundbreaking as the first publication in which Western medicine and traditional medicine shared a common platform.

U codes (U00–U99), also called codes for special purposes, are in Chapter XXII of the fourth edition of ICD-10 [4]. While this chapter includes codes such as U04 for severe acute respiratory syndrome (SARS), most of the codes in this chapter were developed to incorporate patterns or disorders diagnosed through Korean medicine (U20–U99). In Korea, doctors of Korean medicine are advised to use KCD 6, which is based on Western medicine, as their

primary code system; however, when the doctor cannot correlate the diagnosis specifically to KCD 6, the doctors are to supplement the diagnosis with a U code [5]. While KCDOM2 (1994), which was based on Korean medicine, was used by doctors of Korean medicine instead of KCD 5, the overlap and mismatch of some diseases between KCD and KCDOM caused serious confusion. Therefore, U codes were developed to support the patterns and symptoms diagnosed only through Korean medicine while incorporating many of the disease codes from KCDOM2 that showed similar characteristics to KCD 6 codes. For example, terminology in Korean medicine that refers to cancer was absorbed into KCD 6 because the symptoms of the two different codes were almost identical; however, terminology in Korean medicine referring to patterns of disorders, such as qi deficiency pattern/syndrome, remained under U codes [3]. Therefore, through the third revision, KCDOM eliminated the overlapping disease classifications between the previous KCDOM and KCD5 and reorganized the remaining disorders and patterns into U codes, which reduced possible duplicate coding and allowed pattern identification and diagnosis through Korean medicine. The incorporation of KCDOM3 into KCD 6 was also conducted to meet the needs of doctors of Korean medicine to more effectively reflect the patient's condition. As a result, one of the major characteristics of KCDOM3 is its relationship with KCD 6 [5].

One approach towards better health care is quantification of the burden of disease [6]. Burden of disease is a crucial input into health policy, because it provides an account of health loss due to different risks through a disease-by-disease analysis [7]. Most health analyses concentrate on mortality, thereby omitting nonfatal, chronic diseases that affect quality of life [8]. At the same time, a focus on noncommunicable or chronic diseases has gained support as the morbidity and comorbidity of chronic diseases in the general population have increased [9]. The measurement of the burden of diseases, or Global Burden of Disease Study (GBD), was initiated in 1992, with three major goals: (1) to provide information on nonfatal health outcomes, as most of the health policies are generally focused on mortality; (2) to develop epidemiological assessments for major disorders without bias; and (3) to quantify the burden of disease with a measure that could also be used for cost-effectiveness analysis [10]. Research is currently being conducted in different countries for diverse risk factors, such as recent analyses of the global burden of disease due to ischemic heart disease, and to determine if there is epidemiological convergence across countries [1, 11]. Different approaches have been taken in burden of disease studies, including disability weights to cover the burden of disease more elaborately [12]. The foremost milestone, one of the most important milestones, of the GBD study was the development of the composite indicator disability-adjusted life years (DALYs), which is being used throughout diverse academic research as a summary measure of the overall burden of disease and is expressed as the number of years lost due to ill-health, disability, or early death [8].

Using DALYs, the burden of different diseases and risk factors have been analyzed in Korea using nationally representative data provided by health-related government agencies such as the Health Insurance Review & Assessment Service (HIRA) and National Health Insurance Service (NHIS) [13]. To analyze the burden of disease using nationally representative big data, disease codes (KCD) that are collected as part of the patient's health care utilization have to be categorized by definitions of the causes of disability and death in previous burden of disease studies [14]. In other words, the disease codes are regrouped and redistributed into different clusters to define risk factors [15]. However, previous studies have not included the portion of health care utilization classified under U codes when calculating the burden of diseases by disability and death causes, although the nationally representative data include information for health care utilization coded under the U codes, such as the number of visits and costs [16]. Therefore, an understanding of the U codes from the perspective of Western medicine is needed to redistribute the uncalculated burden of diseases under U codes to other codes.

Because data with main disease codes not covered by KCD 6 were overlooked in previous studies of the burden of disease, this study hypothesized that the collection of the subdisease codes within a year of data collection would reflect what was covered by the main disease code. In other words, the assumption was that, within the annual collection of data, the combination of main disease code and subdisease code would cover the diseases for a patient throughout a year.

2. Materials and Methods

2.1. Structure of U Codes. U codes can be divided into three components (Table 1): Korean medicine disorders (U20–U33), Korean medicine patterns (U50–U79), and four constitution medicine patterns (U95–U98). Because the U codes were created to define disorders or patterns that could not be defined using the disease classification system of Western medicine presented in KCD 6, the disorders and patterns in the U codes do not correspond directly to disease names in the KCD. Therefore, to incorporate the U codes into the burden of disease algorithm of the KCD, the underlying disorders and diseases in Western medicine were analyzed in this study using a data-based approach, via a redistribution algorithm of U codes into KCD 6 codes.

2.2. Data Source. The National Health Insurance Service-National Sample Cohort (NHIS-NSC) of 2012, which includes data for 1 million patients, was used for data analysis. NHIS-NSC data provide information on the utilization of healthcare based on the NHI claims from medical institutions to the NHIS from inpatient and outpatient clinic visits for each individual patient [17]. NHI claims data contain principal and additional diagnoses, hospitalization/outpatient treatment, dates of examinations, medical fees, details of medical services, prescribed medications, hospital codes, and patients' sex and age and are categorized on the basis of the examination documented in the claims from the medical institutions [18]. For this study, the main disease and subdisease codes were collected for outpatients of Korean medicine clinics from the 2012 NHIS-NSC data. U codes

Table 1: Summary of U codes or code for special purposes in the Korean Classification of Diseases 6, which was revised in 2009.

3-digit code	Code name	Number of 4-digit subcategories
U20–U33	**Disease name in Oriental medicine**	**97**
U20-U21	General diseases	12
U22	Mental and behavioral disorders	3
U23-U24	Diseases of the nervous system	12
U25	Diseases of eye, tongue, and throat	6
U26	Diseases of the circulatory system	4
U27	Diseases of the respiratory system	8
U28	Diseases of the digestive system	10
U29	Diseases of the skin and subcutaneous tissue	8
U30	Diseases of the musculoskeletal system and connective tissue	7
U31	Diseases of the genitourinary system	10
U32	Diseases of the female genitourinary system and those related to pregnancy	8
U33	Diseases of retardation and development, childhood, and adolescence	9
U50–U79	**Disease pattern/syndrome in Oriental medicine**	**191**
U50	Disease pattern/syndrome of six excesses	9
	Disease pattern/syndrome of the six meridians	45
	Greater yang disease pattern/syndrome	14
	Yang brightness disease pattern/syndrome	6
U51–U57	Lesser yang disease pattern/syndrome	6
	Greater yin disease pattern/syndrome	3
	Lesser yin disease pattern/syndrome	10
	Reverting yin disease pattern/syndrome	6
U58	Disease pattern/syndrome of defense-qi-nutrient-blood	9
U59	Disease pattern/syndrome of triple energizer	4
	Disease pattern/syndrome of qi-blood-yin-yang-fluid-humor	30
	Disease pattern/syndrome of qi	6
U60–63	Disease pattern/syndrome of blood	6
	Disease pattern/syndrome of qi-blood-yin-yang	9
	Disease pattern/syndrome of fluid and humor	9
	Disease pattern/syndrome of viscera and bowels	94
	Liver disease pattern/syndrome	14
	Heart disease pattern/syndrome	12
	Spleen disease pattern/syndrome	7
	Lung disease pattern/syndrome	11
	Kidney disease pattern/syndrome	8
U64–U79	Gallbladder disease pattern/syndrome	4
	Stomach disease pattern/syndrome	5
	Large intestine disease pattern/syndrome	4
	Small intestine disease pattern/syndrome	3
	Bladder disease pattern/syndrome	2
	Disease pattern/syndrome of thoroughfare, conception vessels, and uterus	7
	Combined disease pattern/syndrome of viscera and bowels	17
U95–U98	**Disease pattern/syndrome of Four-Constitutional Medicine**	**18**
U95	Soeumin disease pattern/syndrome	5
U96	Soyangin disease pattern/syndrome	5
U97	Taeumin disease pattern/syndrome	5
U98	Taeyangin disease pattern/syndrome	3

as the main disease code were redistributed to the KCD 6 codes.

2.3. Data Analysis

2.3.1. Redistribution of U Codes to KCD 6 Codes. The primary goal was to use the data from the U code visits that also had subdisease codes in 2012 to the remaining visits with only U codes as main disease codes and without any subdisease codes.

The method to redistribute the U codes to KCD 6 codes was derived from garbage codes [1]. A garbage code redistribution algorithm was developed in a previous study of the burden of disease to explain the unknown cause of death based on the underlying cause in ICD-10 [14]. Similarly, the redistribution algorithm of U codes to KCD 6 codes aimed to explain disorders or patterns not explained by Western medicine based on the underlying cause found in the KCD 6.

First, U codes as the main disease code were collected, which accounted for 151,967 visits in 2012. These data became the target for data analysis, which was conducted with the 30 most commonly used U codes, covering approximately 80% of the total U code visits. Then, the subdisease codes and their frequencies were collected. In this process, subdiseases coded with U codes, S codes (injury, poisoning, and certain other consequences of external causes), R codes (symptoms, signs, and abnormal clinical and laboratory findings, NEC), and Z codes (factors influencing health status and contact with health services) were excluded before determining the frequencies.

Before the redistribution of the main disease U codes to subdisease KCD 6 codes, a reorganizing process was conducted to rule out the codes that were irrelevant to the main disease codes. Subdisease codes can be used for diseases other than the main disease in many cases. To avoid this problem, only subdisease codes that were relevant to the main U codes were selected by doctors of Korean medicine, and the final decision was based on agreement of trained KMD doctors. For example, in the case of U303 (neck stiffness), the codes that were not directly related to pain or abnormal sensation of the neck, such as digestive disorders or urinary disorders, were removed. This process was based on consultation with medical professionals and professors and researchers at the College of Korean Medicine, Kyung Hee University, as well as review of the beta version of ICD-11, which includes traditional medicine in its structure based on the ICTM. By reviewing the beta version of ICD-11, the definition and explanation for each of the disorders or patterns in the U code were studied for the specific symptoms or signs replaced by KCD 6 codes. Symptoms or signs of the disorders or patterns in the U code that were not mentioned in the corresponding ICD-11 definition were removed before data analysis.

2.3.2. Calculation of the Proportion of U Codes in KCD 6 Codes. After selecting the KCD 6 codes among the subdisease codes and calculating the frequencies, each of the frequencies was replaced with the ratio of each U code and KCD 6 code within the total frequency of the corresponding U code. For example, in the case of U303 (neck stiffness), the frequency of the KCD 6 code in the subdisease code was converted into an intercode proportion, which equaled 1, within U303:

$$[\text{Inter-U code proportion}] = \frac{[\text{Frequency of KCD 6 sub disease code}]}{[\text{Total frequency of the corresponding U code}]}. \quad (1)$$

Then, each of these proportions was expanded and converted into the proportion within the total 151,967 visits that was only coded by U code and therefore missed in the original analysis of burden of disease, comprising the target data for analysis:

$$[\text{U code-KCD 6 expected frequency}] = [\text{Inter-U code proportion}] * 151,967. \quad (2)$$

Finally, this proportion within the missed data was converted into a proportion within the total frequency of corresponding KCD 6 codes in the year 2012. Through this process, this study was able to quantify the proportion of the burden of disease in each KCD 6 code that was related to a U code or how much the missed data coded by U code added to the proportion of each burden of disease based on the KCD 6 codes. This process was conducted for each of the KCD codes in the subdisease codes in the U code data:

$$[\text{U code Proportion}] = \frac{[\text{U code-KCD 6 expected frequency}]}{[\text{Total frequency of the corresponding KCD 6 code}]}. \quad (3)$$

However, when the frequency of the corresponding KCD 6 codes did not exceed 1,500, which was about 1% of the total U code frequency in our data, this process could result in overfitting of the total data. The process was designed under the assumption that the diseases in the KCD 6 codes followed a normal distribution; however, when the morbidity of the disease is too low, this process could stretch the proportion over the actual morbidity. Therefore, in such cases, the actual frequency, instead of the expected frequency, within the total U code data was used to calculate the proportion

$$[\text{U code Proportion}] = \frac{[\text{Frequency of KCD 6 sub disease code}]}{[\text{Total frequency of the corresponding KCD 6 code}]} \quad (4)$$

if the total frequency of the corresponding KCD 6 code was <1,500.

Furthermore, the cooccurrence of U codes and the corresponding KCD codes was visualized to show the relationship between the burdens of disease based on U codes and KCD 6 codes. Specifically, each of the inter-U code proportions was visualized to show the relationship between the U codes and KCD 6 codes in the NHIS-NSC data from 2012.

The data were analyzed using SAS 9.3 (SAS Institute), and the data were visualized using Python.

Table 2: Thirty most commonly used U codes in Korea, 2012.

Code	Name	Frequency (2012)
U303	Neck stiffness	6,552
U240	Numbness	3,142
U234	Sequela of wind stroke	2,680
U670	Pattern/syndrome of heart fire flaming upward	1,684
U238	Impediment disease	1,323
U280	Food accumulation	768
U680	Pattern/syndrome of spleen qi deficiency	717
U301	Painful impediment	551
U305	Crane-knee arthritis	488
U304	Joint-running wind	480
U241	Insensitivity	462
U651	Pattern/syndrome of liver qi depression	458
U306	Muscle cramp	411
U236	Tremor	392
U222	Fire disease, hwa-byung	362
U221	Depression, melancholy, and depressive syndrome	326
U302	Fixed impediment	325
U650	Pattern/syndrome of ascendant hyperactivity of liver yang	306
U730	Pattern/syndrome of stomach qi deficiency	291
U230	Head wind	270
U710	Pattern/syndrome of kidney qi deficiency	264
U660	Pattern/syndrome of heart qi deficiency	246
U640	Pattern/syndrome of liver blood deficiency	233
U233	Prodrome of wind stroke	231
U794	Pattern/syndrome of spleen and kidney yang deficiency	225
U784	Pattern/syndrome of liver and kidney yin deficiency	222
U332	Night crying	199
U260	Chest impediment	197
U600	Qi deficiency pattern/syndrome	186
U204	Consumptive disease	173

3. Results

3.1. Redistribution of U Codes, or Codes for Special Purposes, into KCD 6 Codes. Table 2 shows the 30 most commonly used U codes from the data in the NHIS cohort data from 2012 that also had subdisease codes and the number of U code visits in 2012 (n = 24,164). The remaining 151,967 visits had only U codes as the main disease codes, without any subdisease codes.

The most commonly reported U code was U303, or neck stiffness. The most commonly used KCD 6 code in this analysis was related to musculoskeletal diseases (M codes), followed by diseases of the nervous system (G codes). Diseases of the digestive system (K codes) and mental and behavioral disorders (F codes) were also common. For example, U303 (neck stiffness) was redistributed to the following KCD codes: M791 (myalgia), M626 (muscle strain), M759 (shoulder lesion, unspecified), M758 (other shoulder lesions), M750 (adhesive capsulitis of shoulder or frozen shoulder), M255 (pain in joint), M542 (cervicalgia), M548 (other dorsalgia), M751 (rotator cuff or supraspinatus tear of rupture [complete, incomplete] not specified as traumatic), M796 (pain in limb), M549 (backache NOS), M531 (cervicobrachial syndrome), M501 (cervical disc disorder with radiculopathy), M797 (fibromyalgia), M624 (contracture of muscle), G568 (interdigital neuroma of upper limb), and G439 (migraine, unspecified).

Because KCD 6 codes corresponding to U codes were reviewed using the beta version of ICD-11 and with medical professionals prior to the redistribution process, there were no KCD codes without any relevance to the corresponding U codes. The proportions of the U codes to the KCD codes were fairly evenly distributed following the redistribution to enable comparison of the data from the 24,164 visits to the remaining 151,967 visits with only U codes as the main disease codes and without any subdisease codes and the additional adjustments to prevent overfitting values in the redistribution table. The U code proportions ranged from <1% to approximately 20% of the burden of disease for each KCD 6 code; there were few high proportions for each of the U codes (Table 3).

3.2. Visualization of the Relationships between U Codes and KCD 6 Codes. Figure 1 shows the data visualization of the 1-digit KCD 6 code in each U code, showing which KCD 6 chapter or disorder explains each U code and its proportion. A clear relationship between the 30 most commonly used U codes and musculoskeletal diseases is prominent. U codes that did not show a relationship with musculoskeletal diseases were U280 (food accumulation), U332 (night crying), U600 (qi deficiency pattern/syndrome), U670 (pattern/syndrome of heart fire flaming upward), U680 (pattern/syndrome of spleen qi deficiency), and U730 (pattern/syndrome of stomach qi deficiency). In contrast, these codes showed strong relationships with diseases of the nervous system (G codes) and diseases of the digestive system (K codes). There were two major U codes that had strong relationships with mental disorders (F codes): U600 (qi deficiency pattern/syndrome) and U221 (depression; melancholy; depressive syndrome). It is interesting to note that U222 (fire disease, hwa-byung), which is listed in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV), as a culture-bound syndrome, did not show a strong relationship with mental disorders but rather showed a clearly strong relationship with musculoskeletal diseases. The DSM-IV criteria indicate that hwa-byung has strong psychosomatic symptoms rather than direct mental symptoms [19].

4. Discussion

To our knowledge, this is the first study to incorporate U codes into the calculation of the burden of disease in Korea,

Table 3: Redistribution of U codes to Korean Classification of Diseases (KCD) 6 codes.

U code	U code proportion to each KCD 6 code														
U303	M791	M626	M759	M758	M750	M255	M542	G442	M548	M751	M796	G568	M549	G439	M531
	9.25%	9.56%	9.02%	17.62%	5.62%	4.73%	2.79%	16.91%	11.08%	14.29%	2.96%	21.85%	7.75%	10.13%	9.37%
	M501	M797	M624												
	20.54%	7.90%	9.89%												
U240	M179	M626	M759	M758	M541	M538	M175	M171	F453						
	11.58%	8.49%	5.17%	6.85%	77.35%	7.55%	20.38%	2.70%	10.58%						
U234	M545	G518	G510	M179	M796	K30	M791	M544	K580	M255	M171	M759	G819	M542	M752
	1.39%	33.08%	6.12%	2.19%	3.47%	2.32%	1.09%	1.44%	35.92%	2.36%	4.34%	1.81%	7.82%	0.67%	7.98%
	I693	K590	G430	M626	M139	G810	I691	M199	M509						
	4.31%	8.95%	11.94%	1.39%	6.41%	14.68%	6.99%	2.94%	4.22%						
U670	G470	G519	G64	G442	G439	K088	H819	F454	G909	G438					
	44.07%	25.68%	6.55%	14.16%	15.26%	43.28%	2.67%	1.33%	4.41%	9.11%					
U238	M545	M179	M791	M255	M796	M626	M750	K30	G470	M759	G510	G560	M543	M199	H911
	0.69%	1.49%	0.79%	1.51%	1.24%	0.72%	1.24%	0.64%	5.18%	0.53%	1.08%	10.20%	0.86%	3.79%	14.29%
	M653	M544	M542	M549	G562	M170	M171	F329	M501	M708					
	1.33%	0.14%	0.17%	0.92%	20.69%	0.73%	0.40%	7.50%	2.30%	0.44%					
U280	K30	G442	K318	G438	G430	G439	F982	K590							
	5.06%	6.78%	9.77%	11.10%	8.41%	2.57%	1.80%	3.91%							
U680	K30	J310	L80	L208	G442	G700	G470	M542	G439	H521	K522	N944	N959	G245	J300
	1.89%	6.53%	5.40%	11.96%	2.77%	17.54%	2.71%	0.25%	1.53%	1.49%	5.43%	1.67%	2.69%	1.36%	1.59%
	K121	N946													
	0.64%	3.72%													
U301	M545	M759	M544	M511	M791	M543	M626	M171	M255	M549	M238	M624	M758	M796	M179
	0.28%	0.99%	0.50%	2.70%	0.16%	0.68%	0.20%	0.56%	0.30%	1.09%	2.41%	2.45%	0.44%	0.22%	0.09%
	M750	M771	M109	M139	M753	M797	M170	M700							
	0.16%	0.43%	2.50%	1.23%	2.24%	0.73%	0.24%	1.67%							
U305	M796	M179	M791	M159	M255	M626	M722	M729							
	2.17%	1.09%	0.49%	1.46%	0.83%	0.26%	3.94%	0.71%							
U304	G560	M545	M758	M544	M171	M179	M255	M759	M750	M542	M104	M626	M791	M199	
	36.40%	0.15%	1.86%	0.35%	1.16%	0.29%	0.36%	0.30%	0.38%	0.18%	6.82%	0.09%	0.05%	0.97%	
U241	M626	G20	I693	M179	F453	M759	M531	M758	M480	M511					
	1.66%	2.06%	4.35%	0.42%	4.99%	0.49%	2.69%	0.66%	1.00%	0.51%					
U651	M626	M791	G430	M759	M545	M544	M758	F453	G440	M751	G442	M255	F454	F411	F410
	1.06%	0.36%	15.46%	0.45%	0.06%	0.19%	0.72%	2.91%	3.35%	1.30%	1.11%	0.22%	0.50%	3.44%	4.92%
	G438	M624	M750												
	1.05%	1.01%	0.11%												
U306	M545	M791	K30	M796	M255	M626	M239	M759	M179	M543	M771	G560	F480	M542	M170
	0.02%	0.04%	0.06%	0.07%	0.05%	0.02%	1.10%	0.02%	0.01%	0.03%	0.05%	0.22%	0.55%	0.01%	0.02%
U236	M179	G258	M159	M626	F459	G250									
	2.26%	10.78%	2.68%	0.32%	0.68%	0.54%									
U222	M545	M791	K30	G470	M759	M626	M255	F454	H571	F510	M199	M519	M542	M722	M796
	0.15%	0.39%	0.47%	3.89%	0.35%	0.15%	0.20%	0.75%	5.14%	4.85%	1.30%	0.96%	0.10%	1.21%	0.13%
	K219	M179	F453	G438	G442	I119									
	2.08%	0.04%	0.31%	0.40%	0.16%	3.66%									
U221	G470	F453	F519	G438	F454										
	16.34%	15.55%	6.88%	4.73%	0.41%										
U302	M179	M545	M791	M480	M624	M796	M626	M792	M544	M17	M508	M541	G430	G64	M139
	0.69%	0.13%	0.17%	2.77%	4.38%	0.41%	0.20%	3.76%	0.05%	4.09%	1.21%	1.67%	0.88%	0.32%	0.65%
	M235	M542													
	0.51%	0.03%													

Table 3: Continued.

U code	U code proportion to each KCD 6 code												
U650	M545	M791	M626	M171	M544	G438	G439	G519	F502	M542	M796	M255	M549
	0.21%	0.35%	0.35%	0.97%	0.14%	1.49%	0.60%	0.61%	8.57%	0.06%	0.08%	0.05%	0.21%
U730	K30	C259	K295	K296	C169								
	1.46%	19.57%	6.81%	3.75%	1.23%								
U230	T676	G244	G442										
	11.43%	0.56%	5.82%										
U710	M478	M545	F453	M791	M626	G438	M179	M255	N951				
	5.22%	0.13%	3.95%	0.14%	0.17%	1.98%	0.07%	0.11%	2.29%				
U660	G700												
	8.77%												
U640	M253	M758	M759	M249									
	1.14%	2.32%	0.89%	0.29%									
U233	M622	M179	G442	I630	M796	G501	G819	G909					
	2.26%	0.57%	1.89%	15.00%	0.45%	0.42%	0.76%	0.55%					
U794	K30	M171	M791	M626	N318	M544	M179	F458	F480	M750	M758	M796	N944
	0.76%	1.72%	0.26%	0.36%	17.14%	0.04%	0.04%	1.40%	0.33%	0.02%	0.04%	0.02%	0.56%
U784	M543	M626	M545	L031	M242	M791	H111	M199	M489	M549	E282	M759	
	1.70%	0.36%	0.06%	2.15%	3.38%	0.09%	2.64%	1.30%	3.64%	0.48%	3.39%	0.04%	
U332	K30	F982	L211										
	2.10%	1.20%	6.67%										
U260	K219	M626	M624										
	13.19%	0.58%	3.33%										
U600	F500	K30	K590										
	5.17%	0.72%	6.42%										
U204	M545	M750	M759	M796	M170	M544	M626	M255	M772				
	0.09%	0.67%	0.36%	0.42%	0.85%	0.09%	0.08%	0.09%	0.94%				

Values are reported as the proportion of the U code in each KCD 6 code, %.

with a specific focus on the analytic methods and results to assess the burden of diseases coded under U codes that have been overlooked in previous studies. Many of the U codes were redistributed within KCD 6 classifications for musculoskeletal diseases and diseases of the nervous system.

Until now, standardized compilations of methods for the analysis of traditional medicine in studies of the burden of disease have been lacking. Of the few studies that have focused on systematically understanding disease patterns explained in traditional medicine, some have shown possible links between the disorders and patterns and KCD or ICD [2, 20]. The present study, which enabled quantification of the utilization of health care services within Korean medicine, showed the additional proportion of the burden of disease for each KCD 6 code that could be assumed as the underlying factor in each of the U codes analyzed. Using this method, this study enabled a more complete analysis of the burden of disease in Korea, by including the part of the NHIS-NSC data represented by Korean medicine health care utilization. Information in the NHIS-NSC is organized by the type of medical institutions—Western medicine, Korean medicine, dental medicine, or pharmaceutical. NHIS provides an annual report, called the *National Health Insurance Statistical Yearbook*, which includes summaries of the utilization of each type of medicine from the NHIS-NSC data. Table 4 provides the recent (2010–2012) trend in health care utilization by the type of medicine from the yearbook [21]; the utilization of Western medicine and Korean medicine did not drastically change over the years.

The redistribution of many of the U codes into musculoskeletal diseases and diseases of the nervous system based on the KCD 6 supports the results of previous studies, in which Korean medicine was mainly utilized for musculoskeletal diseases [22, 23]. These results reflect the current utilization of Korean medicine in health care; many of the patients who visit Korean medical clinics have these diseases. Approximately 30% of patients with musculoskeletal diseases visit Korean medical clinics for treatments such as acupuncture [24]. In addition, many patients with diseases of the nervous system, such as facial palsy, cerebral infarct, or dementia, visit traditional medicine hospitals [25, 26]. The present results, including those illustrated in Figure 1, should be understood within the current Korean medicine healthcare utilization, as part of the official health care system.

Although the data were limited to claims records from the NHIS-NSC, the results of the present study show how each of the disorders or patterns in Korean medicine can be understood in terms of KCD 6 codes. This data-driven

Table 4: Trend in health care utilization from the *National Health Insurance Statistical Yearbook*, Korea.

	2010	2011	2012
Number of patients			
WM	44,818,780 (77.9%)	45,200,513 (78.0%)	45,764,919 (78.1%)
KM	12,689,192 (22.1%)	12,724,688 (22.0%)	12,795,918 (21.9%)
Total treatment cost ($)			
WM	31,211,729,553 (94.8%)	33,173,091,418 (94.7%)	34,616,590,233 (94.6%)
KM	1,701,831,541 (5.2%)	1,838,759,399 (5.3%)	1,962,494,521 (5.4%)
Number of total claims			
WM	604,017,783 (79.0%)	615,979,142 (79.3%)	682,586,833 (80.3%)
KM	91,356,214 (12.0%)	92,010,198 (11.8%)	96,378,959 (11.3%)
Number of outpatient claims			
WM	593,702,030 (78.8%)	605,084,745 (79.0%)	670,812,474 (80.0%)
KM	91,227,649 (12.1%)	91,850,417 (12.0%)	96,181,670 (11.5%)

WM: Western medicine; KM: Korean medicine.

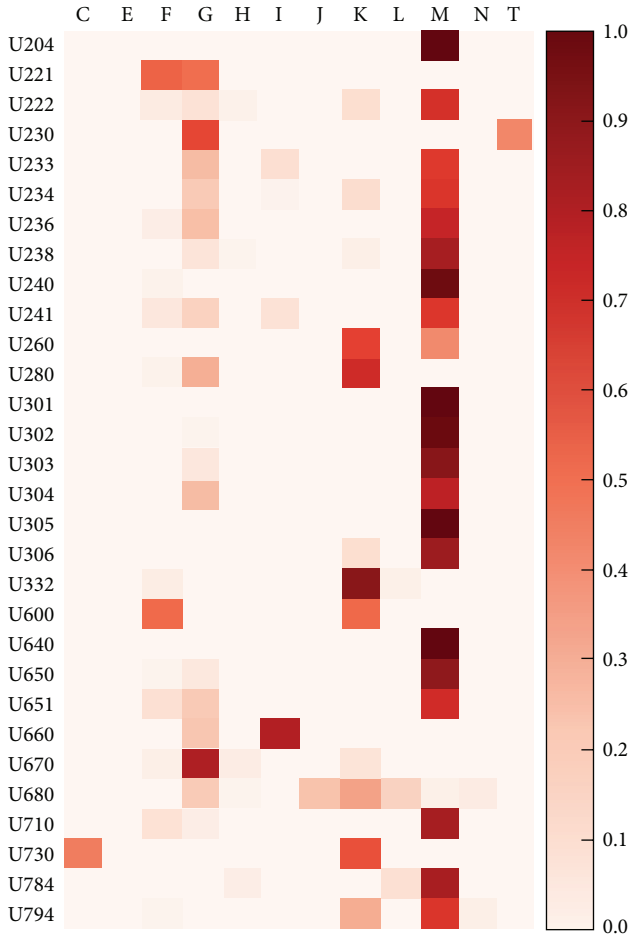

Figure 1: Visualization of the probability of the cooccurrence of the 30 most commonly used U codes in the 2012 National Health Insurance Service data in Korea and each chapter of the Korean Classification of Diseases 6 codes.

approach provides a new perspective in understanding and explaining disorders and patterns in Korean medicine, or within the larger scope of traditional medicine, via the disease classification system in Western medicine [27]. Previous efforts have focused on academic or experimental approaches, providing explanations of the physiological or functional symptoms explained in Korean medical or traditional medicine texts through the scientific lens of Western medicine or biomedicine or suggesting a possible mechanism for disorders and patterns in Korean medicine through experimental methods [2, 20, 28]. In contrast, a data-driven approach does not rely on the prior categorization of diseases as latent variables; rather, the data-driven approach enables a direct comparison of diseases between Western medicine and Korean medicine through data.

There are a few limitations in our study. First, the data source was based on claims from medical institutions to the NHIS. In other words, the data source and analysis did not include health care services not covered by the NHIS, including the out-of-pocket (OOP) sector. It is important to note that the portion of Korean medicine health care service that is not covered by NHIS is fairly large; therefore, a large part of Korean medicine health care utilization would not have been reported in the NHIS-NSC data [29, 30]. Second, the analysis was conducted for the 30 most common U codes in the NHIS data for the year 2012, which could have produced two issues. First, the most common U codes could change by year, with trends in health care utilization, which could therefore change the burden of disease. Also, the proportion that this study added to the current analysis of the burden of disease could change over time, yielding different data in another year. However, since this study aimed to produce the proportion in which the burden of disease for the year 2012 could develop, these two problems did not cause major errors in the current project. Furthermore, we aim to continue this project and apply the same method to another year to see the possible changes in the assimilated U codes and their proportions.

