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SPECIALTY SECTION This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 03 September 2022 ACCEPTED 14 October 2022 PUBLISHED 01 December 2022

#### CITATION

Lu P-H, Chung C-H, Chuo H-E, Lin I-H and Lu P-H (2022) Efficacy of acupoint stimulation as a treatment for uremic pruritus: A systematic review and meta-analysis. *Front. Med.* 9:1036072. doi: 10.3389/fmed.2022.1036072

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# Efficacy of acupoint stimulation as a treatment for uremic pruritus: A systematic review and meta-analysis

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**Background:** Uremic pruritus causes sleep disturbances, poor quality of life, and increased morbidity in patients with chronic kidney disease. Acupuncture has been shown to improve uremic pruritus. There is limited evidence of the efficacy of traditional Chinese therapies. We conducted a systematic review and meta-analysis to evaluate the efficacy of acupoint stimulation therapy in patients with uremic pruritus.

**Methods:** A systematic search of seven databases (up to Sep 2022) was conducted for randomized controlled trials that evaluated the clinical efficacy of acupuncture, acupressure, auricular acupressure, acupoint injection, acupoint thermal therapy, acupoint sticking therapy, or transcutaneous electrical acupoint stimulation in the treatment of patients with uremic pruritus. Two reviewers selected eligible articles for inclusion in the meta-analysis and evaluated the risk of bias *via* Cochrane Collaboration. The results of pruritus assessments and uremic pruritus-related laboratory parameters were analyzed.

**Results:** Forty trials published between 2002 and 2022, including a total of 2,735 participants, were identified for inclusion in the meta-analysis. The effective rates for acupuncture, auricular acupressure, and the combination of acupoint injection and acupoint massage were significantly greater in patients with uremic pruritus compared to the control group. The levels of serum BUN, PTH, and histamine levels were significantly lower vs. control group.

**Conclusions:** Acupuncture, auricular acupressure, and the combination of acupoint injection and acupoint massage seem to be effective in improving uremic pruritus in patients with chronic kidney disease. However, further investigation of these potential treatments is now warranted in larger patient populations and over a longer time frame.

Systematic review registration: https://www.crd.york.ac.uk/prospero/ display\_record.php?ID=CRD42022354585, identifier: PROSPERO CRD42022354585.

#### KEYWORDS

acupoint injection, acupressure, acupuncture, chronic kidney disease, uremic pruritus

## Introduction

Uremic pruritus (UP) is a common cutaneous change that occurs in about 55% of patients with chronic kidney disease (CKD) who are undergoing dialysis (1). The manifestation of UP varies in severity, distribution, and duration, and UP can cause sleep disturbances, depressive symptoms, qualityof-life deterioration, and increased morbidity (2). Several pathophysiologic mechanisms and factors may be involved in UP, including inflammation, high serum calcium concentration, and histamine-dependent or non-histaminergic pruritogens, such as proteases, opioids, and substance P (3). Markers of dialysis inefficiency and mineral metabolism [e.g., high levels of phosphate, calcium, parathyroid hormone (PTH), and intact parathyroid hormone (iPTH)] may be associated with an increased risk of UP (4), for which treatments include topical, systemic, and immunomodulatory therapies (2); however, some UP patients remain refractory to traditional treatments (5).

Many complementary therapies have been evaluated in patients with UP, but with variable efficacy (5). Recently, traditional Chinese therapeutic methods, namely acupuncture, auricular acupressure (AA), acupoint massage (AM), acupoint injection (AI), and acupoint thermal therapy (ATT), demonstrated benefits in patients with UP. The benefit of acupuncture may be due to increased levels of anti-inflammatory cytokines, resulting from an altered type 1 to type 2 T-helper cell balance (6). Moreover, stimulation of Quchi (LI11) significantly reduced pruritus in patients with UP (7).

AI of autologous serum stimulates a non-specific immune response and decreases sensitivity to pruritus (8). Other medications, such as antihistamines, Gastrodin, Angelica, and Salvia, have also been administered as injections. For ATT, local acupoint infrared (AIR) radiation can improve nerve sensitivity and promote peripheral blood circulation, which may help patients with UP (9). Transdermal therapeutic administration of Chinese medicines at acupoints has also ameliorated pruritus (7).

