Original Article

An Apriori algorithm-based association rule analysis to identify acupoint combinations for treating uremic pruritus

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ABSTRACT

Objective: Uremic pruritus (UP) is a prevalent and troublesome condition affecting individuals with end-stage renal failure, which results in intense pruritus, depression, as well as poor quality of sleep, significantly impacting their quality of life. According to previous studies, acupuncture and acupoint stimulation have been shown to provide additional benefits in treating UP in dialysis patients. In addition, using acupoints combination may yield superior effectiveness compared to utilizing a singular acupoint. To investigate the potential correlations between acupoint combinations, an association-rule analysis was employed. **Materials and Methods:** Apriori algorithms stand out as highly potent techniques for identifying associations in databases; this study utilized an association rule mining to examine the association rules of key acupoint groupings that could be employed for treating UP. **Results:** The analysis utilized information derived from the meta-analysis encompassing 40 randomized controlled trials that used acupuncture to treat UP. In total, 64 acupoints were analyzed, and 71 association rules were found. The following acupoint combinations: Auricular shenmen (TF4), Quchi (LI11), and Geshu (BL17); Auricular heart (Extra14), Sanyinjiao (SP6), and Auricular lung (CO14); and Auricular heart (Extra14), Xuehai (SP10), and Auricular lung (CO14) showed the strongest associations. **Conclusion:** Acupoints involving Auricular shenmen (TF4), Quchi (LI11), Geshu (BL17), Auricular heart (Extra14), Sanyinjiao (SP6), Auricular lung (CO14), and Xuehai (SP10) can be regarded as the core combination of acupuncture points for managing UP.

KEYWORDS: *Acupoints combinations, Acupuncture, Apriori association rule, Chronic kidney disease, Uremic pruritus*

INTRODUCTION

*U*remic pruritus (UP) presents a challenging dermatological issue that impacts around 40% of dialysis patients. UP has the potential to cause depression, impair sleep quality, and adversely affect the overall quality of life for dialytic individuals [1,2]. The pathogenetic mechanisms of UP remain vague, while it is known to involve a complicated interaction between several factors, such as skin pruritogens, the nervous system, and the immune system [3]. There are various treatment options available for UP, including topical treatments such as emollients, steroids, and capsaicin, as well as phototherapy and systemic treatments, including opioid antagonists and agonists, antihistamines, mast cell stabilizers, and leukotriene receptor antagonists [3,4]. However, side effects of the treatments for UP have been reported, including anticholinergic effects from antihistamines [5], skin atrophy resulting from topical steroid use [6], and dizziness and somnolence associated with gabapentin [7]. Therefore, finding a safe and effective complementary treatment for UP is imperative.

Complementary alternative medicines, including Chinese herbal bath therapy and acupuncture, have been shown to have fewer adverse drug reactions compared with Western medicine [8]. In previous systematic reviews and randomized controlled trials (RCTs), acupoint stimulation techniques, such as acupuncture, acupressure [9-11], auricular acupressure [12], and transcutaneous electrical acupoint stimulation (TEAS) [13], have been identified as safe and effective alternative therapies for reducing the itching sensation. A possible mechanism of

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alleviating pruritus involves regulating mast cell degranulation, reduction of histamine release, and endogenous opiate-like substance stimulation [8,12]. The studies mentioned above have provided evidence of the efficacy of acupoint stimulation in UP treatment. Nevertheless, there is a lack of agreement on the established acupuncture points to be used or the optimal combinations of acupoints for treating UP.