5. Conclusions

This study analyzed the burden of disease from U codes in the year 2012 using NHIS-NSC data. Although there are

some limitations, quantification of the proportion of U codes to KCD 6 codes and redistribution of those codes enable a better understanding of Korean medicine health care utilization. Furthermore, the relationship between U codes and KCD 6 codes through data visualization provides a way of understanding U code disorders and patterns from the KCD 6 perspective. Furthermore, it provided a deeper understanding of the disorders and patterns of U codes through KCD 6 diseases. This data visualization showed that musculoskeletal diseases accounted for a large part of Korean medicine utilization. Furthermore, the methodology applied in this study serves as an initial study to quantify U codes through KCD 6 codes, providing guidelines for further research of the burden of diseases, including other countries with a dual health care system similar to that in Korea.

Conflict of Interests

The authors declared that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

In-Hwan Oh and Bo-Hyoung Jang contributed equally to this study.

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Research Article

The Study of Misclassification Probability in Discriminant Model of Pattern Identification for Stroke

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Background. Pattern identification (PI) is the basic system for diagnosis of patients in traditional Korean medicine (TKM). The purpose of this study was to identify misclassification objects in discriminant model of PI for improving the classification accuracy of PI for stroke. *Methods.* The study included 3306 patients with stroke who were admitted to 15 TKM hospitals from June 2006 to December 2012. We derive the four kinds of measure (*D*, *R*, *S*, and *C* score) based on the pattern of the profile graphs according to classification types. The proposed measures are applied to the data to evaluate how well those detect misclassification objects. *Results.* In 10–20% of the filtered data, misclassification rate of *C* score was highest compared to those rates of other scores (42.60%, 41.15%, resp.). In 30% of the filtered data, misclassification rate of *R* score was highest compared to those rates of other scores (40.32%). And, in 40–90% of the filtered data, misclassification rate of *D* score was highest compared to those rates of other scores. Additionally, we can derive the same result of *C* score from multiple regression model with two independent variables. *Conclusions.* The results of this study should assist the development of diagnostic standards in TKM.

1. Introduction

Due to the development of modern medicine, the average lifespan for human beings is anticipated to rise beyond 85 years of age within the following 20 years [1]. In the meantime, since the rate of aging in South Korea is expected to surge up to 35.1% by 2050, ranking 2nd in the world close to Japan (37.7%), geriatric diseases and the health of the elderly have emerged as one of the most critical social problems of improving the quality of life in the future [2]. In particular, stroke is one of the representative geriatric diseases, along with dementia. Personal and social insecurities caused by the disease have continued to grow. In addition, stroke ranks as the top mortality risk to Koreans among the single diseases and contributes to more than 70% of the in-patients at traditional Korean medical hospitals [3, 4]. In traditional Korean medicine (TKM), specific or nonspecific symptoms of patients are diagnosed by observing, listening, asking, and feeling their pulse under the diagnostic system of pattern identification (PI) in order to determine the cause, nature, treatment method, and treatment drugs of a disease [5–7]. This PI diagnosis collects specific or nonspecific symptoms of patients and classifies them into one of the hundreds of symptom classes. It is the essential core technology forming the backbone of diagnosis and treatment in oriental medicine. However, the PI diagnosis holds limited objectivity and reproducibility due to the lack of standardized measurement indices, and objectification problems have always arisen with respect to personal deviations among TKM physicians based on their knowledge and experience [6–8].

As the necessity for the standardization of diagnostic systems has recently come to the fore, studies have been underway to objectify diagnosis.

In the study titled "Fundamental Study for the Standardization and Objectification of Pattern Identification in Traditional Korean Medicine for Stroke (SOPI-Stroke)," which was conducted over 9 years from 2005 to 2013, the Korea Institute of Oriental Medicine (KIOM) proposed a standardization plan for PI/syndrome differentiation of stroke, established stroke PI diagnostic indices, built a database system relating

Table 1: Results using the classification of discriminant model.

		Classification result N (%)				
		QD	DP	YD	FH	Total
Physician's diagnosis	QD	498 (66.94)	115 (15.46)	95 (12.77)	36 (4.84)	744 (22.50)
	DP	118 (10.61)	783 (70.41)	69 (6.21)	142 (12.77)	1112 (33.64)
	YD	70 (14.64)	55 (11.51)	276 (57.74)	77 (16.11)	478 (14.46)
	FH	46 (4.73)	147 (15.12)	127 (13.07)	652 (67.08)	972 (29.40)
	Total	732 (22.14)	1100 (33.27)	567 (17.15)	907 (27.44)	3306 (100.00)

QD: Qi deficiency pattern; DP: Dampness-phlegm pattern; YD: Yin deficiency pattern; FH: Fire-heat pattern.

to TKM clinical technologies by setting up a clinical index database, and founded a scientific basis for stroke and PI by discovering stroke and PI biological indices, to which the latest research methods, such as OMICS, were applied. Studies were carried out to discover biological indices that could be helpful to stroke prevention by finding out what the stroke risk factors were [9–16].

Consequently, the purpose of this study was to identify misclassification objects in discriminant model of PI for improving the classification accuracy of PI for stroke patients. Although current TKM PI diagnostic tools for stroke were developed after several years of research and prepared for public release, the tools still need corrections and modifications in many aspects [17–19]. In this study, the key topics for discussion involve appropriate statistical methods to reduce the probability of diagnostic misclassification.

2. Methods

2.1. Subjects. The study included 3306 patients with stroke who were admitted to 15 oriental medical university hospitals from June 2006 to December 2012. Each patient provided informed consent to undergo procedures that were approved by the respective institutions' Institutional Review Boards (IRB). Informed consent of all the study patients was obtained after a thorough explanation of the details. We enrolled stroke patients for enrollment within 30 days of the onset of their symptoms, provided that their diagnosis was confirmed by an imaging diagnosis such as computerized tomography (CT) or magnetic resonance imaging (MRI). Patients with traumatic stroke such as subarachnoid, subdural, and epidural hemorrhage were excluded from the study.

2.2. Measured Variables. Each patient was seen by two experts at the same department within each site. All experts who were well trained in standard operation procedures (SOPs) were participating in this study. The experts had at least three years of clinical experiences with stroke after finishing regular college education about TKM for six years. The examination parameters were extracted from parts of a case report form (CRF) for the standardization of stroke diagnosis that had been developed by an expert committee organized by the KIOM [7, 11, 12].

2.2.1. The Korean Standard PI for Stroke-3. PI process for differentiating stroke with four TKM types: the Fire-heat (FH) pattern, Dampness-phlegm (DP) pattern, Yin deficiency (YD) pattern, and Qi deficiency (QD) pattern [11, 12]. The FH pattern is characterized by any symptom of heat or fire that is contracted externally or engendered internally. The DP pattern is characterized by impeding Qi movement and its turbidity, heaviness, stickiness, and downward-flowing properties. The QD pattern is characterized by qi deficiency with diminished internal organ function, which is marked by shortness of breath, lassitude, listlessness, spontaneous sweating, a pale tongue, and a weak pulse. The YD pattern is characterized by yin deficiency with diminished moistening and the inability to restrain yang, which is usually manifested as fever [7, 9–13, 20]. The Korean Standard PI for Stroke-3 consists of 44 clinical indices and each clinical index belongs to its respective PI (Supplemental Table 1, in Supplementary Material available online at http://dx.doi.org/10.1155/2016/1912897).

2.3. Statistical Methods. After determining 12 different types of misclassification through discriminant analysis, we plotted it on the profile graphs according to types. And then we derive the four kinds of measure (D, R, S, and C score) based on the pattern analysis of the profile graphs. The proposed measures are applied to the stroke data to evaluate how well those detect misclassification objects.

2.3.1. Types of Misclassification. According to the results from the discriminant model classification, 2,209 patients posted correct classifications out of the total of 3,306 patients (66.82%) (Table 1). Out of the 3,306 patients, 1,097 were misclassified (33.2%) and the misclassification types are summarized in Table 2. To analyze the misclassification types, 44 clinical indices of the Korean Standard PI for Stroke-3 were grouped into four upper-class variables (QD, DP, YD, and FH pattern indices). In addition, the average and standard deviation of each upper-class variable was used to attain standardized scores, after which the misclassification types were analyzed (Figure 1).

2.3.2. The Profile Graphs. With 12 misclassification types and 4 correct classification types categorized by the discriminant analysis, the profile graphs were drawn. Specifically, two of the 4 patterns were selected and the correct classification types and misclassification types for each pattern were collected from the TKM physicians and divided. For instance, as described in Figure 2, patients applicable to two misclassification types (FHQD and QDFH) were grouped together.

Table 2: The mean values of the standardized scores for upper-class variables according to misclassification type.

Types of misclassification		N (%)	Z_{QD}	Z_{DP}	Z_{YD}	Z_{FH}
1	DPFH#	142 (12.94)	−0.565	−0.113	−0.251	0.648
2	DPQD	118 (10.76)	1.004	−0.001	−0.312	−0.492
3	DPYD	69 (6.29)	0.118	−0.060	0.902	0.085
4	FHDP	147 (13.40)	−0.426	0.610	−0.114	0.069
5	FHQD	46 (4.19)	0.907	−0.494	−0.233	0.096
6	FHYD	127 (11.58)	−0.291	−0.596	0.956	0.184
7	QDDP	115 (10.48)	0.111	0.605	−0.394	−0.456
8	QDFH	36 (3.28)	0.075	−0.500	−0.373	0.560
9	QDYD	95 (8.66)	0.512	−0.487	0.808	−0.299
10	YDDP	55 (5.01)	−0.229	0.529	−0.153	−0.336
11	YDFH	77 (7.02)	−0.393	−0.525	0.133	0.568
12	YDQD	70 (6.38)	0.914	−0.492	0.240	−0.337
Total		1097 (100.00)	0.067	−0.063	0.110	0.017

QD: Qi deficiency pattern; DP: Dampness-phlegm pattern; YD: Yin deficiency pattern; FH: Fire-heat pattern; DPFH#: physician's diagnosis- Dampness-phlegm pattern, classification result, Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern.

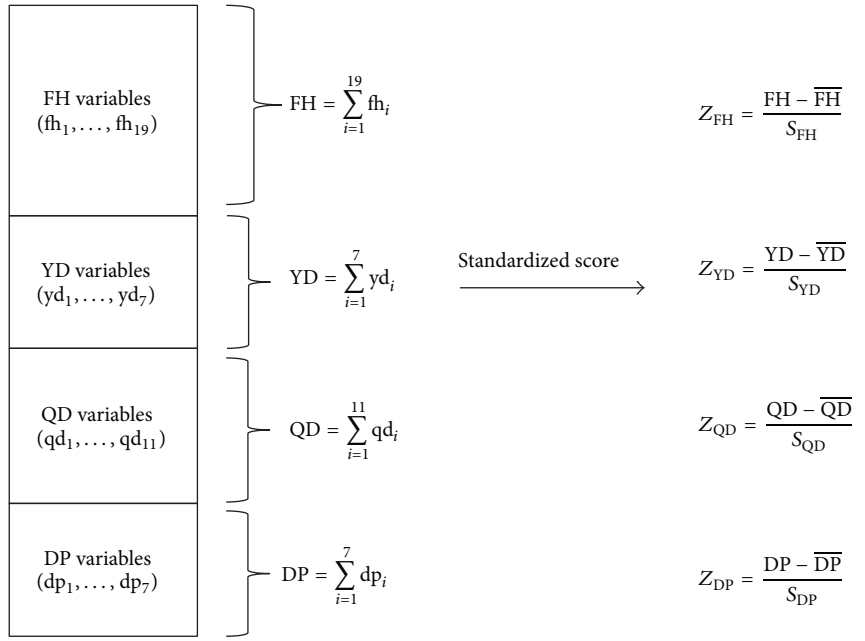

Figure 1: Process of grouping of explanatory variables and standardized scores generation. The mean and standard deviation of each upper-class variable were used to attain standardized scores, after which the misclassification types were analyzed. QD: Qi deficiency pattern; DP: Dampness-phlegm pattern; YD: Yin deficiency pattern; FH: Fire-heat pattern.

Next, the upper-class variable scores of each patient were used to draw a profile plot. At this point, it was critical to arrange the pattern scores of correct classification on the edges and those of the other two pattern scores inside. The profile graphs of the misclassification types (FHQD, QDFH, etc.) and the correct classification types (e.g., FH, QD, YD, and DP) are depicted in Figures 2–7 and the relevant statistics are in Table 3. As illustrated in Figures 2–7, two misclassification types demonstrate a U-shaped pattern and correct classification types an L-shaped or flipped-L-shaped pattern.

2.3.3. Derived Four Measures (D, R, S, and C Scores). In the profile graphs, misclassification observations in most of the 6 cases displayed a bathtub or U-shaped pattern since pattern scores corresponding to actual patterns would be relatively high and the misclassification of a pattern is highly probable if relatively higher scores were observed in the other pattern.

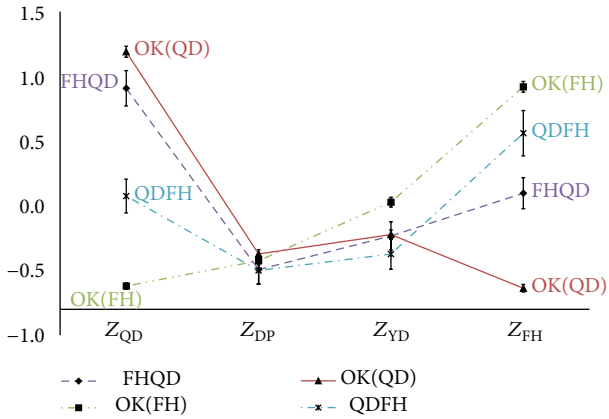

Figure 2: The profiles graphs of the FH and QD. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

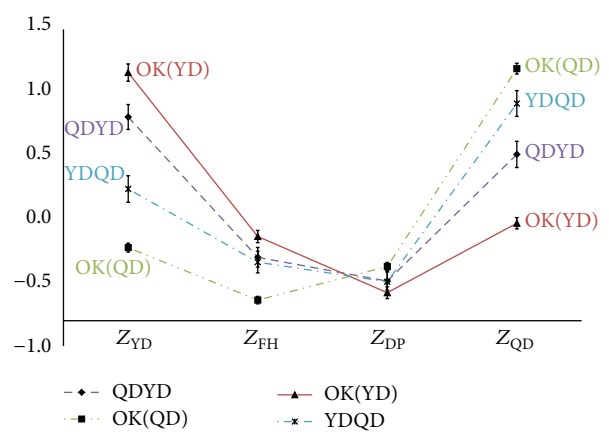

Figure 3: The profiles graphs of the QD and YD. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

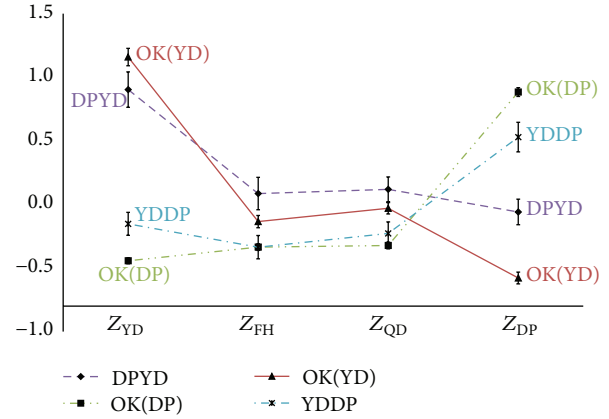

Figure 4: The profiles graphs of the DP and YD. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

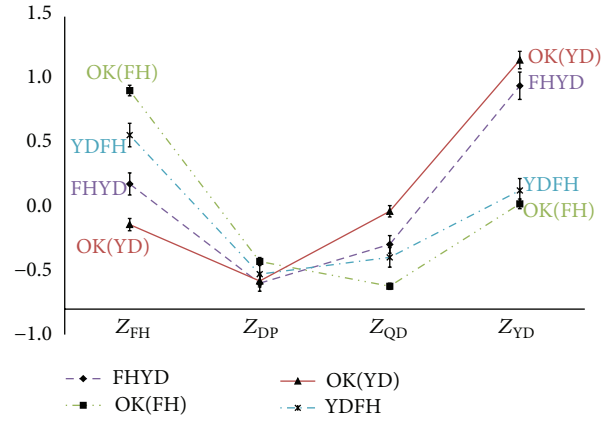

Figure 5: The profiles graphs of the FH and YD. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

In the meantime, correct classification observations showed an L-shaped (or flipped-L-shaped) pattern. Although actual patterns are unknown due to the lack of direct diagnoses from TKM physicians, if a new patient establishes a bathtub-shaped profile simply with 4 upper-class pattern scores (obligatory two high scores and two low scores), this patient is likely to be misclassified through the future discriminant model. Criteria were designed to assess how close a pattern score profile would be to a bathtub shape through various arrangements and simple calculations of the four pattern scores and applied to already discriminated data. By doing so, comparison was conducted to investigate how much misclassification was estimated and how much discrimination rates improved when the estimated misclassification observations were eliminated beforehand.

(1) D Score. Analyzing correct classification and misclassification types with profile graphs, the D value was derived considering that a difference between the maximum value $Z_{(1)}$ and the second-largest value $Z_{(2)}$ of misclassification was smaller than that of correct classification, and classification by the value was attempted (Figure 8). Namely, under the hypothesis that the smaller the D value was, the closer the profile graph was to a bathtub shape and the higher the probability of the respective observations corresponding to misclassification was, the D values were applied to the clinical stroke data.

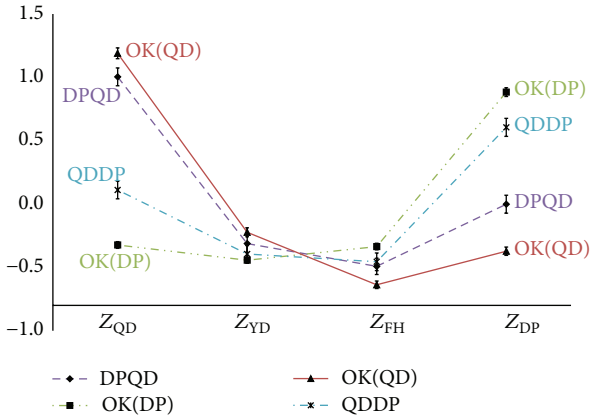

FIGURE 6: The profiles graphs of the DP and QD. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

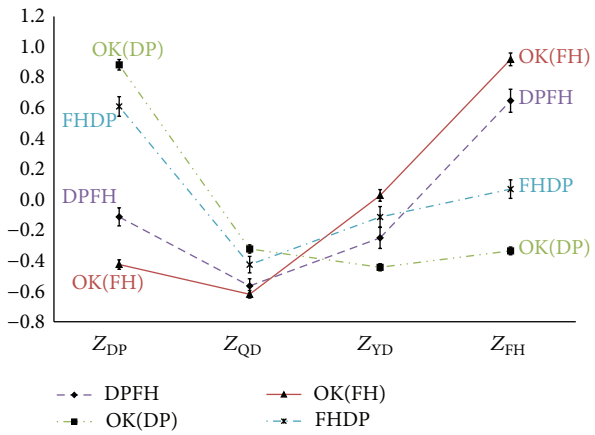

FIGURE 7: The profiles graphs of the DP and FH. Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; OK: the correct classification types.

After sorting the data by the D value in descending order and investigating the frequency and rates of misclassification over 10% intervals (Figure 9), the misclassification probability of the 10% ($N = 331$) filtered data reached 40.79% ($N_m = 135$, $\text{Mean}_m = 0.058$), which was 7.61% p higher than the previously calculated misclassification probability (33.18%) of the total data. The misclassification probabilities of the data filtered from 20% to 90% were lower than that of the 10% filtered data but higher than that of the total data (33.18%). In the data filtered at 10%, 20%, 40%, and 50%, average D values of the misclassifications and correct classifications were barely different from each other, even though the average D values of the misclassifications tended to be higher than those of the correct classifications. In the other data groups, the average D values of the correct classifications were higher than those of the misclassifications (Table 4). Meanwhile, examining the frequencies and rates of the correct classifications in the data selected for D values, the misclassification probability of the correct classifications in the 90% ($N = 2975$) selected data recorded 67.66% ($N_c = 2013$, % of $N_m = 32.34\%$), which was 0.86% p higher than those of the previously calculated correct classifications (66.8%) of the total data. In the 80% ($N = 2645$) selected data, the misclassification probabilities of correct classifications reached 68.28% ($N_c = 1806$, % of $N_m = 31.72\%$), which was 0.62% p higher than those in the 90% selected data. In the data selected from 70% to 10%, the correct classifications gradually increased (Table 4).

(2) R Score. Analyzing correct classification and misclassification types with profile graphs, the R value was derived considering that a difference between the maximum value $Z_{(1)}$ and the minimum value $Z_{(4)}$ of misclassification was smaller than that of correct classification, and classification by the value was attempted (Figure 10). Namely, under the hypothesis that the larger the R value was, the closer the profile graph was to an L-shaped or flipped-L-shaped pattern, and the higher the probability of the respective observations corresponding to correct classification was the R values were applied to the clinical stroke data in the same way as previously (Table 5).

(3) S Score. Analyzing correct classification and misclassification types with profile graphs, the S value was derived considering that the second-largest value $Z_{(2)}$ of misclassification was higher than that of correct classification, and classification by the value was attempted (Figure 11). Namely, under the hypothesis that the larger the S value was, the closer the profile graph was to a bathtub (or U) shape and the higher the probability of the respective observations corresponding to misclassification was, the S values were applied to the clinical stroke data. In this case, the frequency and rates of misclassification over 10% intervals were investigated after sorting the data by the S value in ascending order (Table 6).

(4) C Score. Analyzing correct classification and misclassification types with profile graphs, the C value was derived considering that a difference between the sum of $Z_{(1)}$ and $Z_{(2)}$ and the sum of $Z_{(3)}$ and $Z_{(4)}$ of misclassification was larger than that of correct classification, and classification by the value was attempted (Figure 12). Namely, under the hypothesis that the larger the C value was, the closer the profile graph was to a bathtub (or U) shape, the higher the probability of the respective observations corresponding to misclassification was, the C values were applied to the clinical stroke data in the same way as previously (Table 7).

3. Results

3.1. Estimated Misclassification Probability and Discrimination Rate according to Proposed Four Scores. Table 8 summarizes the misclassification probabilities after the data was sorted

Table 3: Summary of Z scores according to the profile graphs for PI classification types.

	Classification types	N	Z scores (mean ± SE)			
			Z_{QD}	Z_{DP}	Z_{YD}	Z_{FH}
FH, QD classification types	FHQD	46	0.907 ± 0.137	−0.494 ± 0.110	−0.233 ± 0.109	0.097 ± 0.120
	OK(FH)	652	−0.620 ± 0.025	−0.425 ± 0.031	0.028 ± 0.038	0.919 ± 0.042
	OK(QD)	498	1.189 ± 0.043	−0.372 ± 0.033	−0.223 ± 0.035	−0.637 ± 0.030
	QDFH	36	0.075 ± 0.130	−0.500 ± 0.107	−0.373 ± 0.118	0.560 ± 0.175
	Total	1232	0.189 ± 0.034	−0.408 ± 0.022	−0.095 ± 0.025	0.249 ± 0.034
QD, YD classification types	QDYD	95	0.513 ± 0.103	−0.487 ± 0.072	0.808 ± 0.099	−0.300 ± 0.078
	OK(QD)	498	1.189 ± 0.043	−0.372 ± 0.033	−0.223 ± 0.035	−0.637 ± 0.030
	OK(YD)	276	−0.031 ± 0.045	−0.579 ± 0.046	1.159 ± 0.068	−0.135 ± 0.048
	YDQD	70	0.914 ± 0.102	−0.493 ± 0.090	0.240 ± 0.105	−0.337 ± 0.085
	Total	939	0.742 ± 0.034	−0.454 ± 0.024	0.322 ± 0.036	−0.433 ± 0.025
DP, YD classification types	DPYD	69	0.118 ± 0.097	−0.060 ± 0.101	0.903 ± 0.139	0.085 ± 0.127
	OK(DP)	783	−0.323 ± 0.027	0.883 ± 0.034	−0.443 ± 0.024	−0.336 ± 0.026
	OK(YD)	276	−0.031 ± 0.045	−0.579 ± 0.046	1.159 ± 0.068	−0.135 ± 0.048
	YDDP	55	−0.229 ± 0.090	0.529 ± 0.116	−0.153 ± 0.090	−0.336 ± 0.092
	Total	1183	−0.225 ± 0.022	0.471 ± 0.032	0.022 ± 0.032	−0.264 ± 0.023
FH, YD classification types	FHYD	127	−0.291 ± 0.069	−0.597 ± 0.063	0.956 ± 0.108	0.184 ± 0.087
	OK(FH)	652	−0.620 ± 0.025	−0.425 ± 0.031	0.028 ± 0.038	0.919 ± 0.042
	OK(YD)	276	−0.031 ± 0.045	−0.579 ± 0.046	1.159 ± 0.068	−0.135 ± 0.048
	YDFH	77	−0.393 ± 0.077	−0.525 ± 0.086	0.133 ± 0.095	0.568 ± 0.093
	Total	1132	−0.424 ± 0.022	−0.489 ± 0.023	0.415 ± 0.034	0.555 ± 0.032
DP, QD classification types	DPQD	118	1.004 ± 0.071	−0.001 ± 0.071	−0.312 ± 0.070	−0.492 ± 0.064
	OK(DP)	783	−0.323 ± 0.027	0.883 ± 0.034	−0.443 ± 0.024	−0.336 ± 0.026
	OK(QD)	498	1.189 ± 0.043	−0.372 ± 0.033	−0.223 ± 0.035	−0.637 ± 0.030
	QDDP	115	0.111 ± 0.070	0.605 ± 0.071	−0.395 ± 0.067	−0.456 ± 0.069
	Total	1514	0.311 ± 0.028	0.380 ± 0.027	−0.357 ± 0.019	−0.456 ± 0.018
DP, FH classification types	DPFH	142	−0.565 ± 0.047	−0.113 ± 0.059	−0.251 ± 0.069	0.648 ± 0.076
	OK(DP)	783	−0.323 ± 0.027	0.883 ± 0.034	−0.443 ± 0.024	−0.336 ± 0.026
	OK(FH)	652	−0.620 ± 0.025	−0.425 ± 0.031	0.028 ± 0.038	0.919 ± 0.042
	FHDP	147	−0.426 ± 0.054	0.610 ± 0.064	−0.114 ± 0.068	0.069 ± 0.061
	Total	1724	−0.464 ± 0.017	0.283 ± 0.026	−0.221 ± 0.020	0.254 ± 0.026

PI: pattern identification; QD: Qi deficiency pattern; DP: Dampness-phlegm pattern; YD: Yin deficiency pattern; FH: Fire-heat pattern; OK: the correct classification types; Z_{QD}: the standardized scores for upper-class variables according to Qi deficiency pattern; Z_{DP}: the standardized scores for upper-class variables according to Dampness-phlegm pattern; Z_{YD}: the standardized scores for upper-class variables according to Yin deficiency pattern; Z_{FH}: the standardized scores for upper-class variables according to Fire-heat pattern.

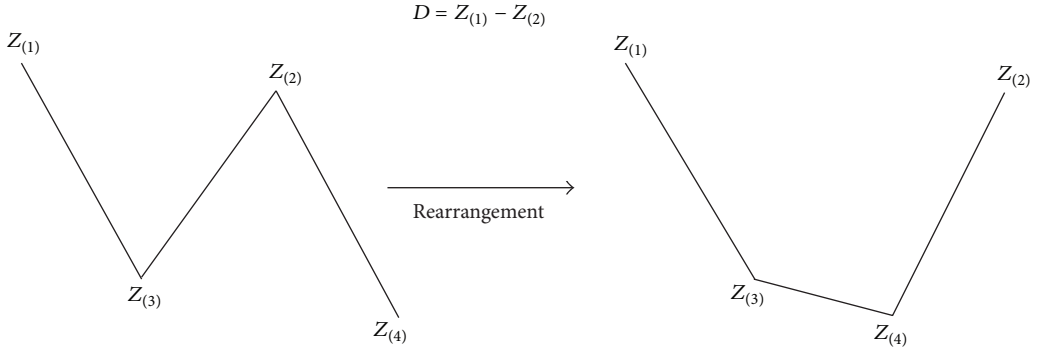

Figure 8: Derived D values based on the pattern analysis of the profile graphs. Under the hypothesis that the smaller the D value was, the closer the profile graph was to a bathtub (or U) shape, and the higher the probability of the respective observations corresponding to misclassification was.

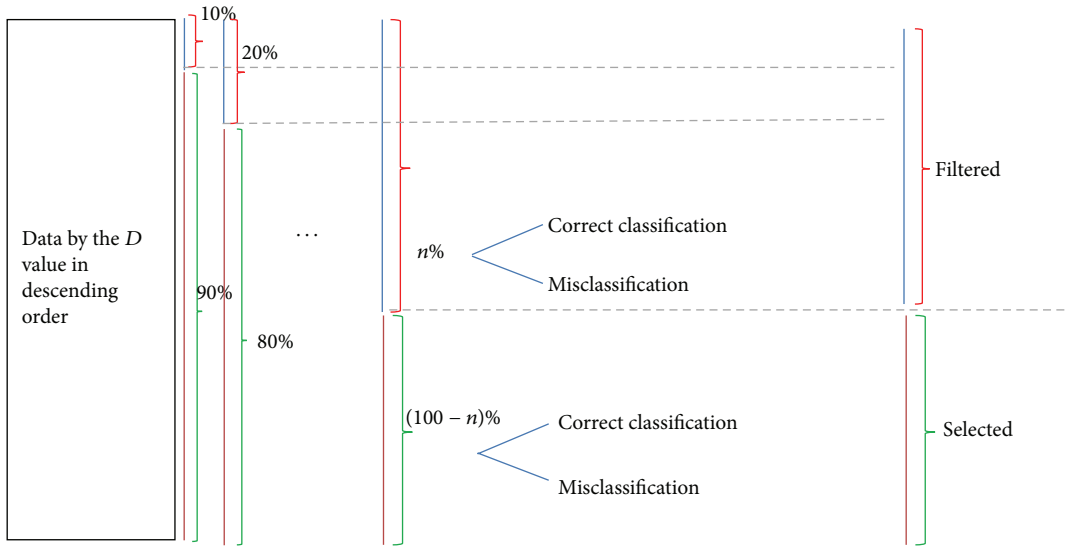

Figure 9: Data filtering and selection method. Data were ranged according to each four measures (D, R, S, and C values) in descending or ascending order by increasing data by 10% intervals.

according to the 4 criteria and investigating the misclassification probability over 10% intervals. If the data were filtered 10–20%, the C score marked 42.60% and 41.15%, respectively, indicating the highest misclassification probability among the criteria. If the data were filtered 30%, the R score stands at 40.32% and the C score at 39.92%. If the data were filtered 40~90%, the misclassification probability of the D score was the highest.

For the data previously selected by 4 scores (D, R, S, and C), discrimination rates were compared. Having the 4 QD, DP, YD, and FH patterns set as reaction variables for the entire clinical stroke data and 44 clinical indices of the *Korean Standard PI for Stroke-3* as independent variables, the discriminant analysis was conducted to calculate the discrimination accuracy (Table 9). If the data were selected at 90%, the discrimination rate of the D score increased to 68.2%, which was the largest increase among the four scores. If the data were selected at 80%, the C score reached 69.0%, making the largest increase. If the data were selected at 70%, the R score posted 70.0%, demonstrating the largest increase in the discrimination rate among the four scores. If the data were selected at 60–10%, the D score recorded the largest increase in the discrimination rate among the four scores.