Increased the number of the mast cells is one etiology for UP (7). Mast cells degranulation could release inflammatory markers such as histamine, tumor necrosis factors, and IL-6 (10). The activation of acupressure at LI11 can destroy mast cell which releasing inflammatory markers that might be the one etiology for UP and improve pruritus (7). Electroacupuncture (EA) at ST36 suppressing the activation of mast cells, leading to decrease of nerve growth factor (NGF) and tropomyosin receptor kinase A (TrkA) proteins (6). Acupuncture at ST36 can stimulate mast cell degranulation within the acupoint area and increase pain threshold (11). Interestingly, AA affects different parts of the body, by reconditioning the meridians, and is more easily accepted by

patients (12). Transcutaneous electrical acupoint stimulation (TEAS) can also decrease the severity of UP (13), and the efficacy of TEAS is not statistically significantly different from that of acupressure (14). The combination of AI with acupressure (AI+A) is used to affect the endogenous opioid system, which might decrease anxiety and insomnia caused by pruritus (15).

To explore alternative treatments for UP, we performed a systematic review of several complementary therapies: acupuncture, AA, AM, AI, ATT, acupoint sticking therapy (AST), and TEAS.

## Methods

## Search strategy

We searched for articles published before 29 Sep 2022 from PubMed, Embase, CINAHL, Cochrane Library, China National Knowledge Infrastructure, Airiti Library, and Wanfang databases. The search string used was based on PubMed medical subject headings and Embase subject headings (Emtree): (chronic kidney disease OR kidney injury OR kidney failure OR chronic renal failure OR end-stage renal disease OR end stage renal disease OR dialysis OR hemodialysis OR peritoneal dialysis) OR (uremic OR uremia OR uremias) AND (pruritus OR itch OR xerosis OR skin problems OR skin disorders) AND (acupuncture OR acupressure OR Shiatsu OR Zhi Ya OR Chih Ya OR Shiatzu OR auricular acupuncture OR ear acupuncture OR auricular acupressure OR ear acupressure OR auricular therapy OR auriculotherapy OR auricular needle OR otopoint OR otoneedle OR auriculoacupuncture OR otopuncture OR acupressure point OR acupoints OR Tui Na).

We also searched for word combinations and free-text phrases containing the terms above and extended the search using the "related articles" function in PubMed. Further, all the retrieved abstracts, studies, and citations were reviewed. Finally, unpublished studies were obtained from the ClinicalTrials.gov registry (16). There were no language restrictions in the search. This systematic review and meta-analysis were registered online with PROSPERO, the international prospective register of systematic reviews of the National Institute for Health Research (ID: CRD42022354585) (17). The search protocol is attached in Supplementary material.

## Study selection

Randomized controlled trials (RCTs) were chosen to assess the efficacy of acupuncture, AA, AM, acupoint far infrared (AFIR), AI, AIR, AST, acupoint ion implantation, and transcutaneous electrical acupoint stimulation (TEAS) in the treatment of patients with UP. The inclusion criteria were: chronic kidney disease under dialysis; the presence of UP; administration of a specified treatment; and the availability of quantitative data for itch severity. If necessary, we contacted study authors for original or missing data. For studies with overlapping data, we selected those with the largest populations to exclude duplicate articles.

#### Data extraction and quality assessment

Two reviewers independently screened the articles and extracted the following information: first author; publication date; participant characteristics; study design; inclusion, exclusion, and matching criteria; AA, AM, AFIR, AI, AIR, AST, or ATENS therapy; and quantitative data for itch severity. In line with the inclusion criteria, the two reviewers assessed the chosen articles for eligibility, and the reviewers' comments were recorded and compared. Any disagreements were submitted to, and reviewed by, a third investigator. Further, we performed a quality assessment of the studies using the "risk of bias" tool recommended by the Cochrane Collaboration (18). Several domains were evaluated, including method of allocation, blinding of participants and investigators, the integrity of outcome data, selective reporting, and other kinds of bias.

## Risk of bias assessment

#### Randomization bias

All 40 studies were RCTs: 10 studies provided no information about randomization; whereas 16 studies described the methods of randomization (nine studies used tables of random numbers, eight used random number generators, one used the drawing of lots, one used blocked randomization, and one study used chart numbers) (Figure 1).

#### Blinding

Seven studies were double-blind, and 33 studies were unblinded.

### Incomplete outcome data

Eleven studies failed to use intention-to-treat analysis. The rate of loss to follow-up was low for most studies, although 10 studies had a dropout rate of more than 5%. Ten studies were also missing more than 5% of the outcome data and lacked evidence to support that data consistency was maintained despite the missing data. Six studies had other reasons for missing data, and 4 failed to report the reason for missing data.



FIGURE 1

Flowchart showing the selection process for the studies included.