Data mining is a new approach used across multiple fields to enhance the generation of research findings from large datasets [14]. The data mining method has been gradually utilized in Chinese medicine to establish principles for selecting and combining acupoints to treat abundant conditions such as asthma [15], insulin resistance [16], and amyotrophic lateral sclerosis [17]. Although clinical practice relies on the combination of acupoints, there are currently no established criteria for determining the essential combinations. Hence, an association rule analysis could prove valuable and feasible in identifying the fundamental rules leading to effective acupoint combinations. Apriori, an algorithm belonging to the category of association rule mining techniques, functions by detecting the presence of item sets within extensive databases and subsequently formulates corresponding association rules utilizing metrics such as support, lift, and confidence [18]. Due to the lack of research on the use of acupoint combinations and standardized criteria, this study used an Apriori association rule analysis utilized data derived from the meta-analysis encompassing 40 RCTs to explore potential core acupoint combinations that were utilized in acupuncture and related techniques to treat UP [11].

MATERIALS AND METHODS

Sources of data and criteria for selection

The analysis stemmed from a previous meta-analysis conducted previously on 40 RCTs examining the efficacy of acupuncture in treating UP [11]. Acupoints for acupuncture and associated manipulation (acupressure, acupoint thermal therapy, auricular acupressure, acupoint sticking therapy TEAS, or acupoint injection) were extracted from the included RCTs published between 2002 and 2022. In total, 2735 patients with UP undergoing dialysis were involved in the meta-analysis. Inclusion criteria included the existence of UP, the application of acupuncture techniques, and the availability of quantitative data concerning itching intensity. Overlapping data with small populations were excluded from this study.

Risk of bias evaluation

The methodological quality of the trials included in the meta-analysis was assessed using the Cochrane tool for assessing the risk of bias (RoB), version 2.0 [19]. The assessment conducted by the RoB 2.0 tool covered five aspects: randomization process, intended intervention, absence of outcome data, measurement of outcomes, and bias in selection. Overall bias was scored high, unclear, or low. A detailed description of this quality assessment has been provided previously [11].

Data analysis

An analysis using Apriori association rule was performed, and graphical representations were generated using R-Studio (Integrated Development Environment for R, version 1.2.5033, provided by RStudio, PBC, located in Boston, MA.) [20]. Previous data from the meta-analysis were classified into 40 columns, each representing a distinct acupuncture formula. The R package "arules" was employed to fit the data, and the R package "arulesViz" generated charts for visualization. Principally, the association rule generated by the Apriori algorithm consists of the antecedent and the consequent parts. The Apriori algorithm links the antecedent part of the items with the consequent part of the items by relying on the observation that these two parts tend to co-occur in the database.

Four prevalent metrics utilized to evaluate associations among items in an Apriori algorithm encompass support, confidence, expected confidence, and lift [14]. The frequency of a specific acupoint occurrence in different acupuncture formulas is defined as support. Confidence is the probability of the consequent item occurring, given the presence of the antecedent item. Expected confidence is a metric that calculates the probability of the consequent item appearing independently of the antecedent in a relationship. Expected confidence is determined by assessing the occurrences percentage where the consequent item is present. Lift is the value derived from dividing the confidence by the expected confidence. Lift indicates the probability of an upsurge in the consequent item when a specific antecedent item is present [14]. In this study, an analysis of the 71 association rules was performed, and the minimum criteria for inclusion were a support degree of at least 10% and a confidence level of at least 60%. The minimum criteria were applied to the metrics to filter out the less significant association rules, resulting in a dataset of 71 association rules. The association rules were arranged in descending order according to the values of the "lift" metric.

RESULTS

Characteristics of the study and assessment of risk of bias

Table 1 presents an overview of the characteristics and methodological features of the included studies. A detailed assessment of the RoB is provided in Supplementary Figure 1. After the RoB analysis, 35, 2, and 3 RCTs were assessed as having a high, unclear, and low RoB, respectively. Possible reasons for the RoB results include only 7 trials mentioned blinding of the outcome measurement, and clear randomization processes were only mentioned in 11 trials.