3.2. Similarities between Secondary Curvature Function and C Score

3.2.1. Curvature Created by $Z_{(1)}$, $Z_{(2)}$, $Z_{(3)}$, and $Z_{(4)}$ Scores. First of all, assume four scores, $Z_{(1)}$, $Z_{(2)}$, $Z_{(3)}$, and $Z_{(4)}$, as dependent variables observed in the x values (e.g., 1, 2, 3, and 4) having equal intervals, as shown in the profile graphs. In addition, assume that $Z_{(1)}$ is a dependent variable when $x = 1$, $Z_{(2)}$ when $x = 4$, $Z_{(3)}$ when $x = 2$, and $Z_{(4)}$ when $x = 3$. This assumption is illustrated in Figure 13.

3.2.2. Estimation of Secondary Curvature. Considering the quadratic curve regression model passing through the four points $(1, Z_{(1)})$, $(2, Z_{(3)})$, $(3, Z_{(4)})$, and $(4, Z_{(2)})$, $Y = \beta_0 + \beta_1 X + \beta_2 X^2 + \epsilon$, the coefficient of β_2 is the secondary curvature value that we wanted. Namely, the larger the β_2 is, the stronger the bathtub shape becomes, boosting the misclassification probability. Assuming that the estimates of β_0, β_1, and β_2 are b_0, b_1, and b_2, these estimates satisfy the following normal equation [21]:

$$\left(X'X\right)b = X'Y. \tag{1}$$

Here

$$X = \begin{bmatrix} 1 & 1 & 1^2 \\ 1 & 2 & 2^2 \\ 1 & 3 & 3^2 \\ 1 & 4 & 4^2 \end{bmatrix},$$

$$b = \begin{bmatrix} b_0 \\ b_1 \\ b_2 \end{bmatrix}, \tag{2}$$

$$Y = \begin{bmatrix} Z_{(1)} \\ Z_{(2)} \\ Z_{(3)} \\ Z_{(4)} \end{bmatrix}.$$

According to Neter et al. [21], a general two-variable regression model,

$$Y_i = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \epsilon_i, \tag{3}$$

Table 4: Types of classifications distribution of filtered/selected data by D value.

Filtered%	Type of classifications distribution of filtered data by D value						Selected%	Type of classifications distribution of selected data by D value					
	N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t		N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t
10%	135 (40.79)	196 (59.21)	331 (100)	0.058	0.053	0.055	10%	42 (12.69)	289 (87.31)	331 (100)	2.399	2.531	2.515
20%	258 (39.03)	403 (60.97)	661 (100)	0.124	0.125	0.125	20%	119 (18.00)	542 (82.00)	661 (100)	1.913	2.112	2.076
30%	382 (38.51)	610 (61.49)	992 (100)	0.184	0.184	0.184	30%	232 (23.39)	760 (76.61)	992 (100)	1.585	1.870	1.804
40%	525 (39.71)	797 (60.29)	1322 (100)	0.252	0.242	0.246	40%	338 (25.57)	984 (74.43)	1322 (100)	1.397	1.668	1.599
50%	647 (39.14)	1006 (60.86)	1653 (100)	0.319	0.319	0.319	50%	450 (27.22)	1203 (72.78)	1653 (100)	1.244	1.508	1.436
60%	759 (38.26)	1225 (61.74)	1984 (100)	0.387	0.402	0.396	60%	572 (28.83)	1412 (71.17)	1984 (100)	1.107	1.375	1.298
70%	865 (37.38)	1449 (62.62)	2314 (100)	0.460	0.492	0.480	70%	715 (30.90)	1599 (69.10)	2314 (100)	0.973	1.265	1.175
80%	978 (36.98)	1667 (63.02)	2645 (100)	0.550	0.593	0.578	80%	839 (31.72)	1806 (68.28)	2645 (100)	0.875	1.154	1.065
90%	1055 (35.46)	1920 (64.54)	2975 (100)	0.630	0.731	0.695	90%	962 (32.34)	2013 (67.66)	2975 (100)	0.788	1.055	0.969

N_m: number of misclassification types; N_c: number of correct classification types; N_t: number of total classification types; Mean_m: mean of misclassification type; Mean_c: mean of correct classification type; Mean_t: mean of total classification type.

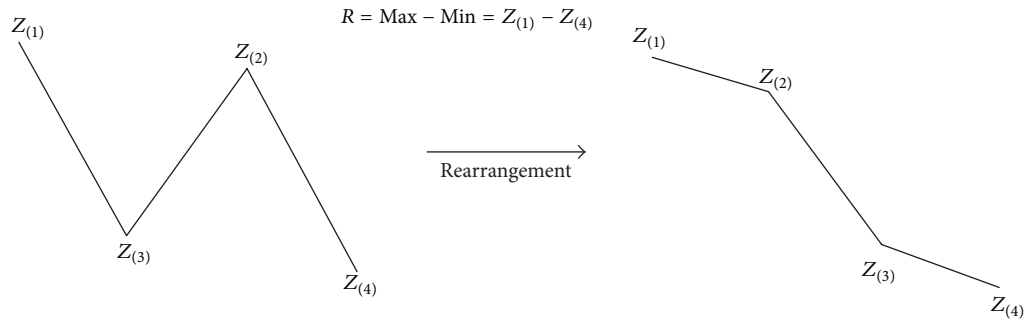

Figure 10: Derived R values based on the pattern analysis of the profile graphs. Under the hypothesis that the larger the R value was, the closer the profile graph was to an L-shaped or flipped-L-shaped pattern, the higher the probability of the respective observations corresponding to correct classification was.

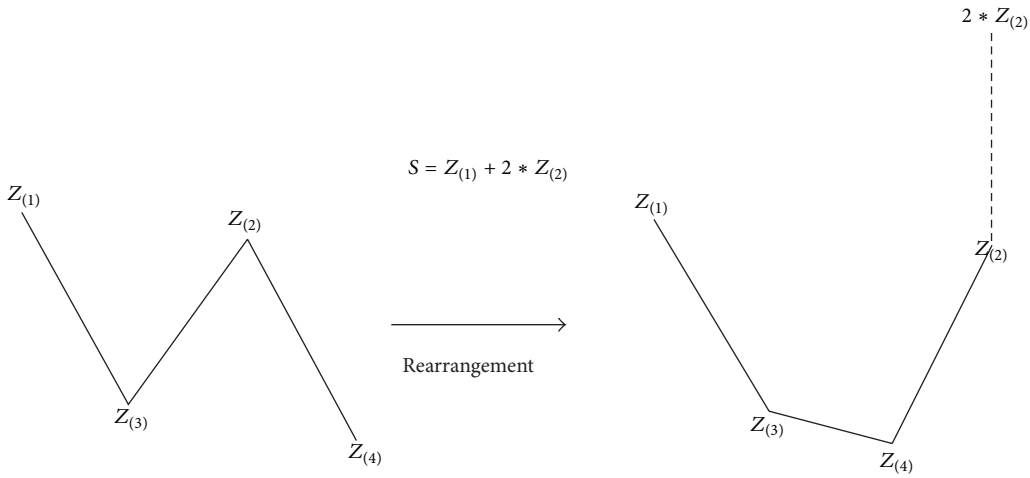

Figure 11: Derived S values based on the pattern analysis of the profile graphs. Under the hypothesis that the larger the S value was, the closer the profile graph was to a bathtub (or U) shape, the higher the probability of the respective observations corresponding to misclassification was.

has a normal equation

$$\left(X'X\right)b = X'Y, \tag{4}$$

which is equal to

$$\begin{bmatrix} n & \sum X_{i1} & \sum X_{i2} \\ \sum X_{i1} & \sum X_{i1}^2 & \sum X_{i1}X_{i2} \\ \sum X_{i2} & \sum X_{i2}X_{i1} & \sum X^2{}_{i2} \end{bmatrix} \begin{bmatrix} b_0 \\ b_1 \\ b_2 \end{bmatrix} = \begin{bmatrix} \sum Y_i \\ \sum X_{i1}Y_i \\ \sum X_{i2}Y_i \end{bmatrix}, \tag{5}$$

and the following normal equations,

$$\begin{aligned} \sum Y_i &= nb_0 + b_1 \sum X_{i1} + b_2 \sum X_{i2}, \\ \sum X_{i1}Y_i &= b_0 \sum X_{i1} + b_1 \sum X_{i1}^2 + b_2 \sum X_{i1}X_{i2} \\ \sum X_{i2}Y_i &= b_0 \sum X_{i2} + b_1 \sum X_{i1}X_{i2} + b_2 \sum X_{i2}^2, \end{aligned} \tag{6}$$

are obtained. In this case, the equations are

$$\begin{aligned} X_{i1} &= i, \quad i = 1, 2, 3, 4, \\ X_{i2} &= i^2, \quad i = 1, 2, 3, 4, \\ Y_1 &= Z_{(1)}, \\ Y_2 &= Z_{(3)}, \\ Y_3 &= Z_{(4)}, \\ Y_4 &= Z_{(2)}. \end{aligned} \tag{7}$$

Now, if

$$\begin{aligned} S_1 &= Z_{(1)} + Z_{(2)} + Z_{(3)} + Z_{(4)}, \\ S_2 &= Z_{(1)} + 2Z_{(3)} + 3Z_{(4)} + 4Z_{(2)}, \\ S_3 &= Z_{(1)} + 4Z_{(3)} + 9Z_{(4)} + 16Z_{(2)}, \end{aligned} \tag{8}$$

Table 5: Types of classifications distribution of filtered/selected data by R value.

Filtered%	Type of classifications distribution of filtered data by R value						Selected%	Type of classifications distribution of selected data by R value					
	N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t		N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t
10%	135 (40.79)	196 (59.21)	331 (100)	0.674	0.677	0.676	10%	65 (19.64)	266 (80.36)	331 (100)	3.790	3.882	3.864
20%	261 (39.49)	400 (60.51)	661 (100)	0.847	0.864	0.858	20%	160 (24.21)	501 (75.79)	661 (100)	3.247	3.418	3.376
30%	400 (40.32)	592 (59.68)	992 (100)	0.991	0.990	0.990	30%	254 (25.60)	738 (74.40)	992 (100)	2.967	3.116	3.078
40%	507 (38.35)	815 (61.65)	1322 (100)	1.099	1.130	1.118	40%	371 (28.06)	951 (71.94)	1322 (100)	2.719	2.905	2.853
50%	623 (37.69)	1030 (62.31)	1653 (100)	1.212	1.252	1.234	50%	474 (28.68)	1179 (71.32)	1653 (100)	2.542	2.710	2.662
60%	726 (36.59)	1258 (63.41)	1984 (100)	1.310	1.369	1.347	60%	590 (29.74)	1394 (70.26)	1984 (100)	2.377	2.556	2.503
70%	843 (36.43)	1471 (63.57)	2314 (100)	1.431	1.486	1.466	70%	697 (30.12)	1617 (69.88)	2314 (100)	2.243	2.411	2.360
80%	937 (35.43)	1708 (64.57)	2645 (100)	1.537	1.623	1.593	80%	836 (31.61)	1809 (68.39)	2645 (100)	2.080	2.288	2.222
90%	1032 (34.69)	1943 (65.31)	2975 (100)	1.660	1.777	1.736	90%	962 (32.34)	2013 (67.66)	2975 (100)	1.942	2.162	2.091

N_m: number of misclassification types; N_c: number of correct classification types; N_t: number of total classification types; Mean_m: mean of misclassification types; Mean_c: mean of correct classification types; Mean_t: mean of total classification types.

Table 6: Types of classifications distribution of filtered/selected data by S value.

Filtered%	Type of classifications distribution of filtered data by S value						Selected%	Type of classifications distribution of selected data by S value					
	N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t		N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t
10%	120 (36.25)	211 (63.75)	331 (100)	5.587	5.763	5.699	10%	100 (30.21)	231 (69.79)	331 (100)	−1.678	−1.625	−1.641
20%	234 (35.40)	427 (64.60)	661 (100)	4.620	4.673	4.654	20%	205 (31.01)	456 (68.99)	661 (100)	−1.159	−1.162	−1.161
30%	333 (33.57)	659 (66.43)	992 (100)	4.051	3.975	4.000	30%	312 (31.45)	680 (68.55)	992 (100)	−0.792	−0.804	−0.800
40%	435 (32.90)	887 (67.10)	1322 (100)	3.580	3.475	3.509	40%	431 (32.60)	891 (67.40)	1322 (100)	−0.469	−0.516	−0.501
50%	554 (33.51)	1099 (66.49)	1653 (100)	3.126	3.085	3.099	50%	543 (32.85)	1110 (67.15)	1653 (100)	−0.167	−0.226	−0.207
60%	666 (33.57)	1318 (66.43)	1984 (100)	2.768	2.731	2.743	60%	662 (33.37)	1322 (66.63)	1984 (100)	0.127	0.043	0.071
70%	785 (33.92)	1529 (66.08)	2314 (100)	2.405	2.411	2.409	70%	764 (33.02)	1550 (66.98)	2314 (100)	0.382	0.335	0.351
80%	892 (33.72)	1753 (66.28)	2645 (100)	2.106	2.093	2.097	80%	863 (32.63)	1782 (67.37)	2645 (100)	0.649	0.642	0.644
90%	997 (33.51)	1978 (66.49)	2975 (100)	1.814	1.777	1.789	90%	977 (32.84)	1998 (67.16)	2975 (100)	0.993	0.963	0.973

N_m: number of misclassification types; N_c: number of correct classification types; N_t: number of total classification types; Mean_m: mean of misclassification type; Mean_c: mean of correct classification type; Mean_t: mean of total classification type.

Table 7: Types of classifications distribution of filtered/selected data by C value.

Filtered%	Type of classifications distribution of filtered data by C value						Selected%	Type of classifications distribution of selected data by C value					
	N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t		N_m (%)	N_c (%)	N_t (%)	Mean_m	Mean_c	Mean_t
10%	141 (42.60)	190 (57.40)	331 (100)	0.846	0.845	0.845	10%	84 (25.38)	247 (74.62)	331 (100)	5.037	5.134	5.110
20%	272 (41.15)	389 (58.85)	661 (100)	1.066	1.085	1.078	20%	177 (26.78)	484 (73.22)	661 (100)	4.345	4.463	4.431
30%	396 (39.92)	596 (60.08)	992 (100)	1.240	1.267	1.256	30%	273 (27.52)	719 (72.48)	992 (100)	3.928	4.040	4.009
40%	516 (39.03)	806 (60.97)	1322 (100)	1.392	1.426	1.413	40%	370 (27.99)	952 (72.01)	1322 (100)	3.636	3.737	3.708
50%	619 (37.45)	1034 (62.55)	1653 (100)	1.520	1.588	1.562	50%	478 (28.92)	1175 (71.08)	1653 (100)	3.378	3.498	3.463
60%	727 (36.64)	1257 (63.36)	1984 (100)	1.664	1.746	1.716	60%	581 (29.28)	1403 (70.72)	1984 (100)	3.161	3.281	3.246
70%	824 (35.61)	1490 (64.39)	2314 (100)	1.799	1.911	1.871	70%	701 (30.29)	1613 (69.71)	2314 (100)	2.945	3.098	3.051
80%	920 (34.78)	1725 (65.22)	2645 (100)	1.941	2.082	2.033	80%	825 (31.19)	1820 (68.81)	2645 (100)	2.746	2.928	2.871
90%	1013 (34.05)	1962 (65.95)	2975 (100)	2.105	2.285	2.224	90%	956 (32.13)	2019 (67.87)	2975 (100)	2.548	2.769	2.698

N_m: number of misclassification types; N_c: number of correct classification types; N_t: number of total classification types; Mean_m: mean of misclassification type; Mean_c: mean of correct classification type; Mean_t: mean of total classification type.

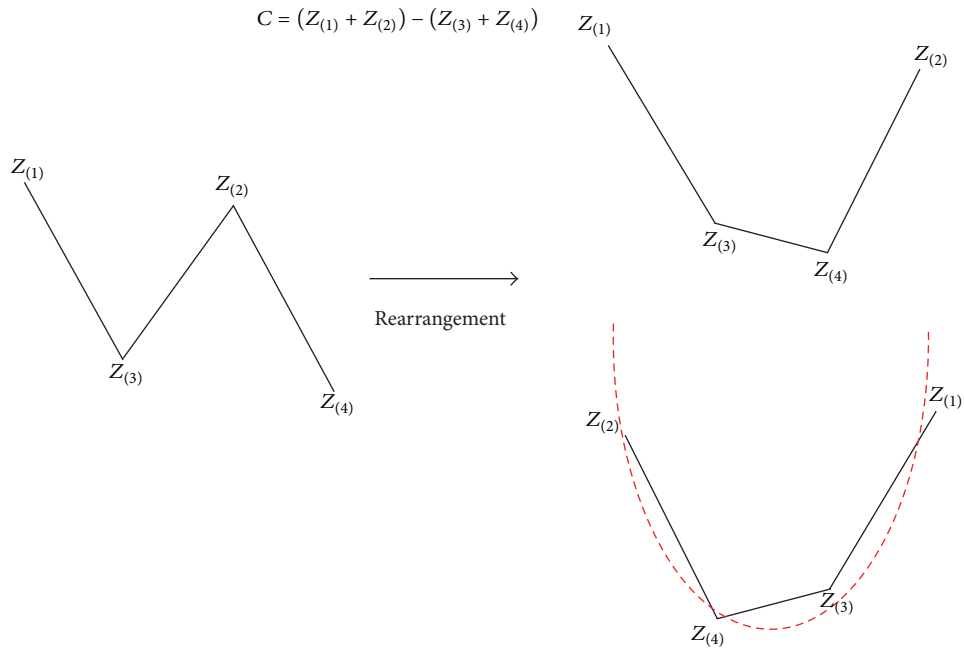

Figure 12: Derived C values based on the pattern analysis of the profile graphs. Under the hypothesis that the larger the C value was, the closer the profile graph was to a bathtub (or U) shape, the higher the probability of the respective observations corresponding to misclassification was.

Table 8: Misclassification rate distribution of the filtered data according to four measures.

Filtered%	N	D	R	S	C
10%	331	40.79	40.79	36.25	42.60
20%	661	39.03	39.49	35.40	41.15
30%	992	38.51	40.32	33.57	39.92
40%	1322	39.71	38.35	32.90	39.03
50%	1653	39.14	37.69	33.51	37.45
60%	1984	38.26	36.59	33.57	36.64
70%	2314	37.38	36.43	33.92	35.61
80%	2645	36.98	35.43	33.72	34.78
90%	2975	35.46	34.69	33.51	34.05

the normal equations should be equal to

$$\begin{aligned} S_1 &= 4b_0 + 10b_1 + 30b_2, \\ S_2 &= 10b_0 + 30b_1 + 100b_2, \\ S_3 &= 30b_0 + 100b_1 + 354b_2 \end{aligned} \tag{9}$$

and, ultimately, we obtain

$$\begin{aligned} \therefore b_2 &= \frac{5}{4}\left(S_1 - S_2 + \frac{S_3}{5}\right) \\ &= \frac{1}{4}\left\{\left(Z_{(1)} + Z_{(2)}\right) - \left(Z_{(3)} + Z_{(4)}\right)\right\}. \end{aligned} \tag{10}$$

Certainly, the values of b_0 and b_1 may be obtained but omitted herein because they are meaningless. In (10), $Z_{(1)}$ and $Z_{(2)}$ are symmetric, and so are $Z_{(3)}$ and $Z_{(4)}$. Namely, when the curvature creates the largest profile with the 4 points, the curvature will not have any changes even if the largest and the second largest scores were switched. This also holds true for the smallest and the second smallest scores.

In the meantime, the b_2 value equals 1/4 of the C score among the 4 criteria obtained. Namely, the previously used C score was equal to $Z_{(3)}$ and $Z_{(4)}$ was simply subtracted from the total of $Z_{(1)}$ and $Z_{(2)}$, which was the same as the secondary curvature created by the 4 scores.

4. Discussion

In TKM, a PI diagnostic system—one of the core technologies in the diagnosis and treatment of oriental medicine—is used to determine the cause and nature of a disease, treatment methods, and treatment drugs for the patients [5–7]. However, the PI diagnosis holds limited objectivity and reproducibility due to the lack of standardized measurement indices. Objectification problems have always arisen with respect to personal deviations among TKM physicians. As the demand for the reestablishment and development of TKM has increased, studies on the establishment of a scientific basis for and the standardization of PI have been actively conducted [7, 12].

In this study, the clinical data of PI diagnosis for stroke were used to analyze and quantify the profile patterns of the misclassification types by applying the proposed scores to the comparative analysis. This was intended to boost the correct classification of objects by detecting those objects with a high probability of actual misclassification and deferring discrimination. Misclassification types were discerned by a discriminant analysis on the actual clinical data of PI diagnosis for stroke and quantified by a profile pattern analysis. The

Table 9: Discriminant rate distribution of the selected data according to four measures.

		Discriminant rate			
	N	D	R	S	C
100%	3306	66.82	66.82	66.82	66.82
90%	2975	**68.24 (+1.42)**	67.63 (+0.81)	66.92 (+0.10)	67.53 (+0.71)
80%	2645	68.62 (+0.38)	68.47 (+0.84)	67.15 (+0.23)	**69.04 (+1.51)**
70%	2314	69.53 (+0.91)	**69.97 (+1.50)**	66.98 (−0.17)	69.49 (+0.45)
60%	1984	**71.98 (+2.45)**	70.82 (+0.85)	66.94 (−0.04)	71.22 (+1.73)
50%	1653	**73.32 (+1.34)**	73.08 (+2.26)	69.03 (+2.09)	71.81 (+0.59)
40%	1322	**75.34 (+2.02)**	74.28 (+1.20)	68.68 (−0.35)	73.75 (+1.94)
30%	992	**77.32 (+1.98)**	76.81 (+2.53)	70.26 (+1.58)	75.81 (+2.06)
20%	661	**83.36 (+6.04)**	80.94 (+4.13)	73.83 (+3.57)	77.61 (+1.80)
10%	331	**89.12 (+5.76)**	87.01 (+6.07)	75.83 (+2.00)	82.78 (+5.17)

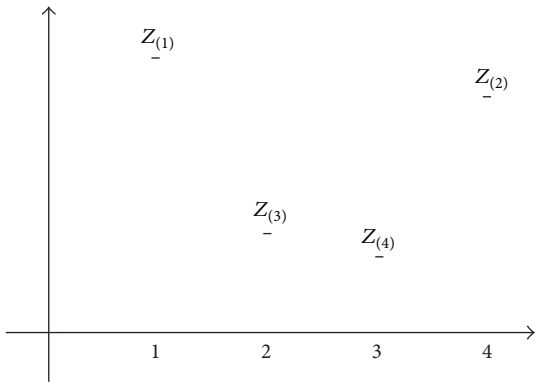

Figure 13: Curvature created by Z scores ($Z_{(1)}$, $Z_{(2)}$, $Z_{(3)}$, and $Z_{(4)}$). $Z_{(1)}$, $Z_{(2)}$, $Z_{(3)}$, and $Z_{(4)}$, as dependent variables observed in the x values having equal intervals. $Z_{(1)}$ is a dependent variable when $x = 1$, $Z_{(2)}$ when $x = 4$, $Z_{(3)}$ when $x = 2$, and $Z_{(4)}$ when $x = 3$.

proposed criteria of each standard were applied to the data already discriminated by the previous discriminant analysis in order to compare how well the misclassification had been estimated and how much the discrimination rate had improved when the estimated misclassification observations were removed in advanced. Particularly, the C score delivered the same results as those from the discrimination of misclassification observations through a secondary curvature. Going forward, the following studies must be performed. First of all, 4 criteria to estimate misclassification were proposed in this study and applied to the actual clinical data, producing the possibility of better estimation of partial misclassification. Nonetheless, it was difficult to notably enhance discrimination rates and additional research appears to be necessary. In addition, 4 pattern groups with a different sample size were used in this study. Hence, the effects of different sample sizes need to be investigated.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Confirmatory and Exploratory Factor Analysis for Validating the Phlegm Pattern Questionnaire for Healthy Subjects

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Background. Phlegm pattern questionnaire (PPQ) was developed to evaluate and diagnose phlegm pattern in Korean Medicine and Traditional Chinese Medicine, but it was based on a dataset from patients who visited the hospital to consult with a clinician regarding their health without any strict exclusion or inclusion. In this study, we reinvestigated the construct validity of PPQ with a new dataset and confirmed the feasibility of applying it to a healthy population. *Methods*. 286 healthy subjects were finally included and their responses to PPQ were acquired. Confirmatory factor analysis (CFA) was conducted and the model fit was discussed. We extracted a new factor structure by exploratory factor analysis (EFA) and compared the two factor structures. *Results*. In CFA results, the model fit indices are acceptable (RMSEA = 0.074) or slightly less than the good fit values (CFI = 0.839, TLI = 0.860). Many average variances extracted were smaller than the correlation coefficients of the factors, which shows the somewhat insufficient discriminant validity. *Conclusions*. Through the results from CFA and EFA, this study shows clinically acceptable model fits and suggests the feasibility of applying PPQ to a healthy population with relatively good construct validity and internal consistency.

1. Background

In Korean Medicine (KM) and Traditional Chinese Medicine (TCM), pathologic pattern identification is a very important diagnostic tool for KM or TCM doctors to evaluate a patient's health status and to decide clinical interventions. Pattern, which is a subcategory of a disease or a disorder, is defined as a diagnostic conclusion based on the pathological changes closely observed and holistically analyzed and may include a variety of information such as causes, locations, and properties of disorders or diseases [1, 2]. To identify a pattern, various kinds of clinical information are needed, and they are acquired by four examinations: inspection, listening and smelling, inquiry, and palpation. However, objective and quantitative tools are essential because intertester reliability cannot be guaranteed due to the subjective aspects of the examinations. Moreover, because the inquiry is an indirect method to acquire clinical information from the patients, inquiry lists or questionnaire items should be developed carefully.

Questionnaires based on the survey methodology are convenient and useful for the measurement and evaluation of subjective concepts or personal feelings and are therefore broadly used throughout various research fields such as psychology, medicine, education, sociology, and marketing. To support KM or TCM clinicians with fast and quantitative analysis of important signs and symptoms in the pattern identification, several KM pattern identification questionnaires were developed and validated [3–7]. Among these, the phlegm pattern questionnaire (PPQ) was developed to evaluate and diagnose the phlegm status of a subject. KM and TCM have broadly defined phlegm concept and narrowly defined phlegm concept. The former induce various signs and symptoms such as dizziness or palpation, which resulted from the internal disruption of the body fluid metabolism. The latter is visible phlegm such as nasal discharge or sputum, mainly from the lungs and the upper respiratory tract [4]. According to the KM and TCM theories, phlegm patterns have a wide spectrum of clinical signs and symptoms and often combine with other pathogenic patterns to form more

complex patterns. According to Zhu Zhenheng, a famous TCM physician in Yuan dynasty, nine out of ten diseases are associated with phlegm. Therefore, phlegm pattern has important clinical value in diagnosing many diseases and identifying patterns in KM and TCM.

In general, the development and validation study of a questionnaire are conducted at the same time, but additional validation studies are needed to apply the questionnaire to another population. Because the factor structure is easily influenced by sampled data, repetitive revalidation studies are needed to overcome the sampling bias and to confirm the latent variable structure. PPQ was validated with the limited dataset obtained during development [4], and there has been no revalidation clinical study on a similar or different population. Therefore, the aims of this study were to investigate the factor structure of PPQ from [4] with a new dataset of healthy people, to figure out the new structure of latent variables, and to discuss its validation and applicability to a healthy population.

2. Methods

2.1. Participants and Criteria. We recruited healthy volunteers in their 20s, 30s, and 40s from two sites in Korea: Kyung Hee University Korean Medicine Hospital in Seoul and Cheonan Oriental Hospital of Daejeon University in Cheonan. Korean Medicine doctors minutely interviewed the 307 volunteers (107 in Seoul and 200 in Cheonan) and included or excluded them according to the inclusion and exclusion criteria of this clinical study. Basically, those who can communicate with clinical research coordinators about their health status were included and then excluded with the following exclusion criteria: medical operation or procedure during one-month-long period prior to interview; excessive control of diet for any clinical treatment or weight reduction; pregnancy or breast-feeding; medication due to any diagnosed disease; severe pain or discomfort from which diseases are suspected. Fourteen participants were excluded according to the exclusion criteria, and four participants withdrew from participation (Figure 1). Finally, data from 289 participants were analyzed, and their basic sociodemographic characteristics are shown in Table 1.

This study design and ethics were approved by the institutional review board of Kyung Hee University Korean Medicine Hospital (KOMCIRB-2014-70) and Cheonan Oriental Hospital of Daejeon University (M2014-01-1). Informed consent was obtained from all individual participants included in the study.

2.2. Phlegm Pattern Questionnaire. The self-rated phlegm pattern questionnaire (PPQ) was developed by Delphi method based on the clinical expert opinions and the contexts of Korean Medicine and Traditional Chinese Medicine. It was revised and validated by various survey methodologies including exploratory factor analysis [4]. The PPQ consists of 25 items and the original form is presented in the Appendix. Each item is rated on a 7-point Likert scale: 1 = disagree very strongly; 2 = disagree strongly; 3 = disagree; 4 = neither agree

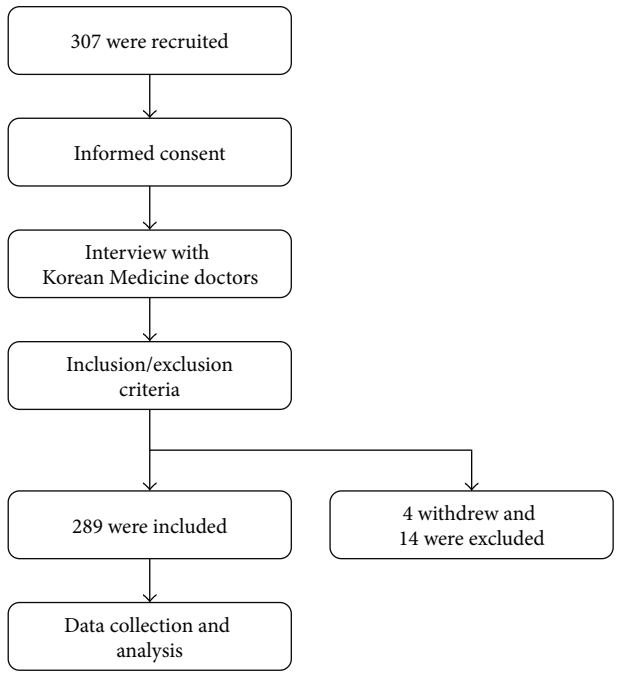

Figure 1: Clinical study procedure.

Table 1: Sociodemographic characteristics of participants (N = 289).

Participants characteristics	Frequency (%) or mean (±SD)
Gender:	
Male	139 (48.1)
Female	150 (51.9)
Age (years):	35.94 (±8.46)
Twenties	79 (27.3)
Thirties	103 (35.6)
Forties	107 (37.0)
Marital status:	
Unmarried	137 (47.4)
Married	141 (48.8)
Divorced	6 (2.1)
No reply	5 (1.7)
Highest education:	
High school	126 (43.6)
Technical or junior college	42 (14.5)
Bachelor's degree	97 (33.6)
Master's degree or higher	23 (8.0)
No reply	1 (0.3)
Occupation:	
Employed	145 (50.2)
Housewife	54 (18.7)
Agriculture	1 (0.3)
Physical labor	6 (2.1)
Student or others	83 (28.7)

SD: standard deviation.