## Data synthesis and analysis

We presented outcomes of the following tools for pruritus assessment to evaluate the efficacy of our chosen complementary therapies: visual analog scale (VAS) and numeric rating scale (NRS; 0-10 points for each scale); 5-dimensional itch scale (5DIS: 5-25 points, and comprising dimensions of degree, duration, direction, disability, and distribution of itching, with 1-5 points for each dimension); the modified Duo's pruritus score (mDuo; 0-40 points); four-item itch questionnaire [FIIQ; evaluations of pruritus localization (1-3 points), severity (1-5 points), frequency (1-5 points), and sleep disturbances due to itching (0-6 points); total 3-19 points]; Pauli-Magnus scale (PMS; 3-45 points); and Dirk R Kuypers score (DRKS; 27 points); Traditional Chinese medicine symptom scale, UP questionnaire, 12-Item Pruritus Severity Scale (12-PSS; 3-22) (19) and Serjip score (Assessment of severity and burden of pruritus) (20).

The statistical package Review Manager (version 5; Cochrane Collaboration, Oxford, England) was used for data analysis. A meta-analysis was conducted based on recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Standard deviations (SDs) were calculated from the provided confidence interval (CI) limits, standard errors, or ranges when necessary. We obtained the mean and SD from studies using the mean difference (MD) or standardized mean difference (SMD) with 95% CIs for continuous outcomes. The random-effects model was applied to pool estimates of SDs and SMDs, considering the diversity of pruritus assessment tools and possible heterogeneity across the trials. We considered heterogeneity in the studies by performing the  $I^2$  test and a null hypothesis test, in which p<0.05 confirmed significant heterogeneity among the outcomes. The Guideline Development Tool developed by the Grading of Recommendations Assessment, Development and Evaluation Working Group was applied to assign the quality of the evidence (21). All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

# Results

## Literature search

The selected studies were all RCTs from 2002 to 2022. A total of 2,735 patients were enrolled in the 36 studies (Figure 2). In total, we filtered out 847 citations: 62 duplicate articles, and 51 articles due to other reasons, were removed by EndNote and the reviewers; further, 734 articles were excluded following the screening criteria for titles and abstracts. We retrieved the full texts of the remaining 102 articles. After assessing for eligibility,

we excluded 62 papers because 15 were reviews, 17 papers were studies conducted in patients undergoing treatments other than our chosen interventions, 18 papers were non-randomized studies, 2 papers did not focus on UP, 3 papers were conference abstracts, 6 papers were presented in the protocol, and 1 paper had incomplete data. After screening, 40 articles fulfilled the selection criteria and were included in the meta-analysis.

### Study characteristics

Data for treatment frequency, duration, acupoint, the pruritus severity assessment tool, corresponding results, and follow-up duration are shown in Table 1. There were 16 studies in the acupuncture group, 13 studies in the AA group, 4 studies in the AM group, 1 study in the AI group, 1 study in the AST group, 1 study in the AFIR group, and 1 study in the ATENS group. There were 3 studies of combination therapies: two of AI+acupuncture; and one of AI+AM. Thirteen studies reported effective rates. Twenty studies reported pruritic scores including data on the VAS, mDuo, 5DIS, NRS, PMS, traditional Chinese medicine (TCM) symptom score, FIIQ, Serjip score, UP questionnaire, and DRKS.

All studies included patients with UP and CKD: in 38 studies, patients received regular hemodialysis, while in the Ding et al. and Chen et al. studies, patients underwent peritoneal dialysis and nocturnal dialysis, respectively (41, 43). There were 16 studies on acupuncture. The treatment frequency was about two to three times per week. The most common acupoint choices were Xuehai (SP10, 9 studies), LI11 (7 studies), Sanyinjiao (SP6), and Zusanli (ST36, each of these acupoints used in 7 studies). Chang et al. added citrate dialysate as UP therapy and the result revealed improved pruritus (31).

There were 13 studies of AA, and the treatment frequency was about three to eight times per day. The meridian in these studies included lung, kidney, heart, stomach, endocrine, subcortical, supracortical, adrenal, and Shenmen (TF4). Chen et al. also compared nocturnal dialysis with hemodialysis (41), and Lin et al. compared the efficacy of AA, fumigation, and the combination of AA+fumigation therapy (45), and Yu et al. used copper scraping therapy at auricular acupoint (35).

There was one study of AFIR, and the treatment frequency was once per day, on 2 days each week. The acupoint used for AFIR was SP6. There was one study of AI, for which the treatment frequency was twice per week. Wang et al. used gabapentin as a control arm, and the acupoints used were LI11 and ST36 (50). There was one study of AIR, in which the treatment frequency was twice per week, and in which the acupoints used were LI11, SP6, and SP10. There were four studies of AM, with a treatment frequency of three times per week, and with acupoints of SP6, SP10, ST36, and LI11. Chen et al. compared high-flux HD with AM+high flux HD in 12-PSS score (54). There was one study of AST, in which the treatment



frequency was once every 2 days: that is, Jiu et al. used Di Fu Zi, Tu Si Zi, Mud An Pi, and Tao Ren as TCMs in sticking therapy applied at the umbilicus (56).