Distribution of the acupoints

This analysis identified a total of 64 acupoints according to the previous meta-analysis articles. Figure 1 illustrates the distribution frequency of the acupoints. The ten most frequently used acupuncture acupoints for treating UP were Quchi (LI11), Zusanli (ST36), Xuehai (SP10), Auricular Shenmen (TF4), Sanyinjiao (SP6), Auricular lung (CO14), Auricular Neifenmi (CO18), Auricular Pizhixia (AT4), Auricular kidney (CO10), and Hegu (LI4).

Association rule analysis of acupoint combinations' item sets using the apriori algorithm

Based on data from 40 RCTs, this study analyzed 71 association rules. A scatter plot was formed to illustrate

Table 1: Overview of the 40 randomized controlled trials incorporated in the meta-analysis assessing acupuncture interventions for uremic pruritus

Study (year)	Study type	Inclusion rule	Acupoints	Overall bias
Ardinata *et al*., 2021 [41]	RCT	HD	LI11	Low
Juan, 2021 [42]	RCT	HD	LI11	Unclear
Jiang *et al*., 2021 [43]	RCT	HD	LI4, LI11, ST36, SP6, SP10	High
Zhang, 2020 [44]	RCT	HD	LI11, SP10, SP6	High
Liu, 2018 [45]	RCT	HD	LI11, SP6	High
Nahidi *et al*., 2018 [46]	RCT	HD	LIV3, LI4, SP6, SP10	Low
Phan *et al*., 2018 [47]	RCT	HD	Quchi, LI11	Low
Chu *et al*., 2018 [31]	RCT	HD	DU20, LI4, LI11, SP6, SP10, ST36	High
Pu, 2017 [48]	RCT	HD	LI4, LI11, LU5 ST36	High
Chang *et al*., 2017 [49]	RCT	HD	BL17, GB31, LI11, ST36, SP10	High
Ono and Mukaino, 2015 [50]	RCT	HD	BL65, BL67, GB38, GB43, HT7, HT9, KI1, KI7, LU5, LU9, LI2, LI11, LR2, LR8, PC7, PC9, SI3, SI8, SP2, SP5, ST41, ST45, TE3, TE10	High
Ma *et al*., 2014 [51]	RCT	HD	SP10, LI4	High
Chang *et al*., 2011 [52]	RCT	HD	BL17, LU5, LI4, LI11, SP10, ST36	High
Chou *et al*., 2005 [53]	RCT	HD	LI11, ST36, SP6, SP10	High
Ruei *et al*., 2002 [54]	RCT	HD	LI11, ST36, SP6, SP10	High
Kao *et al*., 2002 [55]	RCT	HD	LI11, ST36	High
Mai, 2021 [56]	RCT	HD	Endocrine, heart, lung, SF1.2i	High
Yan *et al*., 2021 [57]	RCT	HD	Endocrine, heart, lung, subcortical, shenmen	High
Yu *et al*., 2021 [58]	RCT	HD	Adrenal gland, endocrine, large intestine, lung, shenmen, occiput	High
Zhai, 2021 [59]	RCT	HD	Kidney, stomach, spleen, subcortical, sympathy, shenmen	High
Chen *et al*., 2020 [60]	RCT	HD	Kidney, stomach, spleen, subcortical, sympathy, shenmen	High
Yan *et al*., 2020 [61]	RCT	HD	Endocrine, heart, kidney, lung, shenmen, subcortical	High
Ding *et al*., 2019 [32]	RCT	PD	Endocrine, heart, kidney, lung, shenmen, subcortical	High
He *et al*., 2018 [62]	RCT	HD	Lung, endocrine, adrenal gland	High
Lin, 2018 [63]	RCT	CKD	Adrenal supracortical, endocrine, lung, spleen, stomach, sympathy, wheel area	High
Li and Ma, 2017 [64]	RCT	HD	AT2.3.4i, bladder, HX1, HX6.7i, kidney, lung, heart, liver, spleen, sanjiao, shenmen, SF1.2i	High
Tao, 2016 [65]	RCT	HD	Kidney, Spleen, Stomach, Sympathy, Subcortical, Shenmen	High
Yan *et al*., 2015 [12]	RCT	HD	Shenmen, Kidney, Lung, Endocrine, Subcortical	High
Shr *et al*., 2012 [66]	RCT	HD	Kidney, Lung, Heart, Liver, Spleen, Sanjiao Bladder, Shenmen, HX1, HX6.7i, SF1.2i, AT2.3.4i	High
Hsu *et al*., 2009 [67]	RCT	HD	SP6	High
Wang *et al*., 2021 [68]	RCT	HD	LI11, ST36	High
Deng, 2017 [69]	RCT	HD	LI11, SP10, ST36	High
Wang *et al*., 2004 [70]	RCT	HD	BL17, BI23, EM40, GB31, LI4, LI11, SP6, SP9, SP10, ST36	High
Chen *et al*., 2017 [71]	RCT	HD	DU14, DU23, EM1, EM2, GB20, HT7, LI4, LI11, PC4, ST36, SP6, SP10	High
Yi and Zheng, 2018 [72]	RCT	HD	LI11, SP6, SP10	High
Chen, 2021 [73]	RCT	High-flux HD	LI11	High
Karjalian *et al*., 2020 [37]	RCT	HD	LI11, ST36, SP6, SP10	Unclear
Kılıç Akça and Taşcı, 2016 [13]	RCT	HD	LI11	High
Jedras *et al*., 2003 [74]	RCT	HD	140 acupoints (20 each on the head, hands, trunk, legs)	High
Jiu *et al*., 2015 [75]	RCT	HD	Umbilicus	High