Table 2: Correlation coefficients and average variance extracted (AVE).

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
Factor 1	(0.51)					
Factor 2	0.82	(0.52)				
Factor 3	0.87	0.81	(0.55)			
Factor 4	0.58	0.51	0.51	(0.62)		
Factor 5	0.55	0.61	0.71	0.46	(0.58)	
Factor 6	0.69	0.70	0.73	0.61	0.74	(0.42)

(AVE): average variance extracted.

nor disagree; 5 = agree; 6 = agree strongly; 7 = agree very strongly. Internal consistency of PPQ, which was examined by Cronbach's α, is 0.919, and the proposed optimum cut-off score is five when the 7-point Likert scale is dichotomized where 5, 6, and 7 points are coded as 1, and others are coded as 0.

2.3. Analysis Procedure. First, in order to investigate whether the factor structure can be replicated in the new dataset from 289 participants, confirmatory factor analysis (CFA) was conducted. Several model fit indices and their criteria were used to examine the goodness-of-fit of the model with the given dataset: goodness-of-fit index (GFI), adjusted goodness-of-fit index (AGFI), normed fit index (NFI), Tucker-Lewis Index (TLI), comparative fit index (CFI), and root mean square error of approximation (RMSEA). After evaluating the model fit, we calculated construct reliability (CR) for convergent validity and average variance extracted (AVE) for discriminant validity. Second, after performing the CFA, we extracted a more suitable factor structure from the new dataset. We then performed exploratory factor analysis (EFA) with maximum likelihood factoring. Maximum likelihood and principal axis factoring are generally recommended extraction methods [8]. Extracted factors were rotated by varimax rotation. Finally, the reliability of items in each factor was examined by Cronbach's α.

We used AMOS (SPSS Inc., Chicago, IL, USA) for CFA, SPSS Statistics 19 (SPSS Inc., Chicago, IL, USA) for EFA, and Microsoft Office Excel 2010 (Microsoft, Redmond, WA, USA) for other calculations.

3. Results and Discussion

3.1. Confirmatory Factor Analysis. Six-factor model from a previous study [4] for CFA is presented in Figure 2. Item numbers (PPQxx) in the figure correspond with the item numbers in the Appendix. Factor loadings and CRs for convergent validity are also presented in Figure 1. The model fit indices were as follows: GFI = 0.839, AGFI = 0.799, NFI = 0.817, TLI = 0.860, CFI = 0.878, and RMSEA = 0.074. Discriminant validity of this model can be examined by the correlation coefficients and the AVE in Table 2.

3.2. Exploratory Factor Analysis. Before EFA, the Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity were conducted to evaluate the factorability. The KMO measure of sampling adequacy was 0.922 and the significance of Bartlett's test of sphericity was less than 0.001, meaning that EFA can be applied to the obtained dataset [9].

EFA was conducted with the obtained data to extract the new factor structure and to examine the construct validity. Factors were extracted by the maximum likelihood method and rotated by varimax rotation. The number of factors was decided in consideration of the scree-plot, cumulative variance explained, interpretability, and Kaiser's criterion. A total of five factors were extracted and rotated, and the cumulative variance explained was 51.81%. Items (20), (23), and (19) have factor loading of less than 0.4 for all factors. Factor structures of the EFA results and the previous model from Park's study are compared in Table 4.

3.3. Internal Consistency. One of the most popular estimates of internal consistency is Cronbach's α. Factor Cronbach's α and the item-delete Cronbach's α of each item are presented in Table 5. Generally, if $\alpha \geq 0.9$, the internal consistency is considered to be excellent, and if $0.7 \leq \alpha < 0.9$, it is considered to be good. All the extracted factors have good internal consistency. According to the analysis results, if items (20), (19), and (15) are deleted, Cronbach's α of the corresponding factor increases slightly.

4. Discussion

In this study, we investigated whether a new dataset from healthy subjects is suitable for the 6-factor model devised in a previous validation study [4]. For that, CFA was conducted and model fits were discussed. Next, EFA was conducted to extract the new factor structure from the dataset and compare it with the 6-factor model. Data were obtained in the clinical trial with strict inclusion and exclusion criteria. Subjects are well distributed in their sex, age, and marital status (Table 1). The education level category was weighted towards high school due to the fact that many of the subjects are university students.

To discuss the model fit of CFA, we should consider the criteria of the various model fit indices. It has been suggested that RMSEA values less than 0.05 are good, values between 0.05 and 0.08 are acceptable, values between 0.08 and 0.1 are marginal, and values greater than 0.1 are poor [8]. Therefore, the RMSEA value of 0.074 in this sample indicates an acceptable fit. The GFI value of this sample, 0.84, is below 0.9, but the GFI and AGFI are known to depend on the sample

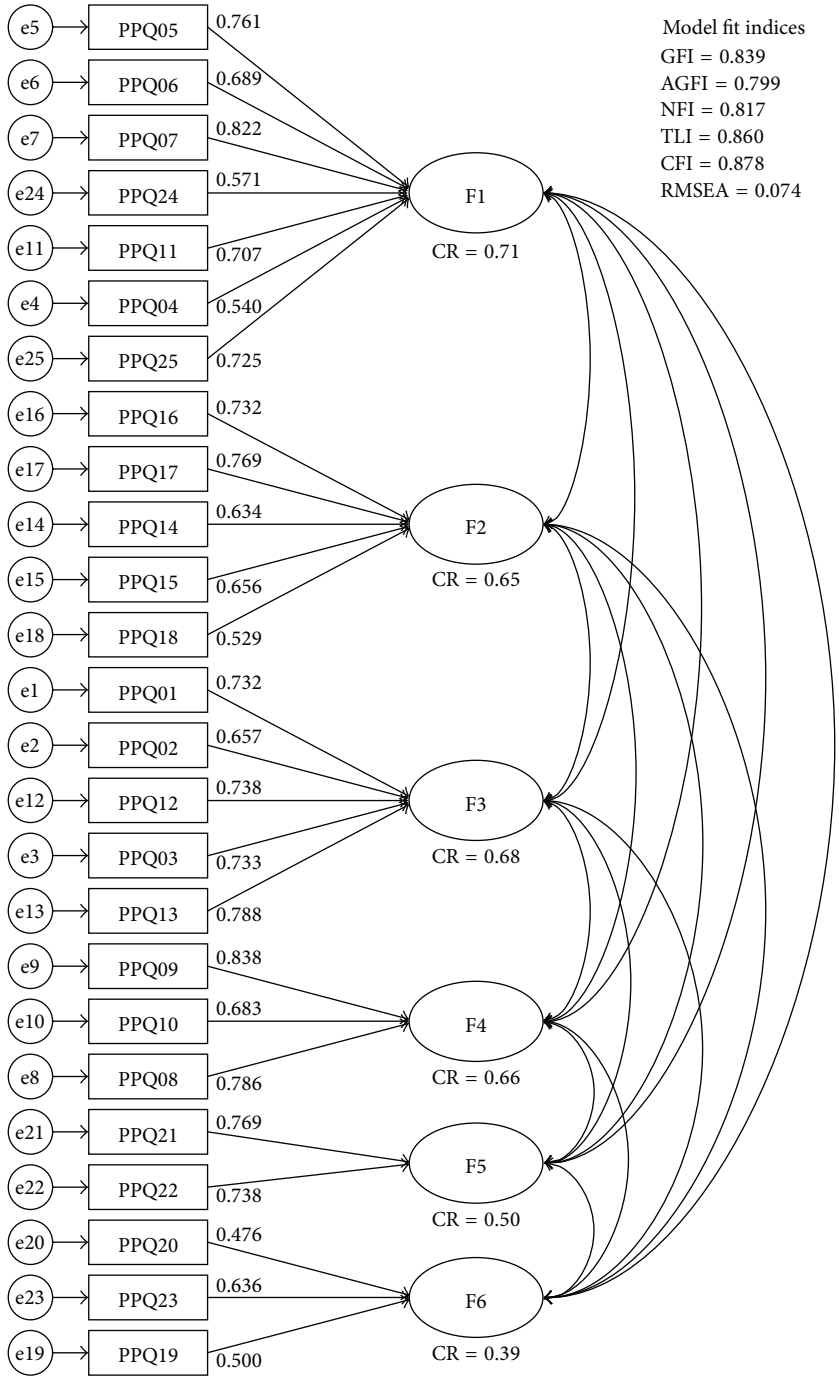

Figure 2: Results of the confirmatory factor analysis of the PPQ for healthy subjects.

size [10]. The CFI value is close to 0.9, which shows a relatively good fit [11]. The other fit indices, NFI and TLI, should be over 0.9 for a good fit [11], but in this sample, the two indices are a little below the criteria. Based on these indices, this sample has an acceptable fit to the 6-factor model.

In general, factor loadings and CR should be equal to or greater than 0.707 for good convergent validity [12]. From the CFA result of this study, fourteen loadings are greater than 0.707 and six loadings are between 0.6 and 0.707. Five loadings (those of items (19), (20), (18), (24), and (4)) are under 0.6. All items of factor 6 showed relatively low convergent validity. CR of factor 6 also has a low evaluation. Low convergent validity means the items have information of other factors rather than the corresponding factor alone. For good discriminant validity, AVE of one factor should be larger than any correlation coefficients between the factor and another one [12, 13]. If any factor has smaller AVE than correlation coefficients, it means the factors

Table 3: Factor loadings results from exploratory factor analysis.

Item	Factor loading				
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Neuropsychologic signs and symptoms					
(5) I feel my heart palpitate.	**0.79**	0.15	0.19	0.07	0.09
(7) I feel heavy in the chest.	**0.70**	0.18	0.17	0.33	0.15
(25) I have flank pain.	**0.58**	0.13	0.22	0.33	0.13
(6) I am startled by faint noise.	**0.57**	0.25	0.13	0.23	0.19
(4) I have ringing in the ears.	**0.53**	0.13	0.14	0.07	0.09
(3) I feel dizzy.	**0.53**	0.26	0.20	0.21	0.37
(11) I feel short of breath.	**0.51**	0.24	0.38	0.24	0.05
(14) I have a poor appetite.	**0.45**	0.24	0.20	0.28	0.14
(24) I have pain in the joints.	**0.43**	0.31	0.17	0.11	0.11
*(20) I have a lump somewhere on my body.	0.30	0.18	0.19	0.07	0.16
Dermatologic and fatigue-related signs and symptoms					
(22) I have dark circles under the eyes.	0.07	**0.70**	0.15	0.16	0.10
(21) My face is yellowish.	0.23	**0.66**	0.21	0.05	0.06
(12) I feel fatigued.	**0.41**	**0.53**	0.08	0.21	0.19
(13) I feel heavy or weak in the limbs.	**0.51**	**0.52**	0.24	0.19	0.11
(18) My stomach or intestine rumbles.	0.28	**0.45**	0.03	0.23	0.07
*(23) I feel itchy.	0.16	0.39	0.24	0.20	0.16
Respiratory signs and symptoms					
(9) I have sputum in my throat.	0.19	0.12	**0.81**	0.12	0.00
(8) I have a cough.	0.24	0.16	**0.71**	0.08	0.15
(10) I feel a foreign body present in the throat, neither swallowed nor ejected.	0.18	0.15	**0.63**	0.10	0.04
*(19) My stool is mucousy.	0.10	0.28	0.29	0.14	0.06
Digestive signs and symptoms					
(16) I have indigestion.	0.19	0.23	0.15	**0.76**	0.18
(17) I have a feeling of fullness in the stomach with just a little food.	0.33	0.27	0.13	**0.70**	0.04
(15) I feel sick in the stomach.	0.35	0.17	0.27	**0.41**	0.17
Head-related signs and symptoms					
(2) I have a headache.	0.31	0.20	0.09	0.16	**0.90**
(1) I feel unclear in the head.	0.38	**0.40**	0.10	0.25	**0.42**
Rotation Sums of Squared Loadings					
% of variance	17.21	11.08	9.62	8.13	5.78
Cumulative%	17.21	28.29	37.90	46.03	51.81

Factors were extracted by maximum likelihood method and rotated by varimax rotation.
Bold values indicate factor loading of greater than 0.40.
*Items whose loadings are less than 0.4 for every factor.

are correlated and that they do not measure well-separated latent concepts; however many correlation coefficients are larger than the corresponding AVEs in Table 2. Therefore, in this model and dataset, the factors are associated with one another. Two explanations are possible. First, latent factors that compose one concept in the real world cannot be absolutely independent. Additionally, because PPQ measures the pathologic phlegm pattern of KM or TCM, the factors of closely associated signs and symptoms can be expressed together. Second, because the subjects are healthy people, it is possible that the distinguishing signs and symptoms of a specific disease other than phlegm pattern were not expressed.

We conducted EFA to extract the new factor structure of the dataset and found a 5-factor structure model (Table 3). Items (20), (23), and (19) have all factor loadings of below 0.4. In fact, item (23) can be thought to have marginal factor loading, 0.39, but the other two items have values of equal to or less than 0.3. Thus, items (19) and (20) may influence the independency of the factors, and this is in agreement with the factor 6 result of the CFA in Figure 2. In comparison with Park's previous study, the dataset obtained in this trial has a more well-separated 5-factor structure. This is because the items of the 5-factor model have greater loadings for their corresponding factor and almost all items can be explained by one factor. However, it is a shortcoming of factor 5 that

Table 4: Comparison of factor structure between this and a previous study.

Factor structure of this study		Factor structure of Park et al.'s study [4]	
Factor 1	Palpitation	Palpitation	Factor 1
	Startled by faint noise	Startled by faint noise	
	Feeling heavy in the chest	Feeling heavy in the chest	
	Joint pain	Joint pain	
	Shortness of breath	Shortness of breath	
	Tinnitus	Tinnitus	
	Flank pain	Flank pain	
	Dizziness		
	Poor appetite		
	Lumps		
Factor 4	Indigestion	Indigestion	Factor 2
	Feeling of abdominal fullness	Feeling of abdominal fullness	
	Sickness	Sickness	
		Poor appetite	
		Rumbling sound	
Factor 5	Headache	Headache	Factor 3
	Unclearness in the head	Unclearness in the head	
		Dizziness	
Factor 2	Fatigue	Fatigue	
	Feeling heavy in the limbs	Feeling heavy in the limbs	
	Dark circle under the eyes	Dark circle under the eyes	Factor 4
	Yellowish face	Yellowish face	
	Rumbling sound		
	Itching		
Factor 3	Sputum	Sputum	Factor 5
	Feeling of foreign body in the throat	Feeling of foreign body in the throat	
	Cough	Cough	
	Mucousy stool		
		Lumps	Factor 6
		Itching	
		Mucousy stool	

Items are shortened and reordered for easier comparison.

it has only two items, since according to the guidelines one factor should have more than two items if possible [14, 15].

Factor comparison of the 5- and 6-factor model is shown in Table 4, which shows the similarity of the factor structure. Items of "fatigue" and "feeling heavy" were combined with head-related signs and symptoms from the previous 6-factor model, but with dermatological signs and symptoms in this 5-factor model. Respiratory signs and symptoms, factor 5 in the 6-factor model and factor 3 in the 5-factor model, are almost identical in the two structures. Items of factor 6 in the 6-factor model—items (19), (20), and (23)—had the least variance explained. In this 5-factor model, they are scattered and bundled with factors 3, 1, and 2, respectively. Moreover, all loadings of the three items are below 0.4. In consideration of the CFA result (Figure 2) and the internal consistency evaluation (Table 5), the three items may be revaluated in a further revision or revalidation study. The other items showed acceptable or good internal consistency with high Cronbach's α (Table 5).

EFA is known as a data-driven method, and CFA as a theory-driven method. So the usage of EFA or CFA should be strictly considered and chosen according to the aim of a study, and aimless application of EFA and CFA to the same dataset should be avoided [16]. One can explore the latent variable structure of a dataset with EFA. On the other hand, CFA requires an *a priori* hypothesis or previous "theory" as CFA is a hypothesis testing method which tests whether the obtained dataset is suitable for a model [16]. Thus, in this study, we used CFA to discuss the model fit of the dataset obtained from the healthy subjects in the clinical trial to the previously extracted PPQ 6-factor structure. Also, we used EFA to extract the new factor structure according to the above-mentioned guidelines. Different from this study, Park's model was constructed with a dataset from patients

Table 5: Internal consistency of factors.

Cronbach's α	item	Cronbach's α if item is deleted
Factor 1 0.881	(5) I feel my heart palpitate.	0.860
	(7) I feel heavy in the chest.	0.858
	(25) I have flank pain.	0.863
	(6) I am startled by faint noise.	0.867
	(4) I have ringing in the ears.	0.876
	(3) I feel dizzy.	0.864
	(11) I feel short of breath.	0.869
	(14) I have a poor appetite.	0.873
	(24) I have pain in the joints.	0.877
	*(20) I have a lump somewhere on my body.	0.882
Factor 2 0.811	(22) I have dark circles under the eyes.	0.774
	(21) My face is yellowish.	0.773
	(12) I feel fatigued.	0.770
	(13) I feel heavy or weak in the limbs.	0.761
	(18) My stomach or intestine rumbles.	0.799
	(23) I feel itchy.	0.809
Factor 3 0.76	(9) I have sputum in my throat.	0.632
	(8) I have a cough.	0.650
	(10) I feel a foreign body present in the throat, neither swallowed nor ejected.	0.689
	*(19) My stool is mucousy.	0.808
Factor 4 0.786	(16) I have indigestion.	0.634
	(17) I have a feeling of fullness in the stomach with just a little food.	0.657
	*(15) I feel sick in the stomach.	0.806
Factor 5 0.765	(2) I have a headache.	—
	(1) I feel unclear in the head.	—

*Cronbach's α increases if item is deleted
— Cronbach's α cannot be calculated because factor 5 has only 2 items.

who visited the hospital to consult with a clinician regarding their health without any strict exclusion or inclusion criterion [4]. Thus it was possible for patients, subhealthy subjects, and healthy subjects to participate in that study. This difference may have resulted in a small difference in factor structure.

In spite of our confirmation of the similar structure of the two models and a few items with relatively low reliability and validity in the models, this is still an exploratory study based on the survey research method and data-driven aspects. To overcome these limitations and to acquire the predictability and validity, prospective clinical trials should be carried out with the gold standard of pattern identification like agreement of several clinicians. If so, factor structures of patient group and healthy group can be compared and diagnostic value of the questionnaire can be discussed more.

5. Conclusion

A revalidation study of PPQ was conducted. A sample dataset obtained from clinical trial under strict conditions did not show the excellent model fit of the previous PPQ model, but the additional EFA indicated similar factor structures exist and it was hypothesized that the difference might come from a few items. In conclusion, PPQ can be applied to a healthy population with good construct validity and internal consistency for evaluating phlegm pattern, and it can be more improved if a few items are adjusted with further studies.

Appendix

Phlegm Pattern Questionnaire

We would like to know more about any problems you have experienced recently. Please answer all the questions by checking the answer that applies to you most closely.

See Table 6.

Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contribution

Hyunho Kim designed and carried out the clinical trial and drafted the paper. Boncho Ku and Jong Yeol Kim participated

Table 6

Condition	1	2	3	4	5	6	7
(1) I feel unclear in the head.							
(2) I have a headache.							
(3) I feel dizzy.							
(4) I have ringing in the ears.							
(5) I feel my heart palpitate.							
(6) I am startled by faint noise.							
(7) I feel heavy in the chest.							
(8) I have a cough.							
(9) I have sputum in my throat.							
(10) I feel a foreign body present in the throat, neither swallowed nor ejected.							
(11) I feel short of breath.							
(12) I feel fatigued.							
(13) I feel heavy or weak in the limbs.							
(14) I have a poor appetite.							
(15) I feel sick to the stomach.							
(16) I have indigestion.							
(17) I have a feeling of fullness in the stomach with just a little food.							
(18) My stomach or intestine rumbles.							
(19) My stool is mucousy.							
(20) I have a lump somewhere on my body.							
(21) My face is yellowish.							
(22) I have dark circles under the eyes.							
(23) I feel itchy.							
(24) I have pain in the joints.							
(25) I have flank pain.							

1: disagree very strongly, 2: disagree strongly, 3: disagree, 4: neither agree nor disagree, 5: agree, 6: agree strongly, and 7: agree very strongly.

in the clinical trial design and performed the statistical analysis. Young-Jae Park contributed to study discussion and preparing the paper. Young-Bae Park contributed to conducting the study and preparing the draft paper. All authors read and approved the final paper.

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Research Article

Effect and Safety of Shihogyejitang for Drug Resistant Childhood Epilepsy

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Objective. Herbal medicine has been widely used to treat drug resistant epilepsy. Shihogyejitang (SGT) has been commonly used to treat epilepsy. We investigated the effect and safety of SGT in children with drug resistant epilepsy. *Design*. We reviewed medical records of 54 patients with epilepsy, who failed to respond to at least two antiepileptic drugs and have been treated with SGT between April 2006 and June 2014 at the Department of Pediatric Neurology, I-Tomato Hospital, Korea. Effect was measured by the response rate, seizure-free rate, and retention rate at six months. We also checked adverse events, change in antiepileptic drugs use, and the variables related to the outcome. *Results*. Intent-to-treat analysis showed that, after six months, 44.4% showed a >50% seizure reduction, 24.1% including seizure-free, respectively, and 53.7% remained on SGT. Two adverse events were reported, mild skin rash and fever. Focal seizure type presented significantly more positive responses when compared with other seizure types at six months ($p = 0.0284$, Fisher's exact test). *Conclusion*. SGT is an effective treatment with excellent tolerability for drug resistant epilepsy patients. Our data provide evidence that SGT may be used as alternative treatment option when antiepileptic drug does not work in epilepsy children.

1. Introduction

Antiepileptic drugs (AEDs) are the most common treatment for epileptic seizures in children. However, approximately one-third of the patients who are given AEDs as the suitable treatment do not achieve optimal seizure control [1]. The patient who has failed to become seizure-free with adequate trials of two AEDs is considered to have drug resistant epilepsy. In particular, severe forms of epilepsy in children such as West syndrome and Lennox-Gastaut syndrome become drug resistant epilepsy despite the use of high doses and several combinations of AEDs. Moreover, the use of AEDs has been associated with various adverse effects, including neurologic toxicity [2]. As a result, there is a constant need for alternative treatment with drug resistant epilepsy.

Complementary and alternative medicine (CAM) is used by patients with various diseases, including epilepsy [3–6]. It has been reported that patients with epilepsy often choose herbal medicine among CAM therapies [7, 8]. Some herbal formulas such as Shihogyejitang (SGT) are often considered as a treatment option of epileptic seizures in the CAM area. SGT, also called chai hu gui zhi tang in Chinese, is a Korean prescription which has been used to treat various disease including epilepsy in traditional Korean medicine. It is composed of nine herbs, Bupleuri radix, Pinelliae tuber, Scutellariae radix, Zizyphi fructus, Ginseng radix, Glycyrrhizae radix, Zingiberis rhizoma, Paeoniae radix, and Cinnamomi cortex. A series of preclinical studies with herbal extracts based on SGT showed that this formula has potential antiepileptic effects [9–15], and clinical studies presented the effect of SGT on reducing seizure frequency with improving cognitive outcome in the patients with epilepsy [16, 17]. However, there have not been enough clinical studies to demonstrate the benefits and adverse effects of SGT for treating epileptic seizures in Korea.

In this study, we conducted a retrospective study aiming to investigate the potential effect and safety of SGT as an

alternative treatment for seizure control in children with drug resistant epilepsy.

2. Methods

2.1. Patient Selection. In this retrospective study, we reviewed the medical records of children under 12 with epilepsy treated with SGT at the Department of Pediatric Neurology, I-Tomato Hospital, Korea, between April 2006 and June 2014. Patients were eligible if they had tried at least two AEDs before starting the treatment with SGT but still had one or more seizure per day. The last follow-up was conducted during November 2014 in order to collect data on the current conditions and the reason for discontinuation of SGT had it occurred. Gachon University Institutional Review Board granted an ethical approval for this study.

Data on the following properties were obtained from medical records: age, gender, seizure type, epilepsy syndromes, initial seizure frequency, AEDs used before starting SGT, developmental status, age at onset of the first seizure, age of staring SGT, and original magnetic resonance imaging (MRI), and EEG data. Classification of seizure types, electroclinical syndromes, and other epilepsies was based on the 2010 ILAE report [21].

2.2. Treatment. SGT was administered until the patients achieved seizure-free and maintained the state of remission for over two years. SGT was stopped when seizures increased or unacceptable toxicity occurred. If seizure frequency had not changed for at least two weeks, SGT was also stopped.

The daily dose of SGT used in this study consisted of the following: 7.0 g of Bupleuri radix (*Bupleurum falcatum* L.), 4.0 g of Pinelliae tuber (*Pinellia ternate* (Thunb.) Breit.), 2.0 g of Scutellariae radix (*Scutellaria baicalensis* Georgi), 2.0 g of Zizyphi fructus (*Zizyphus vulgaris* var. spinosus), 2.0 g of Ginseng radix (*Panax ginseng* C.A. Meyer), 1.5 g of Glycyrrhizae radix (*Glycyrrhiza uralensis* Fisch), 1.0 g of Zingiberis rhizoma (*Zingiber officinale* Roscoe), 2.5 g of Paeoniae radix (*Paeonia lactiflora* Pallas), and 2.5 g of Cinnamomi cortex (*Cinnamomum cassia* Blume). The herbal decoction was made in the hospital pharmacy. All the herbs comprising SGT were mixed with 120 mL of purified water and then decocted for 120 minutes at 102°C to 103°C until half of the original amount of liquid was left. 20 mL of the decoction was packed into each vacuum pouch by an automatic packing machine. Patients of age five or older were asked to administer one pack of the decoction 30 minutes after each meal, three times a day. For patients under five, the daily dosage was adjusted based on the conversion table of von Harnack.

The patients were required to make visits to the hospital every two to four weeks. At every visit, data on the patients' seizure frequency and adverse events were collected.

It was attempted to decrease or completely stop AED intake when the patients' >50% seizure reduction level was being sustained at least four weeks.

2.3. Assessment of Seizure Frequency. The effect of SGT on seizure control was measured mainly by change in seizure frequency. Seizure frequency was obtained through parental reports and seizure diaries. The average seizure frequency per month was compared to the seizure frequency level prior to beginning the SGT treatment. Seizure control was categorized as follows: (1) seizure-free state; (2) >90% reduction; (3) 50–90% reduction; (4) <50% reduction; (5) no change; and (6) increased seizure frequency.

2.4. Endpoints and Statistical Analysis. The primary endpoint of this study was the response rate at six months. The patients who achieved a >50% decrease in seizure frequency compared to the baseline were identified as responders, and response rate was defined as the proportion of the responders.

The secondary endpoints were the seizure-free rate at six months, the retention rate at six months, discontinuation rate of AED intake, and safety. Seizure-free rate was defined as the proportion of the patients who achieved and stayed seizure-free. Retention rate was defined as the proportion of the patients who continued with the SGT treatment. Discontinuation rate of AED intake was defined as the proportion of patients who decreased the number of AEDs including withdraw of AEDs. All patients were evaluated for toxicity, including physical examination and laboratory findings every month during treatment. Laboratory findings included complete blood count with differential count, liver function test, renal function test, and electrolytes.

Statistical analysis was conducted using SPSS (v. 18.0). Two-tailed Fisher's exact test and Mann-Whitney U test were applied for analyzing categorical and continuous variables respectively. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics. Fifty-four patients were eligible for analysis. Patient demographics are summarized in Table 1. The median age of experiencing the first seizure was 7.5 months (range: 1 day to 6 years), and the median age of beginning the SGT treatment was 16.5 months (range: 1 month to 10.3 years). The median seizure frequency was 8 times/day (range: 1/day to 270/day). As for seizure types, 17 patients were classified as experiencing generalized seizure, 14 were experiencing focal seizure, 21 had epileptic spasms, and the remaining two were unclassified. Nineteen patients had West syndrome and 13 patients had Lenox-Gastaut syndrome. Out of 54 patients, 25 showed abnormalities on brain MRI. Excluding only five of all patients, 49 were diagnosed with delayed mental or physical development. The median number of AEDs that were used but had failed as treatments prior to the beginning of the SGT treatment was 3 (range: 2 to 7). The median number of AEDs that were being used at the beginning of the SGT treatment was 3 (range: 1 to 7). The median duration for the SGT treatment was 6 months (range: 1 to 83 months).

3.2. Response Rate and Seizure-Free Rate. The response rate of SGT at six months was 44.4% and the seizure-free rate at six months was 24.1%. The changes of seizure frequency at 1, 3, 6, and 12 months are presented in Table 2.

Table 1: Baseline characteristics of the subjects ($N = 54$).

	Number of patients (%)
Gender	
Male	31 (57.4)
Female	23 (42.6)
Seizure frequency	
1–10 times/day	33 (61.1)
11–50 times/day	13 (24.1)
>51 times/day	8 (14.8)
Seizure type	
Generalized[†]	17 (31.5)
Tonic-clonic	2 (3.7)
Atypical absence	6 (11.1)
Myoclonic	1 (1.9)
Tonic	12 (22.2)
Atonic	5 (9.3)
Focal	14 (25.9)
Epileptic spasms	21 (38.9)
Unclassified	2 (3.7)
Electroclinical syndrome and other epilepsies	
Neonatal epileptic encephalopathy	2 (3.7)
Epilepsy of infancy with migrating focal seizures	1 (1.9)
West syndrome	19 (35.2)
Lenox-Gastaut syndrome	13 (24.1)
Generalized epilepsy without a known structural causes	3 (5.6)
Focal epilepsy	
With a known structural or metabolic causes	4 (7.4)
Without a known structural or metabolic causes	9 (16.7)
Epilepsies of unknown causes	3 (5.6)
Age at the first seizure	
Median (range)	7.5 months (1 day to 6 years)
Age at the start of the SGT	
Median (range)	16.5 months (1 month to 10.3 years)
Brain MRI at starting SGT	
Normal	29 (53.7)
Abnormal	25 (46.3)
Developmental status	
Delayed	49 (90.7)
Normal	5 (9.3)
Number of previously used AEDs	
2	17 (31.5)
3	18 (33.3)
4	12 (22.2)
5	4 (7.4)
>6	3 (5.6)
Previously used AEDs	
Sodium valproate	25 (46.3)
Vigabatrin	24 (44.4)
Levetiracetam	23 (42.6)
Topiramate	22 (40.7)
Phenobarbital	14 (25.9)
Clobazam	12 (22.2)
Lamotrigine	8 (14.8)

Table 1: Continued.

	Number of patients (%)
Oxcarbazepine	8 (14.8)
Clonazepam	7 (13)
Divalproex sodium	5 (9.3)
Rufinamide	4 (7.4)
Zonisamide	4 (7.4)
Phenytoin	3 (5.6)
Carbamazepine	2 (3.7)
Ethosuximide	1 (1.9)
Lacosamide	1 (1.9)
Number of concomitant AEDs at start of herbal medicine	
1	1 (1.9)
2	21 (38.9)
3	15 (27.8)
4	13 (24.1)
5	3 (5.6)
>6	1 (1.9)

SGT, Shihogyejitang; MRI, magnetic resonance imaging; AED, antiepileptic drug.
[†]5 patients had mixed seizure type.

Table 2: Seizure outcomes and retention rates at 1, 3, 6, and 12 months.