Four studies evaluated complementary-therapy combinations: AI+A (n = 2), AI+AM (n = 1), and AM+TEAS (n = 1). Deng et al. assessed AI+A with cetirizine and treated patients twice each week; the acupoints used were LI11, ST36, and SP10 (51). Wang et al. assessed AI+AM twice each week, or three times every 2 weeks; the acupoints used were Jianneiling (EM40), Fengshi (GB31), Hegu (LI4), LI11, ST36, SP6, Yinlingquan (SP9), and SP10 for AM, and Geshu (BI17) and Shenshu (BI23) for AI (52). Chen et al. evaluated AI+AM two to three times per week to treat UP; the acupoints used for AI were LI11 and ST36, and those used for AM were Dazhu (DU14), Shangxing (DU23), Sishencong (EM1), Yintang (EM2),

Shenmen (HT7), Fengchi (GB20), LI4, SP6, SP10, and Ximen (PC4) (53).

### Pruritus assessments

#### Visual analog scale (VAS) score

Meta-analysis of the 15 studies with VAS score assessments (Figure 3A) showed statistically significant experimentalcontrol group improvements in VAS score for acupuncture (MD -2.58; 95% CI: 4.29, -0.87; p = 0.003), AA (MD -1.53; 95% CI: -1.82, -1.24; p < 0.00001), AI (MD -1.03; 95% CI: -1.54, -0.52; p < 0.0001), AI+AM (MD -2.04; 95% CI: -2.73, -1.35; p < 0.00001), AIR (MD -1.85; 95% CI: -3.42, -0.28; p = 0.02), AM (MD -1.72; 95% CI: -2.83, -0.61; p = 0.002),

Study (year)	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	(route, dosage, and	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	Effective rate l	Follow up duration	Acupoint
Acupui	ncture													
Ardinata	RCT	HD	T: 30	T: -	A (3 times/W)	Placebo	Conventional	12 W	IL-31	5DIS	T: 1 (1–5) $\rightarrow$ 1	NA	NA	LI11
et al. (22)			C:30	C: 25~77	HD	+ HD	Tx				(1-5)			
											$4 (2-5) \rightarrow 2$			
											(1-4)			
											$4(2-5) \rightarrow 3$			
											(2-4)			
											$3(1-5) \rightarrow 2$			
											(1-4) C:			
											C: 2 (1-5) $\rightarrow$ 1.5			
											$2(1-5) \rightarrow 1.5$ (1-5)			
											$(1 \ 5)$ $4 \ (2-5) \rightarrow 3$			
											(1-5)			
Fan et al.	RCT	HD	T: 22	T: 62.4	A (3 times/W)	Conventional	Conventional	12 W	Ca, P, BUN, Cr	Grade,	T: 38.20 (4.80)	NA	NA	LI11
(23)			C:20	(4.10)	HD	western	Tx			distribution,	$\rightarrow$ 17.30 (5.50)			
				C: 63.2		medicine				sleep	C: 38.30 (4.30)			
				(4.50)							→ 37.50 (3.20)			
Jiang	RCT	HD	T1	T1: 72.43	Hemoperfusion	Placebo	Conventional	NA	Ca, P, iPTH,	VAS	T1: 2 (3.70) $\rightarrow$ 1	NA	NA	LI4
et al.			(hemoperfusion):	(7.56)	A (3 times/W)	+ HD	Tx		hs-CRP, IL-6	5DIS	(3.29)			LI11
(24)†			14	T2: 73.50	HD						T2: 1.5 (3.08) $\rightarrow$			SP6
			T2	(7.77)							$0 (0.61) \rightarrow 0$			SP10
			(hemoperfusion +								(0.61)			ST36
			A): 14	(9.09)							C: 2.00 (3.70)			
			C: 14								T1: 13.5 (8.64)			
											$\rightarrow 8.5 (5.76)$ T2: 13.5 (7.00)			
											$\rightarrow 6.5 (4.11)$			
											$\rightarrow$ 0.3 (4.11) C: 9.5 (8.44) $\rightarrow$			
											10 (8.23)			