RCT: Randomized controlled trial, CKD: Chronic kidney disease, PD: Peritoneal dialysis, HD: Hemodialysis

the association rules, featuring support values along the x-axis and confidence values along the y-axis. The lift value determined the color of each association rule on the plot, as shown in Figure 2. The results disclosed that each association rule exhibited a notably high lift, indicating a substantially increased likelihood of acupoint combinations co-occurring in association rules compared to the occurrence of a single acupoint. The association rules demonstrated a confidence value of one for all cases, indicating that whenever an antecedent acupoint was present in an acupuncture treatment, the consequent acupoint appeared together. Figure 2 illustrates overlaps among the 71 association rules, presented on both the left and right sides of the figure. However, based on the support values, the antecedent acupoint within each association rule exhibited limited frequency across the 71 formulas, indicating that each formula employed for UP treatment operated independently. Table 2 presents the top ten association rules of the acupoints generated using the Apriori algorithm, ordered based on their lift values.

Figure 3 displays a matrix diagram that depicts the distribution of grouped association rules. The diagram revealed
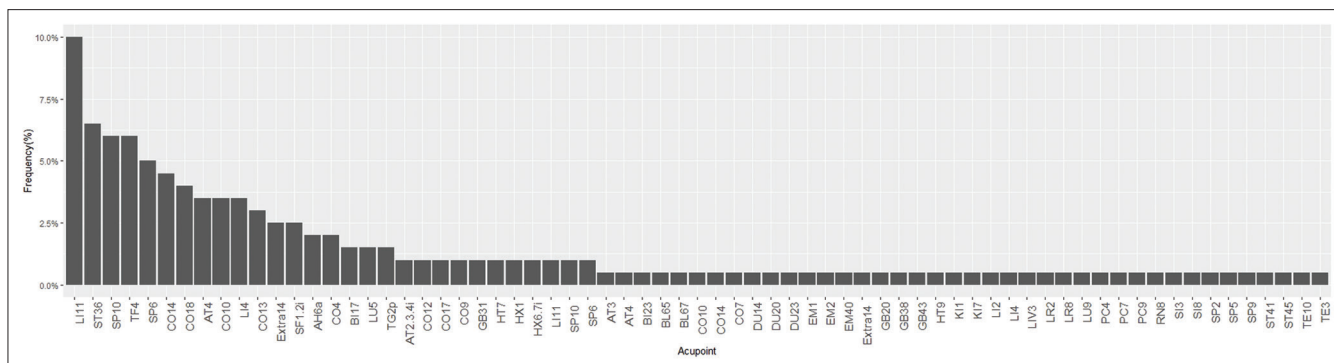
Figure 1: The frequency distribution of acupoints utilized in the meta-analysis encompassing 40 randomized controlled trials on acupuncture treatments for uremic pruritus
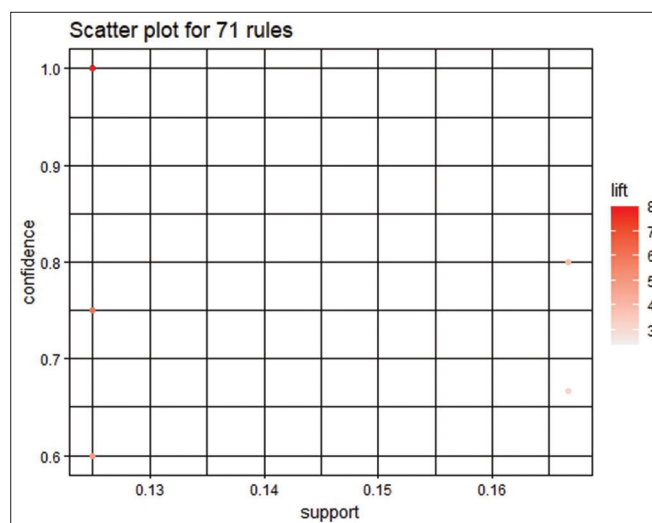

Figure 2: A scatter plot illustrating the 71 association rules derived from the meta-analysis of 40 randomized controlled trials on acupuncture treatments for uremic pruritus

Table 2: Association rules based on the Apriori algorithm for the acupoints utilized in the 40 randomized controlled trials incorporated in the meta-analysis assessing acupuncture interventions for uremic pruritus