	1 month	3 months	6 months	12 months
Responders				
Seizure-free	10	19	13	8
>90% reduction	15	11	10	4
50–90% reduction	13	7	1	0
Nonresponders				
<50% reduction	11	2	1	0
Not changed	3	4	2	0
Increased	2	1	2	0
Response rate	70.4% (38/54)	68.5% (37/54)	44.4% (24/54)	22.2% (12/54)
Retention rate	90.7% (49/54)	81.5% (44/54)	53.7% (29/54)	22.2% (12/54)

The changes of seizure frequency according to types of seizure and epilepsy syndrome are presented in Table 3. Patients with focal seizure type presented significantly more positive responses when compared with other seizure types at six months ($p = 0.0284$, Fisher's exact test). Patients with West syndrome and Lennox-Gastaut syndrome showed more favorable outcomes than patients with other epileptic syndromes, but there was no statistical difference.

The effects of clinical parameters in seizure outcomes are shown in Table 4. The median number of AEDs that had been tried before the initiation of the SGT treatment in responders was significantly smaller than that of the nonresponders at three months ($p = 0.030$, Mann-Whitney U test).

3.3. Retention Rate. The retention rate of SGT at six months was 53.7% (29/54 patients). The retention rates at 1, 3, and 12 months are shown in Table 2.

The main reason for discontinuation was that the guardians of patients felt that herbal medicine as an alternative therapy did not fully meet their expectations ($n = 21$); the guardians of those patients decided to quit the SGT treatment although those patients showed a decrease in seizure frequency during the SGT treatment. 17 of those 21 had a result of >90% reduction of seizure.

Other reasons of discontinuation were ineffectiveness ($n = 15$), financial burdensomeness ($n = 9$), achieving seizure remission for over two years ($n = 5$), adverse events ($n = 1$), and unknown reasons ($n = 1$).

3.4. Long-Term Outcomes. There were eleven patients who continued the SGT treatment for over 12 months. Among these patients, five tapered off the use of AEDs during the SGT treatment and were ordered to discontinue the SGT treatment as they maintained the state of remission for over

Table 3: Seizure outcomes according to seizure types and epileptic syndromes at six months.

	Seizure types			Epileptic syndromes	
	Generalized	Focal	Epileptic spasms	West syndrome	LGS
Number of patients	9	11	9	8	7
Responders					
Seizure-free	3	4	6	6	2
>90% reduction	3	5	2	1	4
50–90% reduction	0	1	0	0	0
Nonresponders					
<50% reduction	1	0	0	0	0
Not changed	1	0	1	1	1
Increased	1	1	0	0	0
Response rate	66.7% (6/9)	90.9% (10/11)	88.9% (8/9)	87.5% (7/8)	85.7% (6/7)

LGS, Lenox-Gastaut syndrome.

Table 4: Effects of clinical parameters on seizure outcomes.

		3 months	6 months	12 months
Age at the onset of first seizure (months)	Responders	13.47 ± 16.85	16.96 ± 19.66	18.92 ± 17.57
	Nonresponders	8.69 ± 7.27	7.71 ± 6.83	9.97 ± 13.24
	p value	0.615	0.146	0.051
Age at the start of the SGT (months)	Responders	35.81 ± 34.77	43.58 ± 38.22	40.42 ± 31.54
	Nonresponders	28.71 ± 26.23	24.07 ± 23.35	31.62 ± 32.56
	p value	0.776	0.086	0.139
Treatment duration (months)	Responders	22.34 ± 26.37	26.62 ± 29.16	21.50 ± 17.66
	Nonresponders	20.02 ± 26.39	16.35 ± 22.54	21.65 ± 28.29
	p value	0.970	0.356	0.382
Number of AEDs that had been tried	Responders	3.00 ± 1.05	3.05 ± 1.16	2.92 ± 1.00
	Nonresponders	3.71 ± 1.21	3.38 ± 1.15	3.31 ± 1.18
	p value	0.030*	0.228	0.313

Data are presented as the mean ± SD. Mann-Whitney U tests were used for comparison between responders and nonresponders. *Statistically significant at $p < 0.05$.
SGT, Shihogyejitang; AED, antiepileptic drug.

two years. These five patients were all confirmed to be seizure-free without medication other than SGT at the last follow-up. The remaining six patients were maintaining a >90% seizure reduction level until their guardians decided on terminating the treatment with SGT. At the last follow-up conducted after the termination of the SGT treatment, two out of the six reported to have maintained a >90% seizure reduction level whereas the remaining four reported an increased seizure frequency.

3.5. AED Usage during the SGT Treatment. The discontinuation rate of AED intake at the last follow-up was 42.6%. In other words, twenty-three patients decreased the number of AEDs including 11 patients who were able to completely withdraw during the SGT treatment. Seventeen out of whom were able to do so with a >90% seizure reduction.

Out of the 54 patients, 29 retained the initial level of AED usage throughout the SGT treatment; 20 of them showed a >50% reduction in seizure frequency.

There were two patients who were prescribed to additional AEDs over the course of the SGT treatment. One of them showed a 50–90% reduction in seizure frequency at one month and a >90% reduction at three months. But seizure frequency at five months had been increased, so valproate was added at five months but it was also not effective. The other patient did not show a response in seizure control with the SGT treatment, but the guardian of the patient strongly wanted to continue the SGT treatment. Therefore, levetiracetam and topiramate had been added after two months of treatment with SGT, but those were also not effective.

3.6. Adverse Events. Adverse events were reported in two patients (3.7%). One patient experienced mild skin rash on his trunk within a week of the SGT treatment, but it was diminished within two days without a change in the administration of SGT. One patient experienced mild fever three months after beginning the SGT treatment. Other

adverse events except these two were not reported in the physical examination and laboratory testing.

4. Discussion

This study evaluated the effect and safety of SGT in children with drug resistant epilepsy. We observed that SGT improved seizure frequency with few adverse events in children with epilepsy who previously had unsuccessful AED trials. Using intention-to-treat analysis, it can be seen that among all patients 44.4% achieved a >50% reduction in seizures including 24.1% seizure-free after six months of the SGT treatment.

Herbal medicines have been widely used in East Asia since ancient times, and some prescriptions of herbal medicine are often regarded as an alternative option for treating epileptic seizures in the field of CAM. In our institution we have different herbal formulas as the treatment options for the patients with epileptic seizures. A herbal prescription suitable for a single individual with epileptic seizures is selected from these options with herbal medicine through the process of the distinct diagnostic method in traditional Korean medicine. SGT is one of the optional formulas for epileptic seizures in our institution. It remains unclear how SGT can make antiepileptic effect. However, several preclinical studies have suggested the mechanism of action of it in which SGT showed inhibitory effects on pentylenetetrazole-induced bursting activities in snail neurons to be characteristic of seizure discharge [10–12] and demonstrated a scavenging activities for free radicals generated within the iron-induced epileptogenic regions of rat brains [15].

There has yet to be a study like this one reporting herbal medicine's effects on children who had not responded to AEDs. Hence, the effect of SGT in this study was assessed by comparing with the results of the studies on the ketogenic diet, a field in which the most research on drug resistant epilepsy exists [22–24]. The results of the three main studies on ketogenic diets with similar patient populations as this study are reported in Table 5 [18–20]. These studies present a range of 26.2–57.8% of patients with a >50% seizure reduction including 13.6–33.2% who became seizure-free at six months. The results of the SGT treatment were comparably favorable to these three studies.

It is worth noting that the ratio of patients who discontinued AED intake was higher in our study than that of the studies on ketogenic diet. The study of Kang et al. reported that 26.1% were able to decrease the number of AEDs, with 6.5% completely withdrawing [18]. In our study, 42.6% were able to decrease the number of AEDs, including 20.4% who completely withdraw. It was attempted in both studies to decrease or completely stop AED intake when the patients' >50% seizure reduction level was being sustained. The patients in our study had chosen herbal medicine as CAM after conventional treatments had failed or resulted in intolerable adverse effects for them. Hence, the high ratio of AED withdrawal during the SGT treatment can be seen as carrying high clinical significance.

Another important consideration with the use of SGT in drug resistant epilepsy is that tolerability and safety are favorable. In our study, two adverse events—drug eruption, fever—were reported. There have been a few reports of drug eruptions with herbal medications containing *Paeonia lactiflora* Pallas, one of the active ingredients in SGT [25, 26]. Although it may have been the cause of the patient's symptom, clinical possibility of SGT causing the fever seems to be low. To our knowledge, fever has not been a reported adverse effect for either SGT or any other prescriptions including the herbs used in making SGT. Other than the patient who discontinued the SGT treatment citing fever as a reason, no patient discontinued the treatment or needed dose modifications due to adverse events. The use of ketogenic diet, which seems to be an effective treatment for drug resistant epilepsy, often accompanies reports on vomiting, diarrhea, kidney stones, growth retardation, food refusal, and so forth, leading to a lower compliance rate [27–29]. Low toxicity and excellent tolerability of SGT qualifies it as a suitable candidate for drug resistant epilepsy in children.

Retention rates in our study are similar to those from the reports on ketogenic diet despite the fact that far more adverse events had been associated with ketogenic diet compared to the SGT treatment (Table 5). In our study, guardians of 21 patients who had discontinued the treatment despite achieving seizure reduction indicated the SGT treatment could not meet their expectations and wanted to try other CAM that might result in complete remission of seizure. Several explanations have been suggested. One possibility is that the patients who choose herbal medicine as CAM have tendencies to have exaggerated expectations, being without the knowledge of its practical effectiveness. This is because of the lack of research that evaluated the effects of herbal medicine. More research in the future should be able to compensate for such shortfall. Another possible explanation is that the guardians of 21 patients may have considered the "cost-effectiveness" of SGT. In Korea, herbal decoctions can be financially burdensome as they are not subject to medical insurance. However, some medications can be prepared in forms of extracts, which can be insurance-coverable. Hence, the cost problem could be mitigated.

The limitation of our study is that it was conducted at a single institution with a single treatment arm. It was also a retrospective review, rather than a controlled experiment, including only 54 patients. Moreover, the lack of similar studies involving SGT led to using studies on ketogenic diet, for which the effectiveness on drug resistant epilepsy was established, for comparison. Comparisons with the effect of ketogenic diet may be biased by differences in patient selection.

5. Conclusion

This study evaluated the effect and safety of SGT for drug resistant childhood epilepsy. We observed that SGT decreased seizure frequency with low toxicity. Therefore, SGT shows a potential for seizure management in children with drug resistant epilepsy. Even though this study has a limitation of not-randomized design with small population, this is the first retrospective study evaluating the efficacy and safety of herbal medicine for epilepsy children.

Table 5: Comparison to studies on ketogenic diet in patients with refractory epilepsy.

	Treatment	Number	Median ageat start of treatment	Response rate						Retention rate		
				At 3 months		At 6 months		At 12 months				
				>50% reduction††	Seizure-free	>50% reduction††	Seizure-free	>50% reduction††	Seizure-free	At 3 months	At 6 months	At 12 months
Our study	SGT	54	16.5 months	68.5%	35.2%	44.4%	24.1%	22.2%	14.8%	81.5%	53.7%	22.2%
Kang et al., 2005 [18]	Ketogenic diet	199	57.9 months†	61.8%	35.2%	57.8%	33.2%	41.2%	25.1%	87.9%	68.3%	45.7%
Sharma et al., 2009 [19]	Ketogenic diet	27	2.5 years	59.3%	11.1%	48.1%	14.8%	37.0%	18.5%	88.9%	55.6%	37.0%
Suo et al., 2013 [20]	Ketogenic diet	317	39.6 months†	35.0%	20.8%	26.2%	13.6%	18.6%	10.7%	62.8%	42.0%	24.3%

†Mean age.

††>50% reduction included seizure-free cases.

SGT, Shihogyejitang.

Based on this study, a large prospective study with a control group should be considered to evaluate the efficacy of SGT.

Conflict of Interests

None of the authors has any conflict of interests to disclose.

Authors' Contribution

Jinsoo Lee and Kwanghyun Son contributed equally to this work.

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Review Article

Pharmacopuncture in Korea: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background. Pharmacopuncture is a new form of acupuncture combining acupuncture with herbal medicine, and it has been used under various conditions in Korea. The aim of this study is to establish clinical evidence for the safety and efficacy of pharmacopuncture in Korea. *Methods*. We searched 9 databases and two relevant journals up to December 2014 using keywords, such as pharmacopuncture. All randomized, controlled trials evaluating pharmacopuncture under any conditions in Korea were considered. *Results*. Twenty-nine studies involving 1,211 participants were included. A meta-analysis of two studies on obesity showed that 5 to 8 weeks of pharmacopuncture reduced weight, waist circumference, and body mass index (BMI) more than normal saline injections. In the 5 studies of musculoskeletal conditions, 7 to 30 days of pharmacopuncture had additional effects on the reduction of pain intensity, and this benefit was maintained by limiting analyses to studies with a low risk of bias for randomization and/or allocation concealment. *Conclusions*. This systematic review suggests the potential of pharmacopuncture for obesity and musculoskeletal diseases. However, it is difficult to recommend pharmacopuncture as an evidence-based treatment because of methodological flaws and small sample sizes of the included studies. Further well-designed trials are needed to draw a definitive conclusion.

1. Introduction

Pharmacopuncture (herbal acupuncture) is a new form of acupuncture treatment combining acupuncture and the injection of herbal medicine to the acupuncture points (acupoints). In Korea, pharmacopuncture was first officially introduced to the traditional Korean medicine (TKM) community in 1967 by Sang-Cheon Nam. While the conventional acupuncture treatment incorporates the physical stimulation of associated meridians and acupoints, pharmacopuncture adds chemical ingredients from therapeutic herbs with pharmacological effects [1]. In the treatment of pharmacopuncture, the typical constitution and conditions of the individual patient are diagnosed, and specific amounts of herbal extracts are injected into meridians and acupoints, providing the effect of both acupuncture and herbal medicine [1].

The effects of pharmacopuncture can be immediately observed after treatment because herbal extracts are directly absorbed without the need to pass through the gastrointestinal tract. Additionally, both patients with difficulty swallowing and those who refuse to take herbal medicine may profit by receiving pharmacopuncture treatment [1]. The major benefits of pharmacopuncture in comparison to conventional acupuncture are more rapid effects, additional synergistic effects of acupuncture and herbal extracts, and the ease for controlling dosage [2].

Since the 1970s, studies on pharmacopuncture conducted mostly in animals have reported that *Astragali Radix* [3, 4],

Angelica gigas [4], *Cornus cervi Parvum* [5], and *Sorbus commixta* Hedl. extracts [6] were effective in pain control, immune enhancement, obesity, and arthritis. Since the 2000s, there are a growing number of clinical trials on pharmacopuncture. Currently, numerous types of pharmacopuncture extracts are used. Pharmacopuncture is applied to treat various disorders, most frequently for musculoskeletal conditions. The effectiveness for these disorders has been well studied [1, 7].

This systematic review aims to summarise existing results of randomized controlled trials (RCTs) conducted in Korea to establish the clinical evidence of the safety and efficacy of pharmacopuncture for various conditions.

2. Methods

2.1. Data Sources and Searches. We searched PubMed, Ovid Medline, and Korean databases, including the Oriental Medicine Advanced Searching Integrated System (OASIS), the Korean Studies Information Service System, RISS4U, Korea Institute of Science and Technology Information, KOREAMED, DBPIA, Korea National Assembly Library, the Journal of Korean Pharmacopuncture Institute, and the Journal of Korean Acupuncture and Moxibustion Medicine Society from inception to December 2014. Reference lists of reviews and relevant articles were examined for additional studies.

The search terms used for PubMed were as follows: (pharmacopuncture∗[All Fields] OR "herbal acupuncture" [All Fields] OR "aqua acupuncture" [All Fields] OR aquapuncture∗[All Fields] OR "acupoint injection" [All Fields]) AND ("randomized controlled trial" [PT] OR "controlled clinical trial" [PT] OR random∗[TIAB] OR placebo [TIAB] OR "drug therapy" [Subheading] OR trial [TIAB] OR groups [TIAB]) NOT Animals [MeSH] NOT Humans [MeSH]. These search terms were slightly modified for other databases. Trials conducted in Korea and published in English or Korean were sought.

2.2. Study Selection

2.2.1. Inclusion Criteria. All RCTs evaluating pharmacopuncture treatment on various conditions were considered. Studies enrolling participants who reported any disorder or disease were eligible for inclusion. Hence, we classified each disorder or disease according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [8] for the analyses.

Studies which assessed the combined effects of pharmacopuncture plus other interventions (e.g., pharmacopuncture plus acupuncture) were also considered when the identical intervention was administered to both the pharmacopuncture group and the control group.

For control groups, we considered placebo or sham, other interventions, and no interventions. Placebo or sham interventions were injections of normal saline or distilled water into the pharmacopuncture points or nonacupuncture points. Other interventions included acupuncture, herbal/western medicine, cupping, tuina, diet therapy, and physical therapy, including hot pack, transcutaneous electrical nerve stimulation (TENS), interferential current therapy (ICT), ultrasound, massage, and exercise.

There was no restriction on the type of outcome measures, but they had to be relevant to the conditions. All the trials were conducted in Korea.

2.2.2. Exclusion Criteria. Nonrandomized trials, animal or cell studies, literature research, and quasi-RCTs (methods of allocating participants to a treatment group which are not truly random, e.g., hospital record number or alternation, and date of birth) were excluded. Trials including healthy participants were excluded.

We did not include trials testing bee-venom pharmacopuncture or injection of conventional medicine because they did not investigate the chemical effects of herbal medicine. Trials comparing different types of pharmacopuncture were excluded because the efficacy of control intervention could not be determined.

2.3. Data Extraction. We reviewed all searched articles to evaluate their eligibility for inclusion. In case of uncertainties, authors were contacted for further information.

After the selection of studies, we extracted the following data from the selected articles: author, year of publication, study design, participants (age, gender), diseases or disorders, pharmacopuncture intervention, control intervention, outcome measures, main results, and adverse events (Table 1). The outcome measures at the end of the treatments were used in data pooling. As for the pharmacopuncture interventions, we summarised each item in terms of the types and methods of pharmacopuncture, regimen, pharmacopuncture points, extraction methods, types of syringe, and amount, depth, and angle of the injection following STRICTA recommendations and the data was modified into the suitable form for trials of pharmacopuncture (Table 2).

2.4. Assessment of Risk of Bias (ROB). We evaluated the ROB for the included studies according to the Cochrane Collaboration's ROB assessment tool [39].

We rated ROB for each item using "Yes (Y, low ROB)," "Unclear (U, uncertain or unknown ROB)," or "No (N, high ROB)." For patient blinding in studies with a placebo control, we assessed the study as having a low ROB when it clearly stated that patients were blinded. For the outcome assessor blinding, we judged that if it was clearly reported that the outcome assessor was blinded or the outcome measure was evaluated by blinded participants only, it was rated as having a low ROB. If the outcome measure was assessed by unblinded participants only, we rated it as having a high ROB. If the outcome measures were mixed with subjective and objective assessments and we could not obviously judge whether the outcome assessor was blinded or not, it was rated as having an unclear ROB. As for the incomplete outcome data reporting it was rated as having a low ROB if the number and reason for attrition were clearly reported in each group and were similar between groups and the percentage of withdrawals

Table 1: Characteristics of the included studies.

Author, year	Design	Types of disease	Sample size (M/F)	Pharmacopuncture group (No. of participants analyzed/randomized)	Control group (No. of participants analyzed/randomized)	Outcome measures	Main results	AE
(IV) Endocrine, nutritional, and metabolic diseases (n = 3)								
Lim, 2013 [9]	Parallel 2 arms	Abdominal obesity	28 (0/28)	(A) Wild ginseng complex pharmacopuncture (14/15)	(B) NSP (14/15)	(1) Anthropometry ① BMI, ② weight, ③ WC ④ HC, and ⑤ WHR (2) Blood test ① TC, ② TG, ③ HDL cholesterol, ④ LDL cholesterol, ⑤ CRP, and ⑥ AST, ALT, γ-GT, BUN, and creatinine (3) Body composition (BFM, BFP, FFM, and BMR) (4) Abdominal fat (TFA, SFA, VFA, and VSR)	(1) ①, ②, and ③ Positive[a] ④, ⑤ NS (2) ①, ②, ③, ⑤, and ⑥ NS ④ Positive[a] (3) NS (4) NS	n.r.
Kim, 2011 (2) [10]	Parallel 2 arms	Abdominal obesity	31 (0/31)	(A) *Capsicum frutescens* L. pharmacopuncture + diet therapy + exercise (13/20)	(B) NSP + diet therapy + exercise (18/20, in case of outcome measures 1, 2, and 4; 16/20, in case of outcome measure 3)	(1) Anthropometry ① BMI, ② WC ③ weight, and ④ WHR (2) Abdominal fat (TFA, VFA) (3) Energy expenditure (4) Questionnaires	(1) ①, ② Positive[a] ③, ④ Positive[b] (2) Positive[b] (3) NA (4) NS	Moderate AEs related with anesthesia cream or pharmacopuncture (4 in group (A), 2 in group (B))
Kim et al., 2009 [11]	Parallel 2 arms	Obesity	52 (8/44)	(A) EAP + diet therapy + EA + HM + exercise (24/35)	(B) NSP + diet therapy + EA + HM + exercise (28/35)	(1) Weight (2) BMI (3) Waist	(1) Positive[a] (2) Positive[a] (3) Positive[c]	n.r.
(VI) Diseases of the nervous systems (n = 6)								
Park et al., 2011 (1) [12]	Parallel 2 arms	Chronic headache	35 (5/30)	(A) CS pharmacopuncture (17/20)	(B) NSP (18/20)	(1) HIT (2) No. of headache-free days (3) SF-36	(1) Positive[a] (2) Positive[a] (3) Positive[a]	Injection-site pain (2 in group (A), 3 in group (B)), ecchymosis (2 in group (A))
Shin et al., 2009 [13]	Parallel 2 arms	Postauricular pain accompanied with Bell's palsy	30 (15/15)	(A) Soyeom pharmacopuncture + A + HM + PT (SSP, massage, exercise, HP, and ICT) (15/15)	(B) A + HM + PT (SSP, massage, exercise, HP, and ICT) (15/15)	(1) VAS (2) Duration of pain (d) (3) Yanagihara score	(1) Positive[a] (2) Positive[a] (3) NS	n.r.

Table 1: Continued.

Author, year	Design	Types of disease	Sample size (M/F)	Pharmacopuncture group (No. of participants analyzed/randomized)	Control group (No. of participants analyzed/randomized)	Outcome measures	Main results	AE
Choi et al., 2009 [14]	Parallel 2 arms	Postauricular pain accompanied with Bell's palsy	30 (14/16)	(A) Soyeom pharmacopuncture + A + HM + PT (SSP, massage, exercise, ICT, and negative) (15/15)	(B) A + HM + PT (SSP, massage, exercise, ICT, and negative) (15/15)	(1) VAS (2) Yanagihara score	(1) Positive[c] (2) NS	n.r.
Kim et al., 2006 [15]	Parallel 2 arms	Functional headache	26 (11/15)	(A) HHT pharmacopuncture (13/13)	(B) NSP (13/13)	(1) VAS (2) BPI	(1) Positive[a] (2) Positive[a]	n.r.
Lim et al., 2005 [16]	Parallel 2 arms	Carpal tunnel syndrome	40 (7/33)	(A) Scolopendrid pharmacopuncture + A + EA + HM + PT (PB, ultrasound, HP, microwave, ICT, and SSP) (20/20)	(B) A + EA + HM + PT (PB, ultrasound, HP, microwave, ICT, and SSP) (20/20)	(1) VAS (2) PRGA based on symptoms and VAS (excellent/good/fair/poor)	(1) n.r. (2) NS	n.r.
Lee et al., 2005 [17]	Parallel 2 arms	Bell's palsy	44 (21/23)	(A) HPP + A + HM + WM + PT (EST, IR, HP, massage, and exercise) (23/23)	(B) NSP + A + HM + WM + PT (EST, IR, HP, massage, and exercise) (21/21)	Yanagihara score	Positive[a]	n.r.
(IX) Diseases of the circulatory system (n = 1)								
Noh et al., 2009 [18]	Parallel 2 arms	Leg spasticity of stroke patients	20 (8/12)	(A) HPP + A (11/11, in case of outcome measures 1, 3, and 4; 10/11, in case of outcome measure 2)	(B) Distilled water pharmacopuncture + A (9/9)	(1) MAS (2) H/M ratio (3) BBS (4) TUG	(1) NS (2) NS (3) NS (4) Positive[a]	n.r.
(XI) Diseases of the digestive system (n = 2)								
Lee, 2013 [19]	Parallel 2 arms	Dyspepsia	60 (16/44)	(A) HPP + HM (30/30)	(B) A + HM (30/30)	NDI-K	NS	n.r.
Park et al., 2008 [20]	Parallel 2 arms	Chronic constipation	21 (5/16)	(A) CS pharmacopuncture (11/12)	(B) NSP (10/12)	(1) Defecation frequency, consistency, and ease of evacuation (2) VAS (3) QOL (4) HRV	(1) Significant difference in (A)[a]; N in (B) (2) Significant difference in (A)[a]; N in (B) (3) N (4) Significant improvement of LF/HF ratio in (A) after 2-week follow-up[a]	Mild AEs such as ecchymosis, pain during injection, and redness in group (A) Moderate pain during injection in group (B)

Table 1: Continued.

Author, year	Design	Types of disease	Sample size (M/F)	Pharmacopuncture group (No. of participants analyzed/randomized)	Control group (No. of participants analyzed/randomized)	Outcome measures	Main results	AE
(XIII) Diseases of the musculoskeletal system and connective tissue (n = 15)								
Seo, 2013 [21]	Parallel 2 arms	Shoulder pain caused by stroke	24 (10/14)	(A) Ouhyul pharmacopuncture + other treatments (13/16)	(B) NSP + other treatments (11/13)	(1) NRS (2) PROM (3) FMMA	(1) NA (2) NS (3) NS	General pain (1 in group (A)), transient local site pain (1 in group (B)), and fatigue (1 in group (B))
Lee et al., 2012 (1) [22]	Parallel 3 arms	Cervicalgia caused by TA	87 (42/45)	(A) HHT pharmacopuncture + tuina + A + HM + IR (34/34)	(B) Tuina + A + HM + IR (29/29) (C) HHT pharmacopuncture + A + HM + IR (24/24)	(1) VAS (2) NDI	(1) Positive[b] (2) Positive[a]	n.r.
Lee et al., 2012 (2) [23]	Parallel 2 arms	Cervicalgia caused by TA	82 (40/42)	(A) HHT pharmacopuncture + A + HM (37/37)	(B) Tuina + A + HM (45/45)	(1) VAS (2) NDI	(1) NS (2) NS	n.r.
Woo et al., 2011 [24]	Parallel 2 arms	Cervicalgia caused by TA	60 (28/32)	(A) Ouhyul pharmacopuncture + A + IR (30/30)	(B) Tuina + A + IR (30/30)	(1) VAS (2) NDI	(1) NS (2) NS	n.r.
Kim et al., 2011 (1) [25]	Parallel 2 arms	LBP caused by TA	81 (44/37)	(A) HHT pharmacopuncture + A + HM (35/49)	(B) Tuina + A + HM (46/49)	(1) ODI (2) VAS	(1) NS (2) NA	n.r.
Jeong et al., 2011 [26]	Parallel 2 arms	Acute LBP	30 (21/9)	(A) BUM pharmacopuncture + A (15/21)	(B) A (15/21)	(1) VAS (2) ODI	(1) Positive[a] (2) NS	n.r.
Jun et al., 2011 [27]	Parallel 2 arms	HNP of the L-spine	20 (9/11)	(A) ShinBaro pharmacopuncture + A + CCP + HM + tuina + PT (ICT, TENS, microwave, and HP) (10/10)	(B) A + CCP + HM + tuina + PT (ICT, TENS, microwave, and HP) (10/10)	(1) NRS (2) ODI	(1) ① LBP decrement: positive[a] ② Sciatica decrement: N (2) NS	None
Im et al., 2011 [28]	Parallel 2 arms	Acute cervicalgia by TA	20 (7/13)	(A) Soyeom pharmacopuncture + A + HM + cupping + PT (ICT, ultrasound, and HP) (10/13)	(B) A + HM + cupping + PT (ICT, ultrasound, and HP) (10/13)	(1) VAS (2) NDI (3) DITI	(1) Positive[a] (2) NS (3) NS	n.r.
Park et al., 2011 (2) [29]	Parallel 2 arms	Cervicalgia	20 (0/20)	(A) Carthami-Flos pharmacopuncture + A + HM + PT (HP, TENS, and ICT) (10/10)	(B) A + HM + PT (HP, TENS, and ICT) (10/10)	(1) VAS (2) NDI (3) MENQOL	(1) Positive[a] (2) Positive[b] (3) Positive[c]	n.r.
Kim et al., 2010 (1) [30]	Parallel 2 arms	OA (knee)	53 (9/44)	(A) Root bark of UDP pharmacopuncture (29/30)	(B) NSP (24/30)	(1) VAS (2) WOMAC (pain/total score) (3) KHAQ (4) SF-36	(1) NA (2) NS (3) NS (4) NS	Nausea, itching (1 in group (A)), and dizziness (1 in group (B))

Table 1: Continued.

Author, year	Design	Types of disease	Sample size (M/F)	Pharmacopuncture group (No. of participants analyzed/randomized)	Control group (No. of participants analyzed/randomized)	Outcome measures	Main results	AE
Song et al., 2009 [31]	Parallel 2 arms	HNP of the L-spine	30 (15/15)	(A) Soyeom pharmacopuncture + A + HM + PT (TENS, HP, and ICT) + wet cupping (15/15)	(B) A + HM + PT (TENS, HP, and ICT) + wet cupping (15/15)	(1) VAS (2) SLRT	(1) Positive[b] (2) NS	n.r.
Kang et al., 2008 [32]	Parallel 3 arms	Acute ankle sprain	52 (17/35)	(A) HHT pharmacopuncture (17/20)	(B) A (17/20) (C) BVP (18/20)	(1) NRS (2) AHS	(1) Negative[b] (2) Negative[a]	n.r.
Lee et al., 2007 [33]	Parallel 3 arms	HNP of the L-spine	60 (28/32)	(A) Ouhyul pharmacopuncture + A + HM + PT (HP, ICT, TENS, and negative) (20/20, in case of outcome measure 1, 2; 6/20, in case of outcome measure 3)	(B) A + HM + PT (HP, ICT, TENS, and negative) (20/20, in case of outcome measures 1, 2; 8/20, in case of outcome measure 3) (C) BVP + A + HM + PT (HP, ICT, TENS, and negative) (20/20, in case of outcome measures 1, 2; 9/20, in case of outcome measure 3)	(1) VAS (2) PRGA based on symptoms and physical examination (excellent/good/fair/poor) (3) SLRT	(1) Positive[a] (2) NA (3) NS	n.r.
Park et al., 2006 [34]	Parallel 2 arms	OA (knee)	60 (35/25)	(A) HPP + PT (HP, ultrasound massage, ICT, FES, and exercise) (30/30)	(B) A + PT (HP, ultrasound massage, ICT, FES, and exercise) (30/30)	(1) Lysholm score (2) Nine-point scale	(1) NS (2) NS	n.r.
Bae and Park, 2004 [35]	Parallel 2 arms	Shoulder pain caused by stroke	41 (19/22)	(A) Ouhyul pharmacopuncture + A + HM + PT (21/21)	(B) NSP + A + HM + PT (20/22)	(1) MBI (2) Weakness grade (3) NIHSS (4) AI (5) VAS	(1) NS (2) Significant difference in (B)[a] (3) NS (4) NS (5) NS	n.r.