10.3389/fmed.2022.1036072

Study (year)	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before $\rightarrow$ after), experimenta control	rate	Follow up duration	Acupoint
Zhang	RCT	HD	T: 30	T: 53.63	A (3 times/W) +	HD	Conventional	4 W	CRP, Hb,	VAS	ΔT: 5 (3-8)	T: 13/35	NA	LI11
et al. (25)			C: 33	(9.40)	HD		Tx		albumin, BUN,		$\Delta C: 2 (-1-4)$	C: 2/35		SP10 SP6
				C: 52.23					Cr, Ca, P, PTH,					
				(7.95)					Eosinophil,					
									IgE					
										mDUO	ΔT: 6.23 (4.83)			
											ΔC: 1.73 (2.82)			
										TCM syndrome	ΔT: 9 (7–11)			
										score	$\Delta C: 0 (-0.5-2)$			
Liu et al.	RCT	HD	T: 40	T: 54.80	A (3 times/W) +	HD	Conventional	4 W	Ca, P, PTH,	Distribution,	Distribution	NA	NA	LI11
26)			C: 40	(3.20)	HD		Tx		histamine	frequency,	T: 2.45 (0.87) $\rightarrow$			SP6
				C: 53.50						severity, sleep	1.41 (0.52)			
				(4.60)							C: 2.49 (0.83)			
											$\rightarrow 2.34 (0.78)$			
											Frequency			
											$\text{T: 3.69 (1.21)} \rightarrow$			
											1.52 (0.52)			
											C: 3.72 (1.32)			
											$\rightarrow$ 3.63 (1.53)			
											Severity			
											$\text{T: 3.59 (1.12)} \rightarrow$			
											1.32 (0.45)			
											C: 3.61 (1.14)			
											$\rightarrow$ 3.21 (1.43)			
											Sleep			
											T: 7.33 (2.14) →			
											2.14 (0.89)			
											C: 7.45 (2.18)			
											$\rightarrow  7.23  (2.09)$			

Lu et al.

Study (year)	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)		Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	Effective rate l	Follow up duration	Acupoint
	RCT	HD	T: 15		A (3 times/W) +	Placebo + HD		6 W	NA	VAS	$\text{T: 9.87 (0.35)} \rightarrow$	NA	NA	SP6 SP10 LIV3
et al. (27)			C: 11		HD		Tx				3.93 (2.85) C:			LI4
				C: 41.36							9.45 (0.93) →			
				(16.21							8.18 (1.40)			
Phan	RCT	HD	T: 18		A (2 times/W) $+$	Placebo + HD		6 W	NA	5DIS	T: 12.00 (3.27)	NA	8 W	LI11 Quchi
et al. (28)			C: 19	(10.08)	HD		Tx				$\rightarrow$ 7.89 (0.83)			
				C: 48.37							C: 12.74 (3.07)			
				(10.81)							$\rightarrow$ 10.63 (3.17)			
Chu et al.	RCT	HD	T: 20		A (2 times/W) +		Conventional	12 W	BUN, Cr, P,	VAS	$T: 8.65 (1.24) \rightarrow$		NA	SP10 ST36 SP6
(29)			C: 20	(11.50)	HD	(10 mg QD)	Tx		PTH, β2-MG		1.45 (0.58)	C: 13/20		LI4
				C: 45.50 (12.00)		+HD					C: 8.60 (1.18) $\rightarrow 5.24 (1.28)$			LI11 DU20
				(12.00)						VAG				
										VAG	T: 7.52 (0.64) → 2.80 (0.65)			
											C: 7.38 (0.45)			
											$\rightarrow 5.75 (1.85)$			
Pu et al.	RCT	HD	T: 27	T· 63 52	A (2 times/W) +	HD	Conventional	10 D	NA	Dirk. R. Kuypers		T: 24/27	NA	LI4 LI11 ST36
(30)	nor	112	C: 27	(5.18)	HD	112	Tx	10 2		scale (DRKS)	10.4 (3.4)	C: 20/27		LU5
( ,				C: 63.42							C: 25.2 (5.1) $\rightarrow$			
				(5.32)							18.9 (4.1)			
Chang	RCT	HD	T1 (A): 16	Total:	T1: A + HD	HD	Conventional	Not	CRP, WBC	Guidelines for	T1: 12.12 (1.78)	T1: 9/16	NA	LI11
et al. (31)			T2 (citrate): 17	45.30	T2: citrate		Tx	mentioned		clinical research	$\rightarrow 9.16(1.67)$	T2: 15/17		GB31
			C: 17	(18.90)	dialysate					of Traditional	T2: 12.17 (1.75)	C: 2/15		ST36
										Chinese Drug	$\rightarrow 4.08 (1.84)$			SP10
										Research	C: 12.08 (1.82)			BI17
											→ 10.80 (1.96)			