Number	Association rules	Support	Confidence	Expected confidence	Lift
1	(CO14)≥(Extra14)	0.125	1.000000	0.125	8.0
2	(Extra14)≥(CO14)	0.125	1.000000	0.125	8.0
3	(BL17)≥(LI11)	0.125	1.000000	0.125	4.8
4	(AH6a)≥(LI11)	0.125	1.000000	0.125	4.8
5	(LU5)≥(LI4)	0.125	1.000000	0.125	4.8
6	(LU5)≥(LI11)	0.125	1.000000	0.125	4.8
7	(CO14)≥(SP6)	0.125	1.000000	0.125	4.8
8	(Extra14)≥(SP6)	0.125	1.000000	0.125	4.8
9	(TG2p)≥(TF4)	0.125	1.000000	0.125	4.0
10	(BL17)≥(TF4)	0.125	1.000000	0.125	4.0

that the association rules were grouped similarly into clusters. The 20 clusters are represented on the horizontal axis, and the items generated by these clusters are represented on the vertical axis. The intensity of color within individual circles corresponds to the magnitude of lift, with darker colors indicating higher lift degrees. The circle size represents the support degree, with larger circles indicating higher support degrees. The acupoint combinations (Auricular shenmen [TF4], Quchi [LI11]) ≥ (Geshu [BL17]), (Auricular heart [Extra14], Sanyinjiao [SP6]) ≥ (Auricular lung [CO14]), (Auricular lung [CO14], Sanyinjiao [SP6]) ≥ (Auricular heart [Extra14]), (Auricular heart [Extra14], Xuehai [SP10]) ≥ (Auricular lung [CO14]), and (Auricular lung [CO14], Xuehai [SP10]) ≥ (Auricular heart [Extra14]) were selected to pair with association rules, items range from the antecedent (left-hand side, LHS) to the consequent (right-hand side, RHS) item sets. The acupoint combinations corresponded with association rules #1 (Auricular lung [CO14]) ≥ (Auricular heart [Extra14]), #2 (Auricular heart [Extra14]) ≥ (Auricular lung [CO14]), #3 (Geshu [BL17]) ≥ (Quchi [LI11]), #7 (Auricular lung [CO14]) ≥ (Sanyinjiao [SP6]), #8 (Auricular heart [Extra14]) ≥ (Sanyinjiao [SP6]), and #10 (Geshu [BL17]) ≥ (Auricular shenmen [TF4]), as shown in Table 2.