Table 1: Continued.

Author, year	Design	Types of disease	Sample size (M/F)	Pharmacopuncture group (No. of participants analyzed/randomized)	Control group (No. of participants analyzed/randomized)	Outcome measures	Main results	AE
(XIV) Diseases of the genitourinary system (n = 1)								
Kim et al., 2008 [36]	Parallel 2 arms	Dysmenorrhea	49 (0/49)	(A) HPP (25/25)	(B) NSP (24/24)	(1) MMP (2) MSSL	(1) NS (2) NS	n.r.
(XV) Pregnancy, childbirth, and the puerperium (n = 1)								
Kim et al., 2010 (2) [37]	Parallel 2 arms	Postpartum women's heat feeling, sweat, and thirst	25 (0/25)	(A) HPP + A + HM (13/16)	(B) NSP + A + HM (12/16)	(1) VAS ① Heating feeling ② Thirst ③ Sweet in movement ④ Sweet during sleeping (2) CBC (3) 7-zone-diagnostic system (4) HRV	(1) ① NS ② NA ③ NS ④ NS (2) NS (3) NS (4) Positive[c]	None

Disease classification according to the ICD-10 code. Data are expressed as mean ± SD unless stated otherwise.

[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

A: acupuncture; AE: adverse event; AHS: ankle-hindfoot scale; AI: activity index; BBS: Berg balance scale; BFM: body fat mass; BFP: body fat percentage; BMI: body mass index; BMR: basal metabolic rate; BPI: brief pain inventory (general activity, mood, enjoyment of life, relations with other people, and sleep); BUM: *Calculus Bovis*.*Fel Ursi*.*Moschus*; BVP: bee-venom pharmacopuncture; CBC: complete blood cell count; CCP: *Coptis chinensis* pharmacopuncture; CS: Carthami-Semen; d: days; DITI: digital infrared thermographic imaging; EA: electroacupuncture; EAP: *Ephedra sinica* Stapf-*Aconitum carmichaeli* Debx. pharmacopuncture; EST: electrical stimulation therapy; F: female; FES: functional electrical stimulation; FFM: fat-free mass; FMMA: Fugl-Meyer motor assessment; HC: hip circumference; HHT: Hwangryunhaedok-tang; HIT: headache impact test; HM: herb medicine; H/M ratio: H-reflex/M-response ration; HNP of L-spine: herniation of nucleus pulposus of lumbar spine; HP: hot pack; HPP: *Hominis Placenta* Pharmacopuncture; HRV: heart rate variability; ICT: interferential current therapy; IR: infraradiation; KHAQ: Korean Health Assessment Questionnaire; LBP: low back pain; M: male; MAS: modified Ashworth scale; MBI: modified Barthel index; MENQOL: menopause-specific quality of life questionnaire; MMP: measure of menstrual pain; MPQ-SF: McGill Pain Questionnaire-Short Form; MSSL: menstrual symptom severity list; N: no significant difference before and after treatment; NA: not assessable; NDI: neck disability index; NDI-K: Nepean Dyspepsia Index-Korean; negative: (B) significantly better than (A); NIHSS: National Institutes of Health Stroke Scale; No.: number; n.r.: not reported; NRS: numerical rating scale; NS: neutral (no significant difference between groups); NSP: normal saline pharmacopuncture; OA: osteoarthritis; ODI: Oswestry disability index; PB: paraffin bath; positive: (A) significantly better than (B); PRGA: patient-reported global assessment; PROM: painless passive range of motion; PT: physical therapy; QOL: quality of life; SFA: subcutaneous fat area; SF-36: short form 36 health survey; SLRT: straight leg raising test; SSP: silver spike point; TA: traffic accident; TC: total cholesterol; TENS: transcutaneous electrical nerve stimulation; TFA: total fat area; TG: triglyceride; TUG: time up and go; UDP: *Ulmus davidiana* Planch.; VAS: visual analog scale; VFA: visceral fat area; VSR: visceral VFA/SFA ratio; WC: waist circumference; WHR: waist-hip ratio; wks: weeks; WM: western medicine; WOMAC: Western Ontario and McMaster Universities.

Table 2: Characteristics of pharmacopuncture interventions in the included studies.

Author, year	Types and methods of pharmacopuncture*	Regimen	Pharmacopuncture points†	Extraction method (does it follow guideline?‡)	Types of syringe	Amount of injection	Depth of injection	Angle of injection	Cointerventions
Meridian field pharmacopuncture (n = 4)									
Park et al., 2011 (1) [12]	CS, fixed	8 sessions (twice a wk for 4 wks)	Bilateral GB20, GB21, and EX-HN5	Alcohol immersion (N)	27 G	0.1 mL each	n.r.	n.r.	None
Jeong et al., 2011 [26]	BUM, partially individualized	3 sessions (for 7 d)	Bilateral BL23, BL25, and BL26 + tender points	n.r.	n.r.	0.05 mL × 10 (total 0.5 mL)	n.r.	n.r.	A
Park et al., 2011 (2) [29]	Carthami-Flos, fixed	15 sessions (once per 2 d for 30 d)	Bilateral GB20, GB21	Pressing (Y)	1.0 mL syringe, 26 G	0.05 mL × 4 (total 0.2 mL)	10–30 mm	n.r.	A + HM + PT (HP, TENS, and ICT)
Park et al., 2008 [20]	CS, fixed	8 sessions (twice a wk for 4 wks)	ST25, ST27, BL52, and CV6	Alcohol immersion (N)	1.0 mL syringe, 27 G	0.1 mL × 7 (total 0.7 mL)	0.5–1 inch	n.r.	None
Eight-principle pharmacopuncture (n = 14)									
Seo, 2013 [21]	Ouhyul, fixed	6 sessions (3 times a wk for 2 wks)	Unilateral LI15, TE14, GB21, SI11, and SI12	Distillation (Y)	30 G	0.1 mL × 5 (total 0.5 mL)	n.r.	n.r.	Other treatments (the type is not mentioned)
Lee et al., 2012 (1) [22]	HHT, partially individualized	8 sessions (twice a wk for 4 wks)	GV16, GB20, GB21, and so forth	n.r.	29 G	Total 1 mL	n.r.	n.r.	A + HM + IR
Lee et al., 2012 (2) [23]	HHT, partially individualized	8 sessions (twice a wk for 4 wks)	GV16, GB20, GB21, and so forth	n.r.	29 G	Total 1 mL	n.r.	n.r.	A + HM
Woo et al., 2011 [24]	Ouhyul, individualized	4 sessions (twice a wk for 2 wks)	Ashi points (neck)	n.r.	1.0 mL syringe	Total 1 mL	n.r.	n.r.	A + IR
Kim et al., 2011 (1) [25]	HHT, fixed	8 sessions (twice a wk for 4 wks)	Bilateral BL23, BL25, GV3, GB30, and so forth	n.r.	29 G	Total 1 mL	n.r.	n.r.	A + HM
Jun et al., 2011 [27]	ShinBaro, individualized	14 sessions (daily for 2 wks)	EX-B2 in the most severe level of disc herniation	Distillation (Y)	1.0 mL syringe, 26 G	1 mL × 2 (total 2 mL)	Intramuscular (3 cm)	Perpendicular	A + CCP + HM + tuina + PT (ICT, TENS, microwave, and HP)
Im et al., 2011 [28]	Soyeom, partially individualized	5 sessions (once per 2 d for 10 d)	Ashi points (neck) + tender points + bilateral GB20, GB21, and GV14	n.r.	1.0 mL syringe, 30 G	0.05–0.1 mL each (total 0.8 mL)	n.r.	n.r.	A + HM + cupping + PT (ICT, ultrasound, and HP)
Song et al., 2009 [31]	Soyeom, individualized	3 sessions (once per 2 d for 7 d)	EX-B2 in the level of disc herniation	n.r.	1.0 mL syringe, 29 G	1 mL × 2 (total 2 mL)	n.r.	n.r.	A + HM + PT (TENS, HP, and ICT) + wet cupping

Table 2: Continued.

Author, year	Types and methods of pharmacopuncture*	Regimen	Pharmacopuncture points†	Extraction method (does it follow guideline?‡)	Types of syringe	Amount of injection	Depth of injection	Angle of injection	Cointerventions
Shin et al., 2009 [13]	Soyeom, fixed	3 sessions (once per 2 d for 6 d)	TE17 on the affected side	Distillation (Y)	1.0 mL syringe, 26 G	Total 0.6–0.8 mL	n.r.	n.r.	A + HM + PT (SSP, massage, exercise, HP, and ICT)
Choi et al., 2009 [14]	Soyeom, fixed	n.r.	TE17 on the affected side	n.r.	n.r.	Total 0.4 mL	n.r.	n.r.	A + HM + PT (SSP, massage, exercise, ICT, and negative)
Kang et al., 2008 [32]	HHT, fixed	3 sessions (once per 3-4 d × 3)	GB39, GB40, GB41, BL60, BL62, and ST36	n.r.	29 G	0.1 mL × 6 (total 0.6 mL)	n.r.	n.r.	None
Lee et al., 2007 [33]	Ouhyul, individualized	for 9 d	Ashi points (lumbar)	n.r.	n.r.	0.6 mL each	n.r.	n.r.	A + HM + PT (HP, ICT, TENS, and negative)
Kim et al., 2006 [15]	HHT, fixed	4 sessions (once per 2 d for 8 d)	Bilateral GB20, GB21, and LI4	Distillation (Y)	1.0 mL syringe, 30 G	0.1 mL × 6 (total 0.6 mL)	n.r.	n.r.	None
Bae and Park, 2004 [35]	Ouhyul, fixed	3 sessions (once per 2 d for 6 d)	SI10, LI15, TE14, and GB21 + Gyun-joong (Master Dong's acupuncture point)	n.r.	1.0 mL syringe	0.05–0.1 mL × 5 (total 0.25–0.5 mL)	n.r.	n.r.	A + HM + PT
Monotype pharmacopuncture (n = 9)									
Lee, 2013 [19]	HPP, partially individualized	6 sessions (3 times a wk for 2 wks)	ST19, ST25, ST27, BL18, BL20, BL21, BL23, and so forth	n.r.	1.0 mL syringe, 0.3 × 8 mm	0.05 mL each (total 0.8 mL)	n.r.	n.r.	HM
Kim, 2011 (2) [10]	*Capsicum frutescens* L., fixed	16 sessions (twice a wk for 8 wks)	Abdomen	n.r.	Mesogun	0.05 mL × 60 (total 3 mL)	n.r.	n.r.	Diet therapy + exercise
Kim et al., 2010 (1) [30]	Root bark of UDP, partially individualized	12 sessions (twice a wk for 6 wks)	ST35, EX-LE5, EX-LE2, and Ashi points on the affected side	Distillation (no guideline)	1.0 mL syringe, 29 G	n.r.	5–15 mm	n.r.	None
Kim et al., 2010 (2) [37]	HPP, fixed	5 sessions (postpartum 6, 8, 10, 12, and 14 d)	CV4, bilateral BL23	n.r.	1.0 mL syringe, 26 G	0.4 mL (CV4), 0.3 mL (BL23) (total 1 mL)	n.r.	n.r.	A + HM
Noh et al., 2009 [18]	HPP, fixed	15 sessions (5 times a wk for 3 wks)	ST36, GB34, BL55, BL56, and BL57	n.r.	1.0 mL syringe, 30 G	0.4 mL × 5 (total 2 mL)	10 mm	Perpendicular	A
Kim et al., 2008 [36]	HPP, fixed	5 sessions§	CV4, bilateral ST36, SP9, and SP6	n.r.	1.0 mL syringe, 26 G (CV4), 30 G (bilateral ST36, SP9, and SP6)	1 mL (CV4), 1 mL (bilateral ST36, SP9, and SP6) (total 2 mL)	Equal to needle length	n.r.	None

Table 2: Continued.

Author, year	Types and methods of pharmacopuncture*	Regimen	Pharmacopuncture points†	Extraction method (does it follow guideline?‡)	Types of syringe	Amount of injection	Depth of injection	Angle of injection	Cointerventions
Park et al., 2006 [34]	HPP, partially individualized	6–9 sessions (2-3 times per wk for 3 wks)	BL23, ST35, EX-LE4, GB34, SP10, and ST34 + Ashi points	n.r.	U-100 insulin syringe	0.1 mL each	n.r.	n.r.	PT (HP, ultrasound massage, ICT, FES, and exercise)
Lim et al., 2005 [16]	Scolopendrid, fixed	8–12 sessions (2-3 times per wk for 4 wks)	Between flexor carpi radialis tendon and median nerve	Alcohol immersion (Y)	1.0 mL syringe	1 mL each	Subcutaneous (flexor retinaculum)	45 degrees	A + EA + HM + PT (PB, ultrasound, HP, microwave, ICT, and SSP)
Lee et al., 2005 [17]	HPP, fixed	3 times per wk (during hospitalization); twice per wk (during the period they visited the clinic) for 5 wks	GB14, SI18, ST4, ST6, TE17, and TE23 on the affected side	n.r.	1.0 mL syringe, 29 G	0.05 mL × 6 (total 0.3 mL)	n.r.	n.r.	A + HM + WM + PT (EST, IR, HP, massage, and exercise)
Others (n = 2)									
Lim, 2013 [9]	Wild ginseng + BUM, fixed	10 sessions (twice a wk for 5 wks)	Left and right sides of four points inferior to and four points superior to the navel points on the stomach and the spleen and gallbladder meridians (total 24 points)	Distillation (wild ginseng, Y) Alcohol immersion (BUM, Y)	n.r.	0.2 mL each (total 5 mL)	n.r.	n.r.	None
Kim et al., 2009 [11]	EAP, fixed	10 sessions (twice a wk for 5 wks)	ST25, CV4, CV6, and GB26	Distillation (Y)	n.r.	0.5 mL × 4 (total 2 mL)	n.r.	n.r.	Diet therapy + EA + HM + exercise

Pharmacopuncture classification according to the treatment rationale.

*Pharmacopuncture method was classified into three categories based on the levels of individualization: "fixed" means all patients receive the same treatment at all sessions, "partially individualized" means using a fixed set of points to be combined with a set of points to be used flexibly, and "individualized" means each patient receives a unique and evolving diagnosis and treatment [38]. †Pharmacopuncture point LI5 refers to 5th point of large intestine meridian and extra points have different nomenclature (e.g., Ex-UE3 means 3rd extra point in upper extremity). Ashi points mean local pain points; ‡guideline for extraction methods is based on the text book published in Korean Pharmacopuncture Institute [1]; §1st: 3–7 days before 1st menstruation; 2nd: within 2 days after the start of 1st menstruation; 3rd: after the end of 1st menstruation; 4th: 3–7 days before 2nd menstruation; 5th: within 2 days after the start of 2nd menstruation.

A: acupuncture; BUM: *Calculus Bovis.Fel Ursi.Moschus*; CCP: *Coptis chinensis* pharmacopuncture; CS: Carthami-Semen; d: days; EA: electroacupuncture; EAP: *Ephedra sinica* Stapf-*Aconitum carmichaeli* Debx. pharmacopuncture; EST: electrical stimulation therapy; FES: functional electrical stimulation; G: gauge; HHT: Hwangryunhaedok-tang; HM: herb medicine; HP: hot pack; HPP: *Hominis Placenta* Pharmacopuncture; ICT: interferential current therapy; IR: infrared radiation; N: no; n.r.: not reported; PB: paraffin bath; PT: physical therapy; SSP: silver spike point; TENS: transcutaneous electrical nerve stimulation; wk: week; wks: weeks; WM: western medicine; Y: yes.

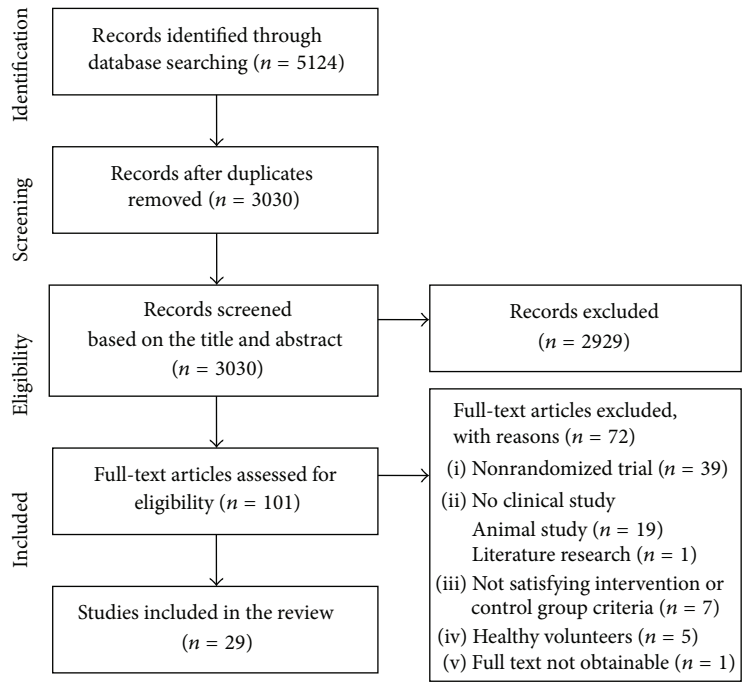


Figure 1: Flow diagram of literature search.

and drop-outs did not exceed 20% for short-term and 30% for long-term follow-up [39]. If there was disagreement, it was resolved by discussion with HL and JIK.

2.5. Data Analyses. Meta-analysis was performed using the Review Manager software (version 5.2 for Windows; the Nordic Cochrane Centre, Copenhagen, Denmark). We used the mean difference (MD) and 95% confidence intervals (CI) to estimate the effect of an intervention for continuous outcomes using a random-effects model.

If it was impossible to perform statistical pooling, studies were assigned to 1 of 4 categories to classify the result for interpretation. The comparison between two groups was based on the results of original study: (1) positive when the pharmacopuncture group was significantly better than the control group, P; (2) negative when the control group was significantly better than the pharmacopuncture group, N; (3) neutral when there was no significant difference between the groups, NS; and (4) not assessable when the results were complicated or the presented data were insufficient, NA.

To address the heterogeneity among the included studies, the I^2 test was used. An I^2 value of 50% or more was considered to be an indicator of a substantial level of heterogeneity [40]. Sensitivity analyses were planned by including studies with low ROBs only or by including pain-related studies with sample sizes ≥40 per arm. We analyzed the trials with low ROBs for randomization and/or allocation concealment only and examined whether the estimate of the intervention effect was affected [41, 42]. For the pain-related trials, studies with ≥40 participants per arm were separately analyzed to see whether any differences in the estimate emerged [43].

3. Results

Our search terms yielded 5,124 records: 49 from Ovid Medline or PubMed and 5,075 from domestic databases or relevant journals. After duplicated studies were removed, 3,030 records were screened. Based on the title and abstract, 2,929 records were excluded; 687 articles were inappropriate for the topic of this review; 2,105 were not clinical studies or were nonrandomized trials; and 137 trials did not satisfy the pharmacopuncture or control group criteria. Out of the remaining 101 studies, a total of 29 RCTs (Korean: $n = 27$; English: $n = 2$) were included in our review. Figure 1 shows a flow diagram of the literature searching as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [44]. Details of the included studies are summarised in Table 1.

3.1. Participants. Overall included RCTs (29): data of 1,321 participants were included in the review. The number of participants in each group ranged from 10 to 37 in the pharmacopuncture group and from 9 to 46 in the control group. The median sample sizes per arm were 17 in the pharmacopuncture group and 18 in the control group.

The types of diseases/disorders were very heterogeneous. Thus, we classified them using ICD-10 codes. The most common disorders were diseases of the musculoskeletal system and connective tissue (XIII, $n = 15$). Among them, there were 5 studies each for low back pain [25–27, 31, 33] and cervicalgia [22–24, 28, 29]; two studies were for knee osteoarthritis [30, 34] and shoulder pain [21, 35] each; and one was for ankle sprain [32]. In the category nervous system disease/disorder [12–17] (VI, $n = 6$), three studies of Bell's

palsy [13, 14, 17], two of headache [12, 15], and one for carpal tunnel syndrome [16] and leg spasticity of stroke patients [18] were found. The other studies could be classified into the endocrine, nutritional, and metabolic diseases [9–11] (IV, $n = 3$), diseases of the digestive system [19, 20] (XI, $n = 2$), diseases of the circulatory system [18] (IX, $n = 1$), diseases of the genitourinary system [36] (XIV, $n = 1$), and pregnancy, childbirth, and the puerperium [37] (XV, $n = 1$).

3.2. Pharmacopuncture Intervention. Details of pharmacopuncture interventions based on the revised STRICTA and modified to suitable patterns for pharmacopuncture are summarised in Table 2 [38].

3.2.1. Types of Pharmacopuncture. When pharmacopuncture was classified by treatment rationale, meridian field pharmacopuncture was practiced in four trials [12, 20, 26, 29], eight-principle pharmacopuncture was administered in 14 studies [13–15, 21–25, 27, 28, 31–33, 35], mono-herbal-type pharmacopuncture was used in nine trials [10, 16–19, 30, 34, 36, 37], and the other two studies could not be classified [9, 11].

The types of pharmacopuncture were highly variable. Out of the 29 included studies, 12 tested monoherbal medicine pharmacopuncture: six studies [17–19, 34, 36, 37] used *Hominis Placenta*; three studies [12, 20, 29] used Carthami-Semen; and *Capsicum frutescens* L. [10], scolopendrid [16], and root bark of *Ulmus davidiana* Planch. (UDP) [30] were used in one study each. The other 17 tested mixed-herbal medicine pharmacopuncture types: five studies [15, 22, 23, 25, 32] used Hwangryunhaedok-tang (*Scutellaria baicalensis*, *Coptis chinensis*, *Phellodendron amurense,* and *Gardenia jasminoides*); four studies [13, 14, 28, 31] used Soyeom pharmacopuncture (*Taraxacum officinale*, *Lonicera japonica*, *Rehmannia glutinosa*, *Forsythia viridissima*, *Coptis chinensis*, *Scutellaria baicalensis*, *Phellodendron amurense,* and *Gardenia jasminoides*); another four studies [21, 24, 33, 35] used Ouhyul pharmacopuncture (*Gardenia jasminoides*, *Corydalis remota*, *Boswellia carteri*, *Commiphora myrrha*, *Prunus persica*, *Paeonia lactiflora*, *Salvia miltiorrhiza,* and *Caesalpinia sappan*); and each used *Ephedra sinica* Stapf and *Aconitum carmichaeli* Debx. [11], *Calculus Bovis*.*Fel Ursi*.*Moschus* (BUM) [26], *Panax ginseng* plus BUM [9], and ShinBaro pharmacopuncture (modification of Chungpa-Juhn (*Saposhnikovia divaricata* Schiskin, *Achyranthes bidentata* Blume, *Acanthopanax sessiliflorum* Seem, *Cibotium barometz* J. Smith, *Glycine max* Merrill, and *Eucommia ulmoides* Oliver)) [27].

3.2.2. Pharmacopuncture Methods. Participants received fixed (i.e., all participants received the same treatment), partially individualized (using a fixed set of points to be given with a set of points to be used flexibly), or individualized pharmacopuncture treatment (each participant received a tailored treatment). Out of the 29 studies, 18 used fixed [9–18, 20, 21, 25, 29, 32, 35–37], 7 studies used partially individualized [19, 22, 23, 26, 28, 30, 34], and the other 4 trials used individualized acupuncture treatments [24, 27, 31, 33].

3.2.3. Treatment Sessions. The number of pharmacopuncture sessions ranged from 3 to 16 over 6 days to 8 weeks.

3.2.4. Pharmacopuncture Points. Regarding pharmacopuncture points used in the studies, 19 studies [11–15, 17–23, 25, 27, 29, 31, 32, 36, 37] used 12 meridian points and/or extra points. Four studies [26, 28, 30, 34] used 12 meridian points, extra points, Ashi points, and tender points together. Two studies [24, 33] used Ashi points only, and one study [35] used 12 meridian points plus Dr. Dong's acupuncture point. Three studies [9, 10, 16] mentioned approximate areas but not the accurate points, such as the abdomen [10], the area between the flexor carpi radialis tendon and the median nerve [16], or the left and right sides of four points inferior to and four points superior to the navel points on the stomach and the spleen and gallbladder meridians [9].

3.2.5. Extraction Methods. As for the extraction methods of pharmacopuncture, 6 studies [11, 13, 15, 21, 27, 30] used distillation of the herbal medicine; three studies [12, 16, 20] used alcohol immersion extraction methods; one study [29] used an extraction method that involved pressing from the herbs; one study [9] used distillation for wild ginseng and alcohol immersion for BUM; and the other 18 studies did not report details about the extraction method. Out of the 11 trials that mentioned extraction methods, 8 studies [9, 11, 13, 15, 16, 21, 27, 29] followed the guidelines of the Korean Pharmacopuncture Institute. Two studies that used Carthami-Semen [12, 20] did not follow the guidelines, in which the pressing extraction method is used to extract Carthami-Semen, but used an alcohol immersion extraction method instead. The other trial [30] used distillation to extract UDP, but there was no guideline for the extraction of UDP.

3.2.6. Types of Injector. In total, 24 studies mentioned the type of injector: 16 studies [13, 15–20, 24, 27–31, 35–37] used 1 mL syringes; one study [10] used a mesogun; and another study [34] reported using a U-100 insulin syringe but did not state the size or gauge of the syringe. The gauge, which indicates the thickness of the needle, was varied. 18 studies stated the gauge: four studies [15, 18, 21, 28] applied a 30-gauge syringe; seven studies [17, 22, 23, 25, 30–32] were done with a 29-gauge syringe; two studies [12, 20] were performed with a 27-gauge syringe; four studies [13, 27, 29, 37] were done using a 26-gauge syringe; and one study [36] used a 26-gauge syringe (CV4) and a 30-gauge syringe (ST36, SP6, and SP9) according to the pharmacopuncture points. Five studies [9, 11, 14, 26, 33] did not mention the gauge.

3.2.7. Amount of Injection. Each amount of injection ranged from 0.05 mL to 1 mL, and the total amount of injection ranged from 0.2 mL to 5 mL. Only one study [30] did not report the amount of injection.

3.2.8. Depth of Injection. Seven studies [16, 18, 20, 27, 29, 30, 36] reported the depth of injection. The depth of injection ranged from 5 to 30 mm according to the pharmacopuncture points.

3.2.9. Angle of Injection. The angle of injection was reported in only three studies: two studies [18, 27] used perpendicular

angles, and one study [16] used oblique angle (45 degrees) when injecting into the wrist area.

3.3. Control Intervention. In this review, control procedures were classified into four types. First, pharmacopuncture was compared with normal saline [9–12, 15, 17, 20, 21, 30, 35–37] or distilled water injections [18] in 13 studies for blinding. Secondly, pharmacopuncture was tested against tuina manual treatment in three studies [23–25]. Thirdly, three studies adopted acupuncture as a control group [19, 32, 34]. Finally, the comparison of pharmacopuncture plus other interventions and other interventions alone groups was investigated in ten studies [13, 14, 16, 22, 26–29, 31, 33]. Other interventions included acupuncture [13, 14, 16, 22, 26–29, 31, 33], herbal/western medicine [13, 14, 16, 22, 27–29, 31, 33], cupping [28, 31], tuina [27], and physical therapy [13, 14, 16, 27–29, 31, 33] (Table 1).

3.4. Outcome Measures. Outcome measures reported in the included studies were very diverse because of the various types of focused diseases. Intensity of discomfort (e.g., measured with the visual analogue scale, the numeric rating scale) was investigated in 20 trials [13–16, 20–33, 35, 37]. All studies focusing on diseases of the musculoskeletal system and connective tissue adhered to it except one [34]. A quality-of-life-related scale was applied in six studies [12, 15, 19, 20, 29, 30]. All trials on Bell's palsy utilized the Yanagihara score [13, 14, 17]. All studies on cervicalgia used a neck disability index [22–24, 28, 29]. Out of the five studies that treated low back pain, three studies were applied using the Oswestry disability index [25–27] (Table 1).

3.5. ROB Assessment. The majority of the included trials were assessed as having a high ROB. Details of the ROB assessments are presented in Table 3.

Twelve out of the 25 studies reported adequate methods of sequence generation, such as using a random number table, computer random number generator, randomization code, or coin toss [9, 11–13, 18, 20–22, 24, 27, 29, 36]. Group assignment was adequately concealed in only four trials using sealed opaque envelopes [12, 30] or central allocation [21, 27].

The participant, practitioner, and outcome assessor each were blinded in only two trials [12, 30]. Double-blinding of the participant and practitioner was conducted in two studies [18, 35]. Participant blinding was performed in four trials [10, 11, 17, 37]. The participant and outcome assessor were blinded in three trials [15, 20, 36] as outcome measures were all subjective and assessed by blinded participants in two trials [15, 36], and the other one mentioned that an independent assessor evaluated constipation symptoms [20].

In terms of addressing incomplete outcome data, 13 studies [13–16, 19, 22–24, 27, 29, 31, 34, 36] were assessed as having a low ROB, as they had no missing outcome data. Nine trials [9, 12, 18, 20, 21, 30, 32, 33, 35] had missing outcome data, but the drop-out rate did not exceed 20% for short-term and 30% for long-term follow-up, and the number and reasons for drop-out in each group were similar. Six trials [10, 11, 25, 26, 28, 37] also had missing outcome data, but the drop-out rate exceeded 20% for short-term and 30% for long-term follow-up. The other study [17] had missing outcome data, but we could not calculate the drop-out rate, as the number of participants randomized in each group was not reported.

As for the selective outcome reporting, we could not locate and compare the protocols of any of the included studies. Therefore, we judged the ROB based on the described methods in each study. One study [16] had a high ROB because the authors (Lim et al.) were supposed to report visual analog scale (VAS) in the methods part, but there was no VAS data in results section.

3.6. Effects of Pharmacopuncture. The key outcomes from the included studies are provided in Table 1.

Low back pain ($n = 5$) [25–27, 31, 33], cervicalgia ($n = 5$) [22–24, 28, 29], obesity ($n = 3$) [9–11], and Bell's palsy ($n = 3$) [13, 14, 17] were the most actively researched fields using pharmacopuncture intervention.

A total of 10 studies were available for statistical pooling (Figures 2 and 3). As for the other 19 trials in which statistical pooling was impossible because of the substantial heterogeneity of the diseases, types of pharmacopuncture, control groups, or outcome measures, we classified the results into four categories: positive (P), negative (N), neutral (NS), and not assessable (NA).

3.6.1. Effects of Pharmacopuncture in Obesity. Among the three studies on obesity, two studies [10, 11] showed that *Capsicum frutescens* L. or *Ephedra sinica* Stapf-*Aconitum carmichaeli* Debx. pharmacopuncture significantly reduced weight, waist circumference, and BMI compared with the normal saline injection group by 1.36 kg, 4.59 cm, and 0.52 kg/m^2, respectively, immediately after treatment (Figure 2(a), MD 1.36, 95% CI: 0.51–2.21; Figure 2(b), MD 4.59, 95% CI: 2.63–6.55; Figure 2(c), MD 0.52, 95% CI: 0.19–0.85). There were no significant heterogeneities among the trials (Figure 2(a), $\chi^2 = 1.16$, degrees of freedom (df) = 1, $p = 0.28$, and $I^2 = 14\%$; Figure 2(b), $\chi^2 = 1.27$, df = 1, $p = 0.26$, and $I^2 = 21\%$; Figure 2(c), $\chi^2 = 0.35$, df = 1, $p = 0.55$, and $I^2 = 0\%$). Another study [9] also reported that body weight, waist circumference, and BMI were more reduced than in the normal saline group, but we did not obtain sufficient data for statistical pooling. Thus, the result was not assessable.