10.3389/fmed.2022.1036072

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Study (year)	•	Inclusion criteria		Age (year- old)	dosage, and	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	Effective rate l	Follow up duration	Acupoint
Ono et al.	P-RCT	HD	T: 24	T: 70.00	A (1 time/W) +	HD	$\text{T: 0.66 (0.15)} \rightarrow$	8 W	Ca, P, Hb, Cr,	NRS	$60 \rightarrow 18$	NA	12 W	LU5 LU9 LI2
(32)			C: 23	(9.60)	HD + M-test		0.76 (0.17) C: 0.64		BUN, albumin,					LI11 HT7 HT
				C: 67.30			$(0.18) \rightarrow 0.64$		leukocyte					SI3
				(13.00)			(0.18)							SI8
														PC7 PC9 TE3
														TE10 SP2 SP5
														ST41 ST45 KI
														KI7 BL65 BL6
														LR2 LR8 GB3
														GB43
										Utility				
Ma et al.	RCT	HD	T: 23		A (3 times/W) +	HD	Conventional	16 W	NA	Clinical effect	NA	T: 18/23	NA	SP10
(33)			C: 23	(13.77)	HD		Tx					C: 1/19		LI4
				C: 60.74										
				(16.36)						5	T + + o < (= oo)			
										mDuo	T: 14.96 (5.89)			
											$\rightarrow 4.35 (4.74)$			
											C: 19.45 (8.71) $\rightarrow 20.21 (8.48)$			
Chang	PCT	HD	A+HDF: 15	A + HDE	A (2 times/W) +	HDE and HD	Conventional	12 W	P, PTH	NA	$\rightarrow$ 20.21 (8.48) NA	A+HDF:	NA	LI4
et al. (34)		IID	HDF: 15	52.30	HD + HDF		Тх	12 11	1, 1 111	14/4	11/1	13/15	1471	LI11
ct ul. (01)			C (HD): 16	(12.60)			TA .					HDF: 10/15		ST36
			0 (112)/ 10	HDF:								C: 3/16		SP10
				49.60										LU5
				(13.40)										BI17
				C: 53.20										
				(15.90)										

Study (year)	•	Inclusion criteria		Age (year- old)	(route, dosage, and	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool		Effective rate l	Follow up duration	Acupoint
										FIIQ	T: 13.03 (1.96)			
											$\rightarrow 8.56 (1.76)$			
											C: 12.22 (2.10)			
											$\rightarrow$ 10.08 (1.84)			
Yu et al.	RCT	HD	T: 50	T: 55.60	Auricular	Loratidine 10	Conventional	4 W	NA	VAS	NA	T: 43/50	8 W	Lung
(35)			C: 50	(1.90)	scraping (1	mg/d	Tx			FIIQ	T: 8.42 (3.30) $\rightarrow$	C: 38/50		Large intestine
				C: 53.60	time/W)						5.41 (2.25)			Shenmen (TF4)
				(2.50)							C: 8.48 (4.21)			Endocrine
											$\rightarrow 6.79(3.02)$			(CO18)
														Adrenal gland
														Occiput
Zhai et al	. RCT	HD	T: 50	T: 62.98	AA (4 times/d)	Loratadine	Conventional	12 W	NA	PSQI	T: 20.21 (2.15)	Itching:	NA	Kidney
(36)			C: 50	(3.65)	+ HD	(10  mg QD) +	Tx				$\rightarrow 13.67 (2.97)$	T: 46/50		Spleen
				C: 63.23		HD					C: 20.34 (2.72)	C: 38/50		Stomach
				(3.92)							→ 17.13 (2.12)			Sympathy
														Subcortical
														TF4
Che et al.	RCT	HD	T: 20	T: 62.40	A (2 times/W) $+$	Placebo needle	Conventional	4 W	NA	severity,	T: 38.20 (4.80)	NA	12 W	SP6
(5)			C: 20	(9.10)	HD	+ HD	Tx			distribution, sleep	$\rightarrow$ 17.30 (5.50)			SP10
				C: 63.20						disturbance	C: 38.50 (3.20)			ST36
				(7.50)						questionnaire	→ 37.50 (3.20)			LI11
Ruei et al	. RCT	HD	T: 80	T: 21–73	A (2 times/W or	Calcitrol (2 ug	Conventional	16 W	NA	NA	NA	T: 71/80	12 M	LI11
(37)			C: 70	C: 24–69	3 times/2W) +		Tx					C: 62/80		ST36
					HD	3 times/2W) +								SP6
						HD								SP10