Figure 4 displays a combination matrix diagram that visually depicts the connections of the association rules derived from the data presented as shown in Figure 3. The locations of the core acupoints are marked in Figure 5.

Discussion

Acupoint stimulation has been shown to play a significant role in improving UP, according to the meta-analysis from which this study was derived [11]. In addition, this study revealed the three core combinations of acupoint stimulations commonly used to treat UP: (Auricular shenmen [TF4], Quchi [LI11] and Geshu [BL17]), (Auricular heart [Extra14], Sanyinjiao [SP6] and Auricular lung [CO14]), and (Auricular heart [Extra14], Xuehai [SP10], and Auricular lung [CO14]). This study appears to be the first to study the potential core acupoint combinations used in acupuncture and related techniques to treat UP.

Previous studies have documented the mechanisms of acupuncture and related techniques, including acupressure, TEAS, and auricular acupressure for treating pruritus [21]. Tang *et al*. found that acupuncture could alleviate acute itchiness through the downregulation of 5-HT, blocking its receptor expression, and electroacupuncture may relieve chronic itching by regulating cytokine and opioid peptide receptor activities [22]. Auricular acupressure has been reported to alleviate UP by reducing histamine levels [12],
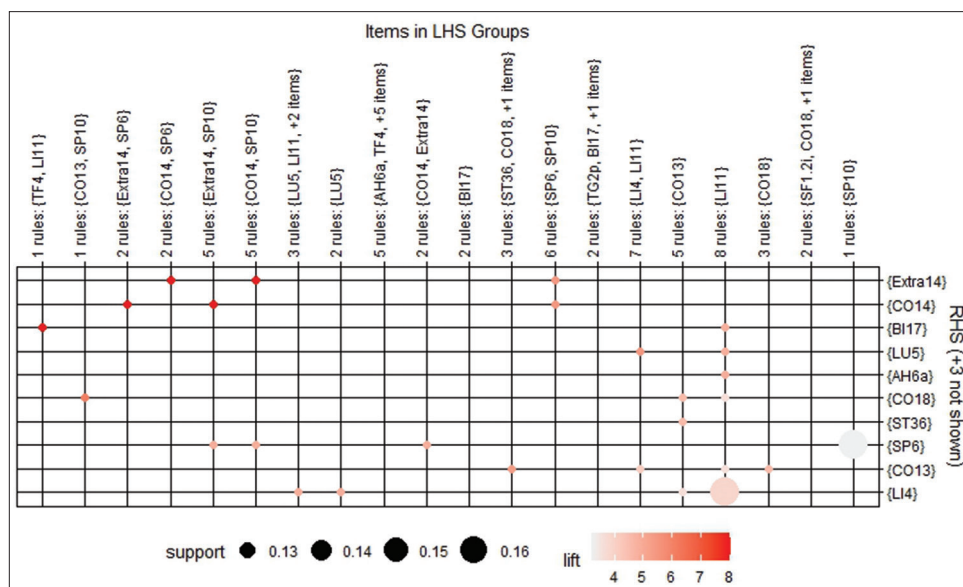
Figure 3: A grouping matrix displaying the association rules derived from the meta-analysis of 40 randomized controlled trials on acupuncture treatments for uremic pruritus
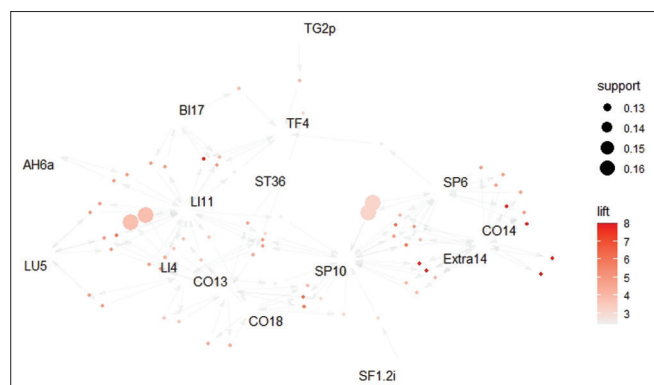