3.6.2. Effects of Pharmacopuncture on Musculoskeletal Conditions. In five studies on musculoskeletal diseases [22, 26–29], pharmacopuncture plus other interventions significantly alleviated pain intensity compared with the other interventions only immediately after treatment (Figure 3(a), MD 1.38, 95% CI: 0.96–1.79, and $I^2 = 10\%$). Three studies that compared pharmacopuncture with tuina manual therapy [23–25] reported that pharmacopuncture was not more effective than tuina in musculoskeletal diseases immediately after treatment (Figure 3(b), MD 0.36, 95% CI: −0.10–0.81, and $I^2 = 15\%$).

As statistical pooling was impossible in the other seven trials, detailed results were described as follows. Two trials

Table 3: Risk of bias (ROB) assessment*.

Author, year	Random sequence generation	Allocation concealment	Blinding			Incomplete outcome data	Selective reporting
			Patient blinding	Practitioner blinding	Outcome assessor blinding		
Seo, 2013 [21]	Y	Y	U	N	Y	Y	Y
Lee, 2013 [19]	U	U	N	N	U	Y	Y
Lim, 2013 [9]	Y	U	U	U	U	Y	Y
Lee et al., 2012 (1) [22]	Y	U	N	N	U	Y	Y
Lee et al., 2012 (2) [23]	U	U	N	N	N	Y	Y
Park et al., 2011 (1) [12]	Y	Y	Y	Y	Y	Y	Y
Woo et al., 2011 [24]	Y	U	N	N	N	Y	Y
Kim et al., 2011 (1) [25]	U	U	N	N	N	N	Y
Jeong et al., 2011 [26]	U	U	N	N	N	N	Y
Jun et al., 2011 [27]	Y	Y	N	N	N	Y	Y
Im et al., 2011 [28]	U	U	N	N	U	N	Y
Park et al., 2011 (2) [29]	Y	U	N	N	N	Y	Y
Kim, 2011 (2) [10]	U	U	Y	U	U	N	Y
Kim et al., 2010 (1) [30]	U	Y	Y	Y	Y	Y	Y
Kim et al., 2010 (2) [37]	U	U	Y	U	U	N	Y
Noh et al., 2009 [18]	Y	U	Y	Y	U	Y	Y
Kim et al., 2009 [11]	Y	N	Y	N	U	N	Y
Song et al., 2009 [31]	U	U	N	N	U	Y	Y
Shin et al., 2009 [13]	Y	U	N	N	U	Y	Y
Choi et al., 2009 [14]	U	U	N	N	U	Y	Y
Kang et al., 2008 [32]	U	U	N	N	U	Y	Y
Park et al., 2008 [20]	Y	U	Y	N	Y	Y	Y
Kim et al., 2008 [36]	Y	U	Y	U	Y	Y	Y
Lee et al., 2007 [33]	U	U	N	N	U	Y	Y
Kim et al., 2006 [15]	U	U	Y	U	Y	Y	Y
Park et al., 2006 [34]	U	U	N	N	U	Y	Y
Lim et al., 2005 [16]	U	U	N	N	U	Y	N
Lee et al., 2005 [17]	U	U	Y	U	U	U	Y
Bae and Park, 2004 [35]	U	U	Y	Y	U	Y	Y

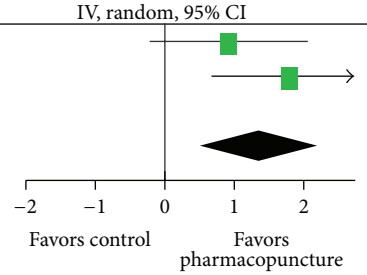
*Based on the guidelines from the Cochrane Back Review Group [39]; "Y" indicates "yes (low risk of bias)"; "U," "unclear"; "N," "no (high risk of bias)."

on HNP of the L-spine [31, 33] showed unassessable effects of Soyeom and Ouhyul pharmacopuncture. Of the two studies on osteoarthritis of the knee, one study [30] contrasted root bark of UDP pharmacopuncture with normal saline injection, and the effect was not assessable. Another study [34] that compared *Hominis Placenta* Pharmacopuncture with acupuncture showed no significant difference between the groups. In shoulder pain caused by stroke [21, 35], the effect of pharmacopuncture was not assessable. For acute ankle sprain [32], acupuncture improved the symptoms better than Hwangryunhaedok-tang pharmacopuncture after 9–12 days of treatments; in other words, they reported a negative effect of pharmacopuncture.

3.6.3. Effects of Pharmacopuncture on Diseases of the Nervous System. The results of pharmacopuncture were composited for each disease. For headache, both Carthami-Semen and Hwangryunhaedok-tang pharmacopuncture improved symptoms compared with normal saline injection [12, 15]. For Bell's palsy, the effect of *Hominis Placenta* Pharmacopuncture was significantly better than normal saline injection [17]. However, for the postauricular pain that accompanies Bell's palsy, the effect of Soyeom pharmacopuncture was not assessable. It may be due to the fact that the pain intensity or duration of pain decreased significantly, while the Yanagihara score did not show a significant difference between the groups [13, 14]. One study on scolopendrid

Study or subgroup	Pharmacopuncture Mean	SD	Total	Normal saline Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Kim et al. (2009)	1.86	1.65	24	0.94	2.47	28	49.3%	0.92 [−0.21, 2.05]
Kim (2011) (2)	2.71	1.71	13	0.92	1.31	18	50.7%	1.79 [0.68, 2.90]
Total (95% CI)			**37**			**46**	**100.0%**	**1.36 [0.51, 2.21]**

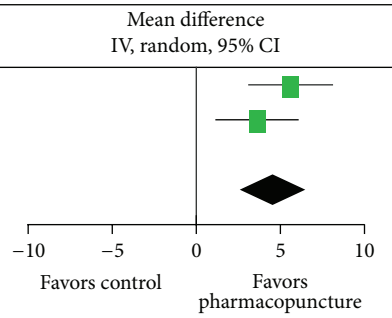
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 1.16$, df = 1 ($p = 0.28$); $I^2 = 14\%$
Test for overall effect: $Z = 3.13$ ($p = 0.002$)



(a) Pharmacopuncture versus normal saline: weight decrement (kg)

Study or subgroup	Pharmacopuncture Mean	SD	Total	Normal saline Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Kim et al. (2009)	8.38	5.38	24	2.77	3.35	28	49.2%	5.61 [3.13, 8.09]
Kim (2011) (2)	6.35	2.51	13	2.74	4.37	18	50.8%	3.61 [1.17, 6.05]
Total (95% CI)			**37**			**46**	**100.0%**	**4.59 [2.63, 6.55]**

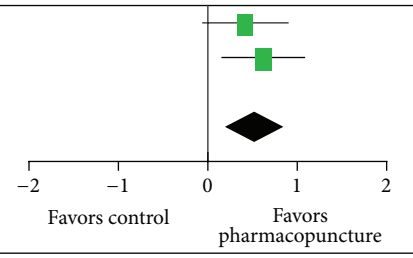
Heterogeneity: $\tau^2 = 0.42$; $\chi^2 = 1.27$, df = 1 ($p = 0.26$); $I^2 = 21\%$
Test for overall effect: $Z = 4.60$ ($p < 0.00001$)



(b) Pharmacopuncture versus normal saline: waist circumference decrement (cm)

Study or subgroup	Pharmacopuncture Mean	SD	Total	Normal saline Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Kim et al. (2009)	0.76	0.67	24	0.34	1.06	28	48.5%	0.42 [−0.06, 0.90]
Kim (2011) (2)	1.04	0.69	13	0.42	0.58	18	51.5%	0.62 [0.16, 1.08]
Total (95% CI)			**37**			**46**	**100.0%**	**0.52 [0.19, 0.85]**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.35$, df = 1 ($p = 0.55$); $I^2 = 0\%$
Test for overall effect: $Z = 3.10$ ($p = 0.002$)



(c) Pharmacopuncture versus normal saline: BMI decrement (kg/m^2)

Figure 2: Effect of pharmacopuncture in obesity. BMI: body mass index; CI: confidence intervals; SD: standard deviation.

pharmacopuncture treatment did not show additional effects on pain intensity in carpal tunnel syndrome [16].

3.6.4. Effects of Pharmacopuncture on Diseases of the Circulatory System. The effect of *Hominis Placenta* Pharmacopuncture compared with distilled water injection was not assessable in leg spasticity of stroke patients due to the complexity of the results. For modified Ashworth scale (MAS), H-reflex/M-response ratio (H/M ratio), and Berge balance scale (BBS), there were no significant differences between groups, while the time up and go (TUG) in pharmacopuncture group was significantly lower than in distilled water injection group [18].

3.6.5. Effects of Pharmacopuncture on Diseases of the Digestive System. One study of *Hominis Placenta* Pharmacopuncture had a similar effect to acupuncture in dyspepsia [19]. The effect of Carthami-Semen pharmacopuncture on chronic constipation was not assessable [20].

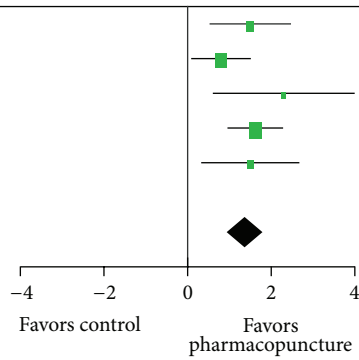
3.6.6. Effects of Pharmacopuncture on Diseases of the Genitourinary System. One study on *Hominis Placenta* Pharmacopuncture for dysmenorrhea showed a similar effect to normal saline injection [36].

3.6.7. Effects of Pharmacopuncture on Pregnancy, Childbirth, and the Puerperium. *Hominis Placenta* Pharmacopuncture had complicated results compared with normal saline injection [37]. There were no significant differences between groups in VAS for heating feeling, sweet during movement and sleeping, and complete blood cell (CBC) count. For thirst, *Hominis Placenta* Pharmacopuncture group showed significant higher VAS than normal saline injection group before the treatment ($p = 0.023$). After treatment, two

Study or subgroup	Pharmacopuncture Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Im et al. (2011)	4.125	1.356	10	2.625	0.744	10	17.3%	1.50 [0.54, 2.46]
Jeong et al. (2011)	3.87	1.06	15	3.07	0.88	15	30.3%	0.80 [0.10, 1.50]
Jun et al. (2011)	4.3	2.5	10	2	1.05	10	6.0%	2.30 [0.62, 3.98]
Lee et al. (2012) (1)	3.75	1.39	34	2.13	1.24	29	34.2%	1.62 [0.97, 2.27]
Park et al. (2011) (2)	7.2	1.13	10	5.7	1.49	10	12.2%	1.50 [0.34, 2.66]
Total (95% CI)			**79**			**74**	**100.0%**	**1.38 [0.96, 1.79]**

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 4.43$, df = 4 ($p = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 6.46$ ($p < 0.00001$)

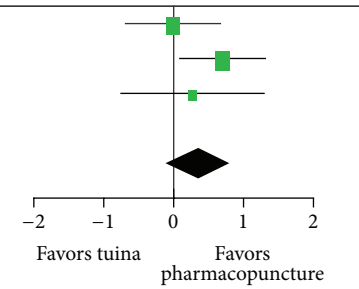


(a) Pharmacopuncture + other interventions versus other interventions: VAS improvement

Study or subgroup	Pharmacopuncture Mean	SD	Total	Tuina Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Kim et al. (2011) (1)	2.94	1.71	35	2.95	1.29	46	37.5%	−0.01 [−0.69, 0.67]
Lee et al. (2012)	3.42	1.42	37	2.72	1.39	45	44.2%	0.70 [0.09, 1.31]
Woo et al. (2011)	4.1	1.95	30	3.83	2.09	30	18.3%	0.27 [−0.75, 1.29]
Total (95% CI)			**102**			**121**	**100.0%**	**0.36 [−0.10, 0.81]**

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 2.36$, df = 2 ($p = 0.31$); $I^2 = 15\%$

Test for overall effect: $Z = 1.52$ ($p = 0.13$)



(b) Pharmacopuncture versus tuina: VAS score

Figure 3: Effects of pharmacopuncture on musculoskeletal conditions. CI: confidence intervals; SD: standard deviation; VAS: visual analog scale.

groups reported similar thirst symptom ($p = 0.510$) without correcting the baseline value. Therefore, we could not assess the results.

3.7. Adverse Events (AEs). Only five studies reported AEs. In the study by Seo [21], they compared Ouhyul pharmacopuncture with normal saline and reported general pain in the Ouhyul group and transient local site pain or fatigue in the normal saline group. Kim [10] compared *Capsicum frutescens* L. with normal saline and reported moderate AEs related to anesthesia cream or pharmacopuncture (4 in the *Capsicum frutescens* L. group, 2 in the normal saline group). In each of the two studies by Park et al. [12, 20], they compared Carthami-Semen with normal saline and reported mild AEs, such as pain during the injection, ecchymosis, and redness in the Carthami-Semen group and moderate pain during the injection in the normal saline group. One study by Kim et al. [30] compared UDP with normal saline and reported mild AEs, such as nausea and itching in the UDP group and slight dizziness in the normal saline group. These AEs disappeared in a short time without specific treatment, and no serious AEs were reported. Another two studies by Jun et al. [27] and Kim et al. [37] reported that AEs did not occur, and the other 22 trials [9, 11, 13–19, 22–26, 28, 29, 31–36] did not mention AEs.

3.8. Sensitivity Analyses. We performed sensitivity analyses by excluding studies with predefined less desirable characteristics, and the results from the musculoskeletal studies were robust.

3.8.1. ROB. When the analyses were limited to two studies with a low ROB for random sequence generation and/or allocation concealment [27, 29], pharmacopuncture had additional benefits in terms of pain relief in musculoskeletal diseases immediately after treatments (MD 1.76, 95% CI: 0.80–2.71, $I^2 = 0\%$). One study with adequate random sequence generation and/or allocation concealment did not provide enough information; thus, the effect of pharmacopuncture compared with normal saline could not be assessed in shoulder pain caused by stroke [21].

3.8.2. Sample Size. There was no study with ≥40 participants per arm.

4. Discussion

Our review on pharmacopuncture aimed to establish the evidence of pharmacopuncture treatment of any disease. The

analyses of two trials on obesity [10, 11] demonstrated a significant benefit from 5 to 8 weeks of pharmacopuncture treatments compared with normal saline injection. The analyses of five trials on musculoskeletal diseases [22, 26–29] represented a significant effect from 7 to 30 days of combined treatment of pharmacopuncture with other interventions (e.g., acupuncture, herb medicine, tuina, and physical therapy) compared with other interventions only. However, these analyses were based on small studies and other interventions used in these trials were varied; thus cautious interpretation is needed. In the musculoskeletal diseases, pharmacopuncture's benefits were maintained by limiting the analyses to studies with a low ROB for randomization and/or allocation concealment [27, 29], which means that they presented robust evidence for the treatment of musculoskeletal diseases. However, the number of participants in these studies was too small (less than 10 per arm), so careful interpretation is required. Pharmacopuncture does not appear to be associated with serious AEs, but the evidence is limited.

Most of the included studies had methodological weaknesses. Thirteen out of 25 studies [9, 11–13, 18, 20–22, 24, 27, 29, 30, 36] had low ROBs for adequate randomization and/or allocation concealment. Among them, only three studies [12, 21, 27] had both appropriate randomization and allocation concealment. It is well known that inadequate allocation concealment/random sequence generation leads to the overestimation of treatment effects [41, 42], and unconcealed allocation is the most important source of bias in RCTs [45]. When we limited our analyses to the studies rated as having low ROBs for randomization/allocation concealment, pharmacopuncture's benefit was maintained.

There were some limitations in this review. Our review only included trials conducted in Korea and published in Korean or English. Therefore, we could not necessarily remove a potential language bias. Egger et al. [46] reported that studies published in non-English languages or studies published in journals that are not indexed in Medline are likely to increase the effect estimates, and this may have relevance to this review. In addition, pharmacopuncture, an acupuncture-related intervention, may be highly culture specific. According to the 2007 National Health Interview Survey (NHIS) data, only 6.5% of the Americans reported ever receiving acupuncture [47]. Upchurch et al. also reported that there was significant difference in the use of acupuncture by ethnicity and race. Asian women reported the highest usage [48]. Thus, further research is necessary to determine whether the interventions are applicable and acceptable in other countries.

The included trials were mostly of poor quality; thus, the reported data are likely to be overestimated. In addition, most of the included studies were small. Median sample sizes per arm were 17 in the pharmacopuncture group and 18 in the control group. The effect size of small studies may have been inflated due to poor methodological design and conduct [49]. Moore et al. [43] reported in a simulation study that at least 40 participants per arm are required to obtain clinically relevant results in trials of pain; however, there were no studies with ≥40 participants per arm, and we could not analyze it separately.

The efficacy of the treatment used for the control group, such as acupuncture, herbal medicine, and tuina manual therapy, was not yet established; therefore, we could not attribute "positive" results solely to the effectiveness of pharmacopuncture. Additionally, clinically meaningful information on follow-up results was sparse in the majority of the included trials. Therefore, the available evidence prevented us from further examining how long its benefit was maintained.

As we included all conditions/diseases, the focus of our review may seem blurred. However, this review provides an overview of the entire primary pharmacopuncture researches conducted in Korea. The results help to set priorities and directions for future research on pharmacopuncture.

Although this review represented the applicability of pharmacopuncture, the standardisation of pharmacopuncture intervention was not performed. Thus, in the future, it is absolutely necessary to standardise it to apply pharmacopuncture in routine clinical practice. The degree of pharmacopuncture stimulation could be influenced by the following factors: (1) pharmacopuncture types; (2) concentration and extraction methods of pharmacopuncture; (3) amount, depth, and angle of injection; (4) syringe types, including thickness and length; (5) pharmacopuncture points; and (6) number of sessions based on the STRICTA guidelines [38]. Currently, the Korean Pharmacopuncture Institute suggests guidelines for pharmacopuncture treatment. The classification of pharmacopuncture, such as meridian field, eight-principle, or monoherbal medicine-type, is determined by the diagnosis of patient's conditions. The total amount of injections depends on the severity of the disorder, the age of the patient, the injecting area, and the characteristics and concentration of the pharmacopuncture extract. Using various types of injectors or syringes depends on the type of pharmacopuncture, its dosage, the area of the body part, and the depth of the injection. Syringe needles are generally between 26 and 32 gauges. Different needles are utilized for different uses.

However, the standardisation of these factors has yet to be completed, and there is no firmly established research method for pharmacopuncture studies; therefore, pharmacopuncture interventions of the included trials were very heterogeneous. In addition, future studies should include not only a test of the efficacy and safety of pharmacopuncture but also an examination of the validity of the intervention based on the standardised guidelines.

5. Conclusions

The results of this review demonstrate the effectiveness of pharmacopuncture for the treatment of obesity and musculoskeletal diseases compared with normal saline injections and other interventions, respectively; however, given the methodological flaws and small sample sizes, the available evidence is insufficient to recommend pharmacopuncture as an evidence-based treatment option. In the future, the standardisation of pharmacopuncture intervention and the adequate reporting of pharmacopuncture intervention in accordance with STRICTA guidelines are needed.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Jong-In Kim and Jimin Park designed this review. Jimin Park and Myeong Soo Lee searched the databases, screened studies for inclusion, extracted data, and evaluated the quality of the included studies. They were checked by Jong-In Kim, Byung-Cheul Shin, and Hyangsook Lee. Boryang Kim, Hyangsook Lee, and Jimin Park conducted the analyses and discussed their findings with Jong-In Kim, Myeong Soo Lee, and Byung-Cheul Shin. All authors read and approved the final paper.

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Research Article

Effect of Herbal Prescriptions in Accordance with Pattern Identification in Acute Cerebral Infarction Patients: Based on Fire-Heat Pattern

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Objectives. This study was conducted to verify the necessity of corresponding prescription to the diagnosed pattern in acute cerebral infarction patients. *Methods.* We studied cerebral infarction patients hospitalized within 30 days after the ictus. Forty-four clinical indicators, Motricity Index (MI) score, Scandinavian Stroke Scale (SSS) score, and herbal prescriptions were checked twice, two weeks apart. The probability of each pattern was calculated based on the clinical indicators. Changes in MI score, SSS score, and the probability of fire-heat pattern were compared between the pattern-prescription correspondence group and the noncorrespondence group. *Results.* Increments of MI score and SSS score in the correspondence group were significantly greater than those of the noncorrespondence group ($p = 0.003$, $p = 0.001$) while the baseline score of the two groups showed no significant difference. Probability of fire-heat pattern decreased significantly in the correspondence group ($p = 0.013$) while the noncorrespondence group showed no significant difference after the treatment. *Conclusion.* Acute cerebral infarction patients who are diagnosed as fire-heat pattern showed better improvement in dysfunctions caused by the disease when they took the pattern corresponding prescriptions. This study provides evidence for the necessity and usefulness of pattern identification in Traditional Korean Medicine.

1. Introduction

In South Korea, the political and social status of Traditional Korean Medicine (TKM) almost equals that of Western medicine. This is due to a strong preference for TKM in Korean people. When 1,000 people living in Seoul were asked to choose between Western medicine doctors and TKM doctors if they had developed a stroke, 25% of the subjects chose TKM doctors, and 45% of the subjects responded that they were willing to receive TKM treatments [1]. Also, a survey demonstrated that 40% of stroke patients tried TKM treatments after they were discharged from a Western medicine hospital [2]. Among many diseases, TKM has been favored especially for the treatment of stroke.

Considering the large role in the treatment of stroke, significant amount of effort was put into accumulating scientific evidence of the efficacy and safety of TKM. As a result, questionnaire for the pattern identification and guidelines for assessing the clinical indicators were developed over the years [3, 4]. These guidelines allowed us to accumulate coherent data, and by using these data, we were able to work out equations for standardization of pattern identification for stroke patients [5, 6]. These works enhanced the objectivity and reproducibility of pattern identification and remedied its shortcomings. However, the necessity and usefulness of pattern identification have not been verified yet. Many herbal prescriptions have been proven to have a beneficial effect in acute stroke patients [7–9], but the relation between the efficacy and the pattern identification was not indicated.

In this study, to verify the necessity and usefulness of pattern identification, we compared the two groups of the patients diagnosed as fire-heat pattern. The group who took the herbal prescriptions in accordance with the pattern identification and the group of people who did not take the herbal prescriptions accordingly were compared to demonstrate if the corresponding prescription taking group shows better outcome. Also, we performed a correlation study between the changes in clinical indicators and the improvement in

dysfunctions to identify if the changes in symptoms are relevant to recovery of poststroke dysfunctions.

2. Materials and Methods

2.1. Subjects. We enrolled ischemic stroke patients within 30 days after their ictus from Kyung Hee Korean Medical Center and Kyung Hee East-West Neo Medical Center. Imaging diagnosis such as computerized tomography (CT) or magnetic resonance imaging (MRI) was checked to confirm the ischemic stroke. We excluded traumatic strokes such as subarachnoid, subdural, and epidural hemorrhage. Also, we excluded patients with brain tumor, Alzheimer's disease, multiple sclerosis, or any other neurodegenerative diseases. Informed consent of all the participants was obtained after a thorough explanation of the details. Over a 3-year period from May 2011 to January 2014, 300 patients were included in the study. The Institutional Review Board of the Kyung Hee Korean Medical Center and Kyung Hee East-West Neo Medical Center approved the present study (KOMCIRB-2011-02, KOMCIRB-2012-04, KHNMCOHIRB-2011-002, and KHNMCOHIRB-2012-003).

2.2. Study Design and Interventions. After the admission, two different TKM doctors identified the pattern of each patient based on the clinical indicators they show, and we confirmed the pattern only if the two TKM doctors had the same opinion. We used the Case Report Form (CRF) and the Standard Operation Procedures (SOP) developed by the Korean Institute of Oriental Medicine [3, 10] to reduce inconsistency in pattern identification carried out by different TKM doctors. Table 1 shows the forty-four clinical indicators contained in the CRF, and there were four possible patterns to choose from, which were fire-heat pattern, Yin Deficiency Pattern, Phlegm Dampness Pattern, and Qi Deficiency Pattern. The patients whose patterns were not decided because the opinions of the two TKM doctors differed were dropped out. After the pattern identification, the patients were allocated into each group according to their confirmed pattern.

All subjects were studied twice, 2 weeks apart. During the 2-week period, all participants received conventional Western medicine treatment such as antiplatelet agent, risk factor control (e.g., hypertension, diabetes mellitus, dyslipidemia, and cardiac disease), and rehabilitation exercise. TKM treatment was also administered to all of the patients, which includes herbal prescription, acupuncture, and electroacupuncture. The contents of acupuncture and electroacupuncture treatment are shown in Table 2. The herbal prescriptions applied to each patient were selected according to the patient's condition and associated symptoms by the TKM doctors who were irrelevant to the present study. The prescriptions used during the treatment period were checked, and we classified the prescriptions based on the guideline suggested in the SOP (Table 3).

2.3. Measurements. Baseline characteristics such as age, sex, Body Mass Index (BMI), period from onset to admission, medical history, alcohol and smoking habits, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [11, 12] of the stroke types were checked. To estimate the motor function, we used Motricity Index (MI) score [13], which is a reliable scale in assessing motor impairment after stroke. Scandinavian Stroke Scale (SSS) score [14] was used to evaluate the degree of dysfunctions in the subjects. The assessors for the MI and SSS scores did not have the information about the herbal prescriptions the patients are taking.

To assess the changes in the clinical indicators, we used the logistic equations for calculating the probability of each pattern suggested by Kim et al. [5]. The same CRF and SOP used in the present study were used in their research, and the logistic equations were derived based on the clinical data of 480 stroke patients as a result of regression analysis. The equations for the probability of four patterns are as follows:

$$\begin{aligned} A = {} & 3.021 \times (\text{reddened complexion}) + 1.052 \\ & \times (\text{eyeball congestion}) + 0.682 \\ & \times (\text{aversion to heat}) - 1.388\,(\text{pale tongue}) \\ & + 0.727 \times (\text{thick fur}) - 1.134 \\ & \times (\text{teeth marked tongue}) + 1.295 \\ & \times (\text{strong pulse}) - 1.122 \times (\text{thin pulse}) \\ & - 0.972 \times (\text{slippery pulse}) - 2.865, \\ B = {} & 3.552 \times (\text{flushed cheeks}) + 1.024 \times (\text{thirst}) \\ & + 1.740 \times (\text{afternoon tidal fever}) + 0.963 \\ & \times (\text{dry fur}) + 0.982 \times (\text{rapid pulse}) - 1.932 \\ & \times (\text{strong pulse}) - 3.705, \\ C = {} & 0.578 \times (\text{overweight}) - 0.754 \times (\text{fatigue}) - 1.754 \\ & \times (\text{pale complexion}) - 2.189 \\ & \times (\text{reddened complexion}) - 2.719 \\ & \times (\text{flushed cheeks}) + 1.496 \times (\text{pale tongue}) \\ & + 2.365 \times (\text{slippery pulse}) - 1.136, \\ D = {} & -0.882 \times (\text{overweight}) + 2.417 \\ & \times (\text{pale complexion}) - 2.869 \\ & \times (\text{reddened complexion}) - 2.252 \\ & \times (\text{flushed cheeks}) + 1.451 \\ & \times (\text{eyeball dryness}) - 1.577 \\ & \times (\text{night sweating}) - 1.474 \times (\text{nausea}) \\ & + 1.165 \times (\text{reversal cold of the extremities}) \end{aligned}$$

Table 1: Clinical indicators related to pattern identification.

Overweight	Body Mass Index >23 (kg/m^2)
Insomnia	Inability to sleep or abnormal wakefulness
Fatigue	Lack of strength
Pale complexion	A white complexion with a hint of blue or gray, often caused by yang collapse or exuberance of cold
Yellow complexion	Yellow discoloration of the face, generally suggesting accumulation of dampness
Reddened complexion	A complexion redder than normal, indicating the presence of heat
Darkish complexion	Dark discoloration of the face, often occurring in cold syndrome, water retention, or blood stasis
Flushed cheeks	Localized flush in the cheeks, indicating yin deficiency
Headache	Pain in the head
Eye congestion	Congestion in eyeballs indicating presence of heat
Eyeball dryness	Subjective feeling of dryness in the eyeballs
Phlegm rale	An abnormal breathing sound by phlegm in the airways
Faint low voice	A voice that is faint and low, scarcely audible
Tongue sore	Ulceration in the oral cavity or tongue
Halitosis	Bad smell from the mouth
Thirst	Feeling of dryness of the mouth with a desire to drink
Bitter taste in the mouth	A subjective bitter sensation in the mouth
Night sweating	Sweating during sleep that ceases on awakening
Chest discomfort	Unwell feeling of stuffiness and fullness in the chest
Nausea	An unpleasant sensation with an urge to vomit
Aversion to heat	Strong dislike of heat, also known as heat intolerance
Afternoon tidal fever	Fever more marked in the afternoon
Heat in the palms and soles	Subjective feverish feeling in the palms and soles
Vexing heat in the extremities	Uncomfortable heat sensation in the extremities
Reversal cold of the extremities	Pronounced cold in the extremities up to the knees and elbows, also the same as cold extremities
Reddish yellow urine	Dark yellow or even reddish urine, indicating heat
Pale tongue	A tongue less red than normal, indicating Qi and blood deficiency
Red tongue	A tongue redder than normal, indicating the presence of heat
White fur	A tongue coating white in color
Yellow fur	A tongue coating yellow in color
Thick fur	A tongue coating where the underlying tongue surface is not visible
Dry fur	A tongue coating that looks dry and feels dry to the touch
Teeth marked tongue	A tongue with dental indentations on its margin
Enlarged tongue	A tongue that is larger than normal, pale in color, and delicate
Mirror tongue	A completely smooth tongue free of coating, like a mirror
Floating pulse	A superficially located pulse which can be felt by light touch and grows faint on hard pressure
Deep pulse	A deeply located pulse which can only be felt when pressing hard
Slow pulse	Bradycardia
Rapid pulse	Tachycardia
Strong pulse	A general term for strongly beating pulse
Vacuous pulse	A general term for a feeble and void pulse
Thin pulse	A pulse as thin as a silk thread, straight and soft, and feeble yet always perceptible upon hard pressure
Slippery pulse	A pulse coming and going smoothly like beads rolling on a plate
Flooding pulse	A pulse beating like dashing waves with forceful rising and gradual decline

$$
\begin{aligned}
&- 2.100 \times (\text{thick fur}) + 0.783 \times (\text{deep pulse}) \\
&- 2.214 \times (\text{rapid pulse}) + 0.993 \\
&\times (\text{vacuous pulse}) - 2.572 \times (\text{slippery pulse}) \\
&- 0.907.
\end{aligned} \tag{1}
$$

Put in "1" for the existing clinical indicators and "0" for the nonexisting clinical indicators.