•	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	-	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	Effective rate l	Follow up duration	Acupoint
Kao et al. RCT	1	HD	T: 34	Total	A (2 times/W) +	- Chlorpheniram	inConventional	4 W	NA	NA	NA	T: 33/34	NA	LI11
(38)			C: 34	22~72	HD	+ HD	Tx					C: 24/34		ST36
				(mean										
				43.6)										
Auricular a	cupr	essure (A.	A)											
Mai et al. RCT	•	HD	T: 40	T: 45.70	AA (3 times/d)	HD	Conventional	4 W	QLQ-C30 (life	Pauli-Magnus	T: 25.23 (16.42)	NA	NA	Lung
(39)			C: 40	(15.20)	+ HD		Tx		quality)	scale	$\rightarrow 3.75  (1.42)$			Heart
				C: 44.97							C: 24.85 (17.67)			Endocrine
				(17.30)							$\rightarrow 5.65(1.67)$			Lung
														Heart
														Endocrine
														SF1.2i
Yan et al. RCT		HD	T: 32	T: 57.72	AA (9 times/2ds)	) HD	Conventional	12 W	Ca, P, PTH,	VAS	T: 5.69 (0.97) $\rightarrow$	NA	NA	Kidney
(40)			C: 36	(12.16)	+ HD		Tx		IL-2, IL-6,		2.66 (0.87)			Lung
				C: 61.06					IL-8, IL-10		C: 5.75 (0.94)			Heart
				(11.77)							$\rightarrow$ 4.19 (0.92)			Endocrine
														Subcortical
														TF4
Chen RCT	•	HD	AA+ND: 30	AA+ND:	ND (3 times/W)	HD	Conventional	48 W	Ca, P, PTH,	NA	NA	Itching:	NA	TF4
et al. (41)			ND: 30	44.10	AA+ND: AA		Tx		ALP, vitamin			AA+ND:		Kidney
			C: 30	(1.60)	$(3\sim 5 \text{ imes/d}) +$				D			20/30		Spleen
				ND: 43.90	ND							ND: 8/30		Stomach
				(1.40)								C: 5/30		Subcortical
				C: 44.20										Sympathy
				(1.50)										

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•	•	Inclusion criteria		Age (year- old)	(route, dosage, and	-	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before $\rightarrow$ after), experimenta control	rate	Follow up duration	Acupoint
Yan et al.	RCT	HD	T: 39	T: 57.16	AA (9 times/2ds)	HD	Conventional	12W	Ca, P, PTH,	VAS	T: 5.84 (1.82) →	NA	NA	Kidney
(42)			C: 39	(17.01)	+ HD		Tx		amylase,		3.88 (1.50)			Lung
				C: 54.40					histamine,		C: 5.84 (2.06)			Heart
				(8.37)					IL-2		$\rightarrow 5.37 (1.90)$			Endocrine
														Subcortical
														TF4
Ding	RCT	PD	Total: 65	T: 60.76	AA (8 times/2ds)	HD	Conventional	12 W	Ca, P, PTH,	VAS	$\text{T: 5.29}~(0.97) \rightarrow$	NA	NA	Kidney
et al. (43)			T: -	(12.33)	+ HD		Tx		Hb, CRP,		2.24 (0.78)			Lung
			C: -	C: 64.42					histamine,		C: 5.42 (1.12)			Heart
				(10.47)					IL-2, IL-6,		$\rightarrow 4.10(1.01)$			Endocrine
									IL-8, IL-10					Subcortical
														TF4
										FIIQ	T: 11.71 (2.34)			
											$\rightarrow 8.18(1.70)$			
											C: 12.81 (2.27)			
											$\rightarrow$ 10.29 (1.90)			
										TCM symptom	T: 34.12 (5.89)			
										score	$\rightarrow 25.94(2.93)$			
											C: 36.13 (5.32)			
											$\rightarrow$ 30.32 (4.82)			

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-	-	Inclusion criteria		Age (year- old)	(route, dosage, and	Control (route, dosage, and frequency)	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	rate	Follow up duration	Acupoint
Ie et al.	RCT	HD	T: 34	T: 54.18	AA (4~5	HD	Conventional	4 W	Ca, P, PTH, Cr	, Pauli-Magnus	Scratching	NA	NA	Lung
44)			C: 35	(10.76)	times/2ds) +		Tx		BUN, albumin	, scale	activity			Endocrine
				C: 50.23	HD				Hb		$\mathrm{T:}2.74~(1.33)\rightarrow$			Adrenal
				(12.69)							1.18 (0.39)			
											C: 2.54 (0.85)			
											$\rightarrow 2.14  (0.69)$			
											Distribution of			
											pruritus			
											$\text{T: 1.94 (0.78)} \rightarrow$			
											1.06 (0.24)			
											C: 1.63 (0.73)			
											$\rightarrow 1.60 (0.60)$			
											Awaking from			
											itching			
											$\text{T: 1.53 (2.87)} \rightarrow$			
											0.12 (0.48)			
											C: 1.60 (1.80)			
											$\rightarrow 0.86 (1.00)$			
											Number of			
											nighttime			
											scratching			
											$\text{T: 2.24 (1.52)} \rightarrow$			
											0.65 (0.88)			
											C: 1.83 (1.07)			
											$\rightarrow$ 1.80 (1.08)			
										VAS	$\text{T: 4.59 (2.03)} \rightarrow$			
											1.79 (1.10)			
											C: 3.80 (1.39)			
											$\rightarrow 3.29(1.13)$			