Figure 4: Matrix of combinations illustrating the association rules derived from the meta-analysis of 40 randomized controlled trials investigating acupuncture treatments for uremic pruritus
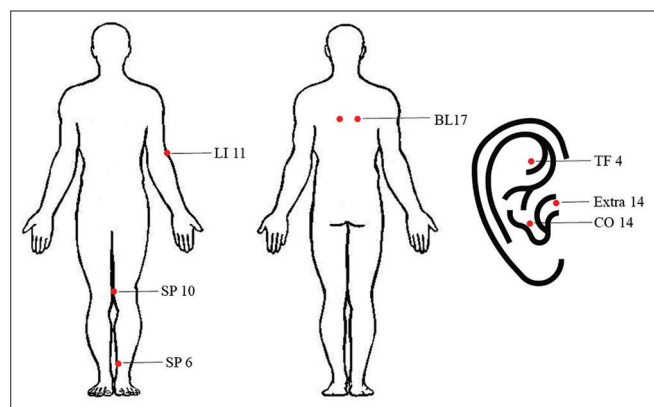

Figure 5: The site of the core acupoints is determined from the association rules obtained in the meta-analysis of 40 randomized controlled trials on acupuncture treatments for uremic pruritus

activating the nociceptor and central analgesic systems [23], and regulating the proportion of T lymphocyte subsets [24]. An RCT conducted by Kılıç Akça and Taşcı reported that acupressure and TEAS had anti-pruritus effects on

dialysis patients according to the reduction in the level of antihistaminic agents [13].

In accordance with the theory of Chinese medicine that "lungs control the skin" the physiology includes regulating the mucosa immune system and activating skin-associated lymphoid tissues, such as immune cells in the epidermis and dermis [25]. According to the theory, "all pains and pruritus belong to the heart" it is believed that the heart controls blood vessels and blood syndromes [26]. The moisture from blood can help alleviate pruritus by nourishing the skin [26]. In addition, the theory "Blood confluence to Geshu (BL17)" indicates the significance of regulating blood circulation by acupoint Geshu stimulation [27]. These theories and mechanisms might explain how the core acupoint combinations with Auricular lung (CO14), Auricular heart (Extra14), Xuehai (SP10), and Geshu (BL17) have shown promising results in effectively alleviating the itching sensation experienced by dialysis patients. Compared to non-UP patients, UP patients exhibit higher levels of P, iPTH, and inflammatory indices [28]. Augmentation of peripheral nerve stimulation can result from elevated levels of calcium and phosphate [29]. PTH is linked to the activation of mast cells, inducing the release of histamine and provoking itching [30]. Our study demonstrated TF4, CO14, LI11, BL17, Extra14, SP6, and SP10 as the core acupoint combination for treating UP.