Probability of Fire-Heat Pattern. Consider

$$P_{\text{FHP}} = \frac{e^{A}}{(1 + e^{A})}. \tag{2}$$

Probability of Yin Deficiency Pattern. Consider

$$P_{\text{YDP}} = \frac{e^{B}}{(1 + e^{B})}. \tag{3}$$

Probability of Phlegm Dampness Pattern. Consider

$$P_{\text{PDP}} = \frac{e^{C}}{(1 + e^{C})}. \tag{4}$$

Probability of Qi Deficiency Pattern. Consider

$$P_{\text{QDP}} = \frac{e^{D}}{(1 + e^{D})}. \tag{5}$$

Patients that display more fire-heat pattern related symptoms show higher probability of fire-heat pattern. The discriminant validity of the equations for the probability of the four patterns is shown in Table 4.

2.4. Statistical Analysis. Statistical analysis was performed by using the Statistical Package for the Social Sciences version 12.0 for Windows (SPSS, Chicago, IL). Chi-square test was used for the categorical variables, and Mann-Whitney test was used for the continuous variables when comparing the two groups. Wilcoxon signed rank test was used for statistical comparisons between the values before and after the treatment. We correlated the changes in the probability of fire-heat pattern with the changes of SSS score and MI score, respectively, using Spearman's rank correlation. A $p < 0.05$ was considered significant.

3. Results

Of the 300 patients enrolled in the study, 68 patients were discharged before the second checkup, and 44 patients with perfect MI and SSS score were excluded as they could not expect further improvement. 40 patients were unable to determine the pattern because the diagnosis of the two TKM doctors differed. 11 patients were dropped out due to missing data. Also, many patients diagnosed as Yin Deficiency Pattern, Phlegm Dampness Pattern, and Qi Deficiency Pattern received different types of herbal prescriptions during the treatment period. Only two patients in the Yin Deficiency Pattern, three patients in the Phlegm Dampness Pattern, and two patients in the Qi Deficiency Pattern received pattern corresponding herbal prescription for the whole 2-week period, so we were unable to secure a sufficient sample size for statistical analysis for those three patterns. Among the remaining 57 patients who were diagnosed as fire-heat pattern, we considered 40 patients who received herbal prescriptions targeting fire-heat pattern related symptoms into correspondence group and the other 17 patients who received herbal prescriptions focusing on clinical indicators of other patterns into noncorrespondence group (Figure 1). After 2-week period of treatment, no aggravation of the neurologic deficit was observed in the patients.

Table 2: Traditional Korean Medicine treatments applied in the study.

Treatment	Contents
Acupuncture (once a day)	LI4, LI11, ST36, LR3, GB20 (both sides), TE5, LI10, ST37, GB39, GB34, SP3, SP4 (debilitated side), GV20, GV26, and CV24
Electroacupuncture (once a day)	LI4, TE5, LI10, LI11, ST36, ST37, GB39, and LR3 (debilitated side)

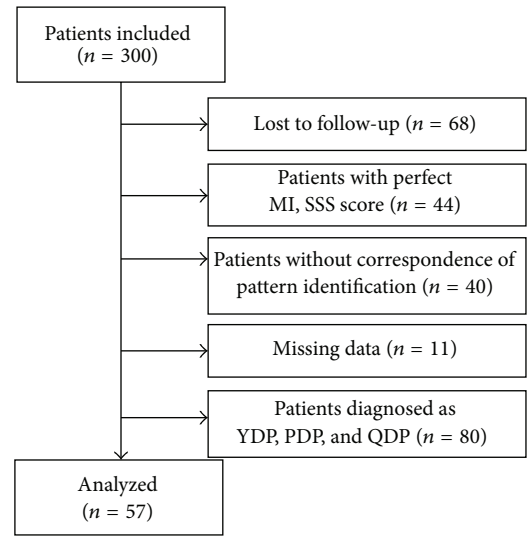

Figure 1: Flowchart of patients enrolled in this study. MI, Motricity Index; SSS, Scandinavian Stroke Scale; YDP, Yin Deficiency Pattern; PDP, Phlegm Dampness Pattern; QDP, Qi Deficiency Pattern.

3.1. Baseline Assessment. General characteristics, period from onset to admission, medical history, alcohol and smoking experience, and proportion of ischemic stroke type according to TOAST classification showed no significant difference between the two groups (Table 5).

Table 3: Classification of prescriptions used in this study by Korean Institute of Oriental Medicine.

Fire-heat pattern	Yin Deficiency Pattern	Phlegm Dampness Pattern	Qi Deficiency Pattern
Yangkyuksanwha-tang	Hyungbangjihwang-tang	Bosimgunbi-tang	Sunghyangjunggi-san
Chungpyesagan-tang	Dokhwaljihwang-tang	Banhabaekchulchunma-tang	Bojungikgi-tang
Yeoldahanso-tang	Jaumganghwa-tang	Sunkidodam-tang	Ssanghwa-tang
Chungsim-tang	Yukmijihwang-tang	Gami-ondam-tang	Boyanghwano-tang
Jihwangbakho-tang	Saryuk-tang		Yikgeebohyul-tang

Table 4: Discriminant validity of probability of four patterns.

	Probability of FHP	Probability of YDP	Probability of PDP	Probability of QDP	p value
FHP group ($n = 57$)	58.7 (38.8)	14.0 (32.0)	10.9 (25.7)	1.4 (8.6)	<0.0001
YDP group ($n = 27$)	17.8 (33.0)	31.2 (42.0)	16.5 (32.1)	4.8 (13.9)	<0.0001
PDP group ($n = 30$)	16.6 (33.9)	0.8 (2.3)	59.9 (42.7)	4.5 (16.2)	<0.0001
QDP group ($n = 23$)	0.1 (0.3)	4.2 (11.8)	19.6 (35.7)	38.2 (43.7)	<0.0001

FHP, fire-heat pattern; YDP, Yin Deficiency Pattern; PDP, Phlegm Dampness Pattern; QDP, Qi Deficiency Pattern.

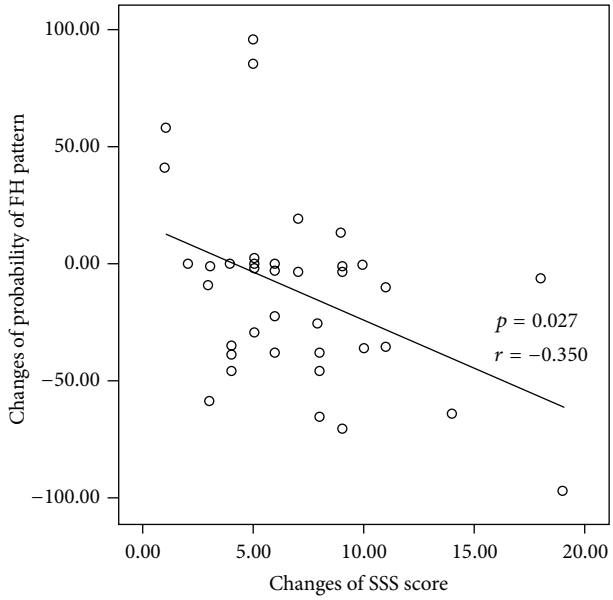

Figure 2: Correlation analysis between the changes of SSS score and the probability of fire-heat pattern in the correspondence group ($p = 0.027$, $r = -0.349$).

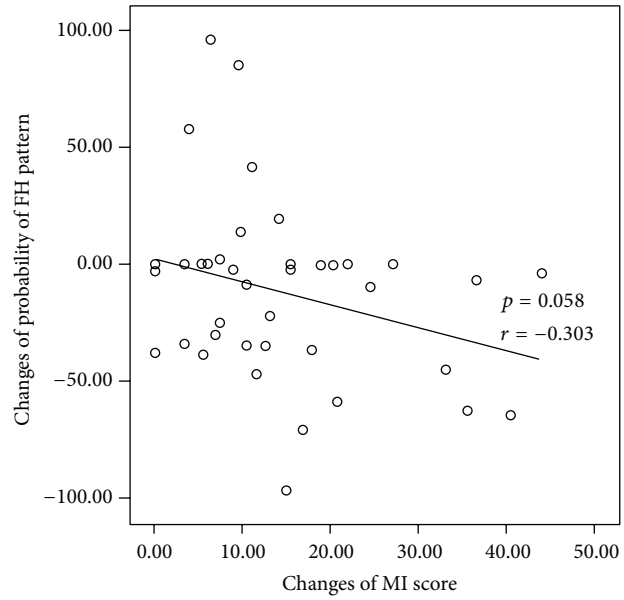

Figure 3: Correlation analysis between the changes of MI score and the probability of fire-heat pattern in the correspondence group ($p = 0.058$, $r = -0.303$).

3.2. MI Score and the SSS Score before and after the Treatment. Both groups showed increase in the MI score and the SSS score, but the increments of the MI score and the SSS score in the correspondence group were significantly greater than those of the noncorrespondence group ($p = 0.003$, $p = 0.001$) while the baseline scores of the two groups showed no significant difference (Table 6).

3.3. Changes in the Probability of Fire-Heat Pattern. The probability of fire-heat pattern was significantly higher than the probability of other patterns in both groups ($p < 0.0001$). The baseline probability of fire-heat pattern between the two groups showed no significant difference. The probability of fire-heat pattern decreased significantly after the treatment in the correspondence group ($p = 0.013$) while the probability of fire-heat pattern in noncorrespondence group showed no significant change. Probability of other patterns showed no significant change after the treatment in both groups (Table 7).

3.4. Correlation Analysis in the Fire-Heat Pattern Corresponding Prescription Group. In the correlation study, the decrease in the probability of fire-heat pattern showed significant correlation with the increase in the SSS score ($p = 0.027$) and missed statistical significance with the increase in the MI score ($p = 0.058$) (Figures 2 and 3).

Table 5: Comparisons of baseline characteristics between the correspondence group and the noncorrespondence group.

	Correspondence group ($n = 40$)	Noncorrespondence group ($n = 17$)	p value
Gender, male (%)	24 (60.0)	8 (47.1)	0.397
Age, yr (SD)	69.2 (10.0)	68.4 (10.0)	0.524
BMI, kg/m^2 (SD)	24.1 (3.0)	24.5 (3.4)	0.848
Treatment period from onset, day (SD)	9.5 (6.2)	12.7 (8.7)	0.142
Past history			
Hypertension (%)	32 (80.0)	12 (70.6)	0.499
Dyslipidemia (%)	15 (37.5)	7 (41.2)	1.000
Diabetes mellitus (%)	15 (37.5)	6 (35.3)	1.000
Heart disease (%)	4 (10.0)	2 (11.8)	1.000
Stroke type			
LAA (%)	11 (27.5)	4 (23.5)	1.000
CE (%)	3 (7.5)	1 (5.9)	1.000
SVO (%)	25 (62.5)	11 (64.7)	1.000
SUE (%)	1 (2.5)	1 (5.9)	0.511
Life style			
Smoking (%)	18 (45.0)	7 (41.2)	1.000
Alcohol (%)	19 (47.5)	5 (29.4)	0.251

BMI, Body Mass Index; LAA, large artery arteriosclerosis; CE, cardiogenic embolism; SVO, small vessel occlusion; SUE, stroke of undetermined etiology.

Table 6: Comparisons of MI score and SSS score between the correspondence group and the noncorrespondence group.

	Correspondence group ($n = 40$)	Noncorrespondence group ($n = 17$)	p value
Visit 1 MI score	54.8 ± 25.7	45.9 ± 31.7	0.382
ΔMI score	14.3 ± 11.3	6.3 ± 9.3	0.003*
Visit 1 SSS score	39.9 ± 10.4	38.1 ± 11.8	0.662
ΔSSS score	6.9 ± 4.0	3.5 ± 3.2	0.001*

MI, Motricity Index; SSS, Scandinavian Stroke Scale.
* $p < 0.05$.

4. Discussion

The aim of this study was to verify the usefulness of the pattern identification. To achieve this goal, we compared the outcome of the treatments in pattern-prescription correspondence group and the noncorrespondence group. While the baseline scores did not differ significantly between the two groups, increments of MI score and SSS score after the treatment were significantly higher in the correspondence group than the noncorrespondence group ($p = 0.003$, $p = 0.001$). This suggests that taking herbal prescriptions in accordance with the diagnosed pattern is more effective in improving functional impairments of acute ischemic stroke patients diagnosed as fire-heat pattern.

A type of herbal prescription is selected based on the clinical indicators a patient is showing, and when used, the herbal prescriptions are expected to alleviate the clinical symptoms. We used the probability of fire-heat pattern as a scale to evaluate the changes in the clinical symptoms of patients diagnosed as fire-heat pattern. As expected, the probability of fire-heat pattern decreased significantly in the correspondence group ($p = 0.013$) while there were no significant changes in the noncorrespondence group. Also, correlation study indicates that the patients with larger increment in the SSS score showed larger decrement in the probability of fire-heat pattern ($p = 0.027$). In our previous study concerning the treatment of acute ischemic stroke patients, motor function recovery in the patients correlated significantly with the improvement in the symptoms related to fire-heat pattern [15], which is consistent with the results of the present study. These results suggest that patients with improved functional impairments tend to show alleviation of clinical symptoms related to fire-heat pattern.

Usage of herbal prescriptions on acute ischemic stroke patients has been studied over the years [7–9], but no research was carried out to verify the necessity and usefulness of the pattern identification. Pattern identification is a meaningful diagnostic tool of TKM as it allows individualized treatment, maximizing its effectiveness and minimizing its adverse effects. We tried comparing the pattern-prescription corresponding group and noncorresponding group in our study in 2011, but the sample size was too small and the treatment period was too short, and the results showed no statistical significance [16]. This is the first study to evaluate the effectiveness of pattern identification in acute ischemic stroke patients diagnosed as fire-heat pattern.

Table 7: Changes of the pattern probabilities in the correspondence group and the noncorrespondence group before and after the treatment.

	Before	After	p value
Correspondence group ($n = 40$)			
Probability of fire-heat pattern	$62.6 \pm 39.3^{\dagger}$	51.1 ± 40.4	0.013^{*}
Probability of Yin Deficiency Pattern	9.8 ± 27.5	5.3 ± 17.9	0.337
Probability of Phlegm Dampness Pattern	6.2 ± 17.8	8.8 ± 16.9	0.149
Probability of Qi Deficiency Pattern	2.0 ± 10.3	3.6 ± 11.1	0.432
Noncorrespondence group ($n = 17$)			
Probability of fire-heat pattern	$49.5 \pm 37.0^{\dagger}$	43.8 ± 35.7	0.374
Probability of Yin Deficiency Pattern	23.9 ± 40.1	32.5 ± 45.4	0.646
Probability of Phlegm Dampness Pattern	22.0 ± 36.7	12.8 ± 31.3	0.182
Probability of Qi Deficiency Pattern	0.0 ± 0.1	11.0 ± 26.0	0.050

$^{*}p < 0.05$.

$^{\dagger}p < 0.05$, compared with the probability of other patterns in the same group.

We could not verify the effectiveness of pattern identification in patients diagnosed as Yin Deficiency Pattern, Phlegm Dampness Pattern, and Qi Deficiency Pattern, because they were not consistent in consuming the herbal prescriptions corresponding with their pattern and therefore were not suitable for the subjects of this study. This was not expected when we designed the study, but due to this outcome, the application of the results in the present study should be limited only in the patients diagnosed as fire-heat pattern. Another limitation is that the probability of pattern does not properly evaluate the severity of the clinical symptoms related to each pattern since the scale was made to determine the pattern not to assess the clinical indicators. We used the probability of patterns in this study because this scale was created based on the data collected using the same CRF and SOP used in the present study. There is no widely accepted scale assessing the severity of the symptoms related to pattern identification, and it should be developed in the future for more researches concerning pattern identification.

In the present study, correspondence group displayed better outcome than the noncorrespondence group, and in the correspondence group, patients with lesser clinical indicators related to fire-heat pattern after the treatment showed better improvement in the recovery of functional impairment. These results imply that herbal prescriptions in accordance with the diagnosed pattern alleviate the clinical symptoms in relation with the diagnosed pattern and are more effective in restoring the dysfunctions caused by the disease than the noncorresponding prescriptions. The results provide evidence for the necessity and usefulness of pattern identification in TKM, but further research is needed to confirm the effectiveness of pattern identification for the other pattern groups.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

A Retrospective Analysis of Patients' Conditions Using Acupuncture in a Traditional Korean Medicine Hospital

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Objective. The aim of this study was to identify the patient demographics, health issues, and type of acupuncture treatments who visited a traditional Korean medical hospital for acupuncture treatment. *Methods.* We retrospectively analysed the data using the electronic medical records (EMRs) of patients treated with at least one treatment of acupuncture from 1 January 2010 to December 2012 in the Chung-Ju Korean hospital at Semyung University. *Results.* The total number of identified patients was 1189 inpatients and 10138 outpatients. The 50–59 age group received acupuncture treatment in the hospital the most, followed by the 40–49 age group. Among the patients undergoing acupuncture treatment because of a diagnosis of pain, 82.74% were outpatients and 72.85% were inpatients. Additionally, all patients with a spine condition received acupuncture treatment. The most common musculoskeletal conditions of patients at the traditional Korean medicine (TKM) hospital were associated with spine conditions, such as low back pain and neck pain. Various treatments have been performed at the hospital in conjunction with acupuncture. The study results show a high prevalence of acupuncture treatment for diagnosed diseases. *Conclusion.* Our study suggests the need to investigate additional TKM hospitals to analyse characteristics of patients who received specific treatments. Analysis of the characteristics of patients treated with Korean acupuncture at the TKM hospital in this study will help future researchers who want to implement strong clinical evidence. However, we cannot completely discount all symptoms because of the retrospective nature of this study, and only one hospital was used, which limits the generalisation of our findings.

1. Introduction

Recently, the use of complementary and alternative medicine (CAM) has grown in popularity worldwide. A study showed that 38.3% of American adults and 52.2% of Australians use some form of CAM [1]. And various researches about CAM use, attitude, and awareness have been conducted. One study reported 6-year comparative economic evaluation of healthcare costs and mortality rates of Dutch patients from conventional and CAM GPs [2]. And one study revealed awareness, use, attitude, and perceived need for complementary and alternative medicine (CAM) education among undergraduate pharmacy students in Sierra Leone [3]. And another study studied CAM Use and Suggestions for Medical Care of Senior Citizens [4].

However, very little is known about the current state of clinical practice in detailed individual CAM treatment. CAM has many diverse treatment methods: acupuncture, moxibustion, cupping and herbal therapy, and so forth. Many traditional Korean medicine (TKM) hospitals use electronic medical records (EMRs), so information is available to analyse characteristics of patients who have received CAM treatment.

Acupuncture is a CAM technique that is used for treating a variety of conditions, especially pain conditions [5]. According to National Health Insurance data from Korea,

pain was the major reason for an annual acupuncture consultation [6]. In the US and UK, the most frequent CAM users were also patients who suffered from back pain or osteoarthritis [7]. A study showed that CAM utilisation is most strongly associated with musculoskeletal disorders [8].

Another study analysed EMR charts and showed that CAM usage was strongly associated with musculoskeletal disorders and pain conditions [9].

Therefore, the aim of this study was to provide information on the characteristics of patients who received acupuncture treatment in an academic hospital using a large sample size and long study duration (3 years).

2. Methods

2.1. Study Design. The medical records of patients treated with acupuncture who received at least one session of acupuncture at the Chung-Ju TKM hospital at Semyung University between 1 January 2010 and 31 December 2012 were retrospectively reviewed.

2.2. Data Sources. The information abstracted from EMRs included the age, gender, total number of outpatients and inpatients, total number of outpatient visits and admission days for inpatients, the name and frequency of diagnosis, frequencies of received acupuncture, and other ancillary interventions using a predefined excel spread sheet (Microsoft; Redmond, Washington, USA).

Diagnosis codes of symptoms were classified into 14 categories of major issues based on the site of symptoms to conduct a more clinically relevant analysis and better interpret the data. We used International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) as selecting method of patient records. Also, we measured the total costs of outpatient and inpatient management per patient.

2.3. Study Criteria. Patients who were treated as inpatients and outpatients at the TKM hospital were included.

The same patient could be duplicated because he or she could have been treated for new pains or discomforts. Therefore, if the same patient was treated for a different diagnosis code, we considered this case to be a new patient.

The exclusion criteria included the following: patients with full private insurance coverage, such as traffic accident patients, patients treated in an emergency room, patients who paid a discounted price because of a signed Memorandum of Understanding (MOU), and patients treated only by herbal medicine to promote health or physical therapy. We only used EMR data; therefore, the visit schedules of patients were not required.

2.4. Data Synthesis. A descriptive statistical analysis was conducted. Continuous data are presented as the means and SDs, and categorical data are presented as percentage and frequency. Continuous data with an asymmetrical distribution are presented as the medians and a percentile range (25th and 75th percentiles). In calculating the mean and SD of the number of sessions per patients, we divided the total sessions by the number of patients. The data were statistically analysed with SAS software, version 9.1.3 (SAS Institute Inc., Cary, NC).

Cost Analysis. We extracted data from the EMRs which are about patient-paid expenses for outpatient and inpatient care government-paid insurance reimbursements and per patient.

2.5. Ethical Considerations. An institutional review board at the Semyung University Chung-Ju TKM hospital approved this study (number 1310-06). IRB waived the receiving of informed consent of individual patients because the electronic records in this study were used anonymously.

3. Results

3.1. The Patient Demographics, Health Issues, and Type of Acupuncture Treatments Provided. The descriptive statistics for patient characteristics are listed in Table 1. The total number of patients was 11327. Of the patients identified, most patients visited the TKM hospital as outpatients (10138/11327, 89.5%). The total number of patients was 11327, including 10138 outpatients and 1189 inpatients. The mean patient age was 48.64 years among outpatients and 49.43 years among inpatients. The percentage of men was 53.82 in outpatient and 42.47 in inpatient. The percentage of women was 46.17 in outpatient and 57.52 in inpatient.

Regardless of inpatient or outpatient status, most patients were aged 40–59 years (outpatient 53.51% and inpatient 46.60%).

3.2. TKM Treatments. Diverse acupuncture styles were used, and patients were treated with multiple interventions. All patients (outpatients and inpatients) received manual stimulation of the needle ($n = 11327$; 100%). And electroacupuncture was used in 69.66% of outpatients and 34.15% of inpatients, and pharmacoacupuncture was used in 15.63% of outpatients and 40.79% of inpatients. Direct moxibustion was used in 0.49% of outpatients and 0.67% of inpatients, whereas indirect moxibustion was used in 2.17% of outpatients and 27.67% of inpatients.

In total, 10138 outpatients received 43767 acupuncture treatments. Acupuncture treatments were performed with an average of 4.32 times per patient. Manual acupuncture plus Infrared (98.57%) was the most used method, followed by electroacupuncture (69.66%), wet cupping (43.13%) and herbal medicine (21.02%).

Each inpatient received an average of 28.23 acupuncture treatments, and a total of 1189 inpatients received 33570 acupuncture treatments. Manual acupuncture plus cupping (77.71%) and herbal medicine (75.95%) were the most performed treatments, followed by Infrared (50.97%), pharmacoacupuncture (40.79%), and electroacupuncture (34.15%) (Table 2).

3.3. Medical Conditions. The diagnostic analysis of acupuncture treatments is shown in Table 3. Approximately 82.74% of

Table 1: Demographic characteristics of patients treated with TKM medical hospital from 2010 to 2012 (n = 11327).

Classification	Outpatients (N = 10138)		Inpatients (N = 1189)	
	n	%	n	%
Number of patients	10138	89.5	1189	10.49
Sex				
Male	5457	53.82	505	42.47
Female	4681	46.17	684	57.52
Mean age (years)*	48.64	14.71	49.43	16.99
Age group (years)	Male/female (n)	Male/female (%)	Male/female (n)	Male/female (%)
>30	568/471	5.6/4.6	75/79	6.3/6.6
30–39	970/569	9.6/5.6	115/69	9.7/5.8
40–49	1464/1162	14.4/11.5	124/153	10.4/12.9
50–59	1462/1337	14.4/13.2	110/167	9.3/14.0
60–69	610/6344	6.0/6.3	33/73	2.8/6.1
70–79	312/408	3.1/4.0	38/108	3.2/9.1
80<	71/100	0.7/1.0	10/35	0.8/2.9
Total	10138	100	1189	100

Values are provided as the * mean (SD) or n (%) where appropriate.

outpatients and 72.85% of inpatients receiving acupuncture treatment were diagnosed with pain. Additionally, all patients with spine condition received acupuncture treatment. The most treated conditions of outpatients were lower back pain (26.69%), neck pain (14.28%), and shoulder pain (11.67%).

The most treated conditions of inpatients were also lower back pain, miscellaneous (21.84%), and neck pain (14.55%). 5471 outpatients and 2556 inpatients had two different diagnosis codes (Table 3).

Medical Costs. The median total cost for outpatient and inpatient care per patient was 80,122 and 1,112,360 Korean Won (Table 4).

4. Discussion

The present study analysed patients who received acupuncture therapy at a TKM hospital by using EMRs. This result is also consistent with previous studies that showed low back pain and lumbar sprain as the most treated conditions in TKM hospitals or Korean clinics [9]. The Scottish Intercollegiate Guideline Network (SIGN) recommended acupuncture for the management of chronic pain with an "A" grade of recommendation. This recommendation means that acupuncture should be considered for short term relief of pain in patients with chronic low back pain [10].

This study revealed that both men and women aged 50–59 years visited the TKM hospital most frequently and men visited the TKM hospital slightly more than women. However, previous research has demonstrated that female patients use TKM hospitals more than men [9]. This difference may be because of regional differences between two hospitals. Additionally, pervious research has focused on a descriptive analysis of patients undergoing pain management, and this study focused on patients who wanted to receive acupuncture therapy.

Acupuncture is usually used in conjunction with various TKM interventions, including infrared, electroacupuncture, wet cupping, herbal medicine, and pharmacoacupuncture, in Korean clinics.

A high use of herbal medicine was observed in inpatient care, which suggests that herbal medicine may be regarded as an essential element of treatment in inpatient management.

The number of acupuncture treatments was high among inpatients compared with outpatients because of the severity of conditions. Among outpatients, the reason for the low proportion of direct and indirect moxibustion was the time limits of patients. The low usage of moxibustion in outpatients may be because of time limits as well.

The limitations of this study include the following. First, we collected all diagnoses of each patient. Therefore, chief complaints or the primary diagnosis of patients was not considered. Most patients had one or two diagnoses, but several had many diagnoses.

Additional information related to patient characteristics, such as pain duration or symptom severity or satisfaction of treatment and cure rate, could not be collected because of limited resources. Therefore, we only showed the characteristics of people who received acupuncture treatment; the results could not provide useful information.

Therefore, only descriptive data were available. Additionally, we could not extract the exact acupuncture points and techniques of ancillary treatments because these data were not extractable from the EMRs. However, we identified that acupuncture was treated with other interventions mostly, and also we identified the real cost of how much patients paid for CAM treatment. This paper will be helpful in the designing of clinical trials or cost effectiveness research. Although several limits exist, this study could be utilised in TKM research as a foundation to identify the characteristics of TKM.

In conclusion, our study suggests the need to investigate additional TKM hospitals to analyse characteristics of

Table 2: Total number and distribution of acupuncture treatment received for 3 years.

	Outpatients (N = 10138)			Inpatients (N = 1189)		
	Total sessions	Number of patients (%)	Mean sessions per patient*	Total sessions	Number of patients (%)	Mean sessions per patient*
Acupuncture						
Manual acupuncture	43767	10138 (100)	4.32 (7.87)	33570	1189 (100)	28.23 (35.24)
Electroacupuncture	30104	7062 (69.66)	4.26 (7.51)	3787	406 (34.15)	9.33 (14.56)
Pharmacoacupuncture	8793	1585 (15.63)	5.55 (9.71)	3308	485 (40.79)	6.82 (11.60)
Manual acupuncture plus cupping						
Wet cupping	16454	4373 (43.13)	3.76 (5.92)	9244	924 (77.71)	10.01 (9.73)
Dry cupping	50	11 (0.11)	4.55 (5.41)	198	20 (1.68)	9.90 (8.50)
Manual acupuncture plus moxibustion						
Direct mox.	315	50 (0.49)	6.30 (9.59)	58	8 (0.67)	7.25 (7.19)
Indirect mox.	822	220 (2.17)	3.74 (5.47)	4535	329 (27.67)	13.77 (17.08)
Manual acupuncture plus chuna	504	146 (1.44)	3.45 (3.95)	173	71 (5.97)	2.44 (2.04)
Manual acupuncture plus herb	65567	2131 (21.02)	30.77 (28.84)	37592	903 (75.95)	41.63 (51.17)
Manual acupuncture plus IR	45691	9993 (98.57)	4.27 (7.86)	3763	606 (50.97)	6.21 (10.72)

IR: Infrared, Values are presented as n (%) or mean (SD).

*Mean session = number of patients/total session.

Table 3: Classification of medical symptoms of patients in acupuncture treatment.

Diagnosis	Outpatients (N = 10138) n (%)	Inpatients (N = 1189) n (%)
Pain		
Spine pain (lumbar)	4166 (26.69)	1188 (31.72)
Spine pain (neck)	2229 (14.28)	545 (14.55)
Spine pain (back, thoracic, and rib)	426 (2.73)	133 (3.55)
Spine pain (etc.)	382 (2.45)	156 (4.17)
Shoulder pain	1822 (11.67)	185 (4.94)
Upper extremity pain (excluding shoulder)	1383 (8.86)	107 (2.86)
Pelvic pain	261 (1.67)	53 (1.41)
Hip/knee pain	909 (5.82)	156 (4.17)
Lower extremity pain	301 (1.93)	76 (2.03)
Ankle/foot pain	881 (5.65)	79 (2.11)
Multiple site pain	153 (0.98)	50 (1.34)
Other conditions		
Facial disease	653 (4.18)	135 (3.60)
Headache	358 (2.29)	64 (1.71)
Etc.	1685 (10.80)	818 (21.84)
Total	**15,609**	**3745**

Values are provided as n (%)
Patients received multiple treatments according to each symptom classification.

Table 4: Costs for the outpatient and inpatient care per patient for 3 years.

Medical costs (per patient)	Outpatients	Inpatients
Government-paid cost	29,620 KRW (16840, 62200)	602,690 KRW (282548, 1142094)
Patient-paid cost	41,806 KRW (22202, 132408)	455,074 KRW (130000, 1014330)
Total expenditure	**80,122 KRW (40992, 209428)**	**1,112,360 KRW (570287, 2080160)**

Data are presented as the medians and percentile ranges (the 25th and 75th percentiles). Exchange rate assumes that 1 £ is worth 1732 KRW.
KRW, Korean Won.

patients who received specific treatments. Analysis of the characteristics of patients treated with Korean acupuncture at the TKM hospital in this study will help future researchers who want to implement strong clinical evidence. However, we cannot completely discount all symptoms because of the retrospective nature of this study, and only one hospital was used, which limits the generalisation of our findings.

In the future, it has to be conducted in several hospitals and more researches of cost effectiveness or prospective observational study should be conducted.

Conflict of Interests

The authors have declared that no competing interests exist.

Authors' Contribution

Ju Ah Lee and Kyung-Jin Yun conceived and designed the experiments. Kyung-Jin Yun, Jiae Choi, and Cham-kyul Lee extracted the data. Mi Mi Ko and Jiae Choi analyzed the data. Ju Ah Lee, Kyung-Jin Yun, and Jiae Choi wrote the paper. Ju Ah Lee and Myeong Soo Lee revised the paper. Eun-Yong Lee monitored data collection. Kyung-Jin Yun and Ju Ah Lee equally contributed to the paper.

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