Three acupoints (SP10, SP6, and LI11) identified in our study were shown to improve UP symptoms and decrease the levels of phosphorus, PTH, and β2-MG of the UP patients by Chu *et al*. [31]. The other four acupoints (CO10, CO14, Extra14, and TF4) mentioned in our study were reported to improve UP symptoms and decrease the levels of phosphorus and PTH of the UP patients by Ding *et al*. [32]. Besides the aforementioned clinical trials, the acupoint (LI11), identified in our study, alleviated pruritus, restlessness, and sleep onset difficulties in a case series of 40 patients with UP underwent dialysis therapy [33]. In another case series treating 8

Table 3: The potential effectiveness of acupuncture's core acupoints in treating uremic pruritus

Point	Chinese name	English name	Primary meridians	Effectiveness
TF4 [76]	Er shenmen	Auricular shenmen	Nil	Increasing vagal tone, regulating systematic functioning, and reducing inflammation
LI11 [53]	Quchi	Crooked Pond	Large Intestine	Stimulating opiate-like substances release which blocks the slower C fiber impulses
BL17 [77]	Geshu	Diaphragm's Hollow	Bladder	Nourishing blood and stopping itching sensation
Extra14 [78]	Xinzang	Auricular Heart	Nil	Nourishing blood to alleviate itching sensation, all pains, and pruritus belong to the heart
SP6 [77]	Sanyinjiao	Three Yin Meeting	Spleen	Promoting blood circulation and intensifying the blood activation sensation
CO14 [79]	Fei	Auricular Lung	Nil	Dispel wind-heat toxin to alleviate the itching sensation and lung control for the skin and hair
SP10 [77]	Xuehai	Sea of Blood	Spleen	Nourishing blood and stopping the itching sensation

individuals, Shapiro *et al.* employed acupoints LI11, ST36, SP6, and SP10, demonstrating effective outcomes for UP [34] and three of the acupoints (LI11, SP6, and SP10) coincided with the acupoint combination we have identified.

The results had similar findings to previous studies on acupoints, which demonstrated that the combination of Geshu (BL17), auricular point Ear shenmen (TF4), and Auricular lung (CO14) effectively reduced immunoglobulin E and interleukin-4 serum levels and enhanced the quality of life of patients with urticaria [35]. In addition, acupuncture of the Auricular lung (CO14) combined with the Auricular heart (Extra14) affected urticaria and alleviated pruritus [36]. Karjalian *et al.* reported that the application of acupressure on Sanyinjiao (SP6), Xuehai (SP10), and Quchi (LI11) resulted in the alleviation of UP in dialysis patients by reducing serum phosphorus and parathyroid hormone levels [37], as shown in Table 3.

Previous studies have disclosed that multi-point acupuncture was more effective than single-point acupuncture in treating primary insomnia [38] and dysmenorrhea [39]. Zhang *et al.* observed more brain activity regions after multi-point acupuncture compared with single-point acupuncture. This outcome could be attributed to the synergistic effect of multiple acupoints [40]. Nonetheless, there is limited supporting evidence of acupoint stimulation without the standard treatment for UP [8]. Therefore, it is crucial to employ data-mining techniques to identify the essential combinations of acupoints for the treatment of UP.

Despite identifying potential core acupoints for acupuncture and related techniques for treating UP, limitations exist within this study. First, the RCTs exhibit a high RoB might be related to the non-blinding outcome measurements and randomization processes. To address this, future studies should provide more detailed descriptions of their randomization procedures. Second, there is still limited information available regarding the mechanism of individual acupoints and their interactions. Finally, the analysis was limited by the small, regionally focused population and restricted by the prescription of acupoint combinations. Therefore, it is recommended that future studies should include a more diverse population and acupoint combinations.

CONCLUSION

The identified acupoint combinations for treating UP by acupuncture and related techniques were #1 Auricular shenmen (TF4), Quchi (LI11), and Geshu (BL17); #2 Auricular heart (Extra14), Sanyinjiao (SP6), and Auricular lung (CO14); and #3 Auricular heart (Extra14), Xuehai (SP10), and Auricular lung (CO14). An Apriori association rule and the observed effectiveness were used to identify core treatment approaches for UP. However, further studies are needed to investigate the interactions between acupoints and the underlying mechanisms of efficacy.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Figure 1: Risk of bias in the selected studies