Study (year)	-	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	rate	Follow up duration	Acupoint
Lin et al.	RCT	CKD	Fumigation: 30	NA	AA (3~5	Conventional	Conventional	8 W	P, PTH	Serjip score	Fumigation: 326	NA	NA	Lung
(45)			AA: 30		times/2ds)	Tx	Tx				$\rightarrow 116$			Spleen
			Fumigation + AA:		(Fumigation						AA: $325 \rightarrow 126$			Stomach
			30		ingredient:						Fumigation+AA	:		Adrenal
			C: 30		Tufulin,						336  ightarrow 136			supracortical
					Huangba,						$\text{C: 316} \rightarrow \text{ 207}$			Sympathy
					Kushen,									Endocrine
					Machixian,									Wheel area
					Licorice,									
					Senecio)									
Li et al.	RCT	HD	T: 40	T: 53.80	AA (4 times/d)	Acrivastine	Conventional	4 W	NA	NA	NA	T: 38/40	NA	A:
(46)			C: 40	(3.60)	+ HD	(8 mg 3	Tx					C: 28/40		Kidney
				C: 55.10		times/d) + HD								Heart
				(1.0.80)										Lung
														Liver
														spleen
														Sanjio
														B:
														Bladder
														SHENMEN
														HX1
														HX6.7i
														SF1.2i
														AT2.3.4i
Fao et al.	RCT	HD	T: 40	T: 55.90	AA (5~8	HD	Conventional	$8{\sim}12W$	NA	itching severity,	T: 19.36 (2.37)	NA	NA	Kidney
(47)			C: 40	(3.10)	times/d) + HD		Tx			frequency, sleep	$\rightarrow  7.36  (2.18)$			Spleen
				C: 56.20							C: 19.71 (2.33)			Stomach
				(3.50)							$\rightarrow$ 13.27 (2.23)			Sympathy
														Subcortical
														Shenmen (TH

TABLE 1 (Continued)

•	•	Inclusion criteria		Age (year- old)	(route, dosage, and	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before $\rightarrow$ after), experimenta control	rate	Follow up duration	Acupoint
Yan et al.	RCT	HD	T: 32	Total	AA (5~8	Placebo + HD	Conventional	6 W	Ca, P, PTH,	VAS	T: 5.75 (2.03) →	NA	NA	Shenmen (TF4),
(12)			C: 30	20~65	times/d) + HD		Tx		histamine,		3.84 (1.69)			kidney (CO10),
									substance P,		C: 5.60 (2.13)			lung (CO14),
									PAR-2,		$\rightarrow 5.57 (2.29)$			endocrine
									tryptase					(CO18),
														subcortical
														(AT4)
Shr et al.	RCT	HD	T: 30	Total	AA (>4 times/d)	HD+HP or HD	Conventional	4 W	Ca, P, PTH,	NA	NA	T: 26/29	NA	A:
48)			C1 (HD+HP): 30	58.00	+ HD		Tx		BUN, β2-MG,			C1: 23/27		Heart
			C2 (HD): 30	(17.00)					Cr			C2: 10/28		Lung
														Liver
														Spleen
														Sanjiao
														B:
														Bladder
														Shenmen (TF4)
Acupoi	nt far in	frared (AF	FIR)											HX1
														HX6.7i
														SF1.2i
														AT2.3.4i
Hsu et al.	RCT	HD	T: 21		AFIR (1 time/d,	HD	Conventional	18 W		Uremic pruritus		NA	NA	SP6
49)			C: 20		2 ds/W)		Tx		Urea, ALK-P,	questionnaire	$\rightarrow 6.43(0.91)$			
				C: 66.90					Hb, PTH		C: 17.55 (2.00)			
				(3.06)							$\rightarrow$ 9.05 (1.59)			
										VAS	T: 18.57 (1.41)			
											$\rightarrow$ 10.71 (1.17)			
											C: 16.50 (1.35)			

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•	•	Inclusion criteria		(year- old)	Treatment (route, dosage, and frequency)	(route, dosage, and	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control	Effective rate l	Follow up duration	Acupoin
Acupoir	nt inject	ion (AI)												
Wang	RCT	HD	T: 55	T: 56.40	AI (2 times/W)	Neurotin + HD	Conventional	4 W	Ca, P, PTH	VAS	$\text{T: 6.43 (1.24)} \rightarrow$	NA	NA	LI11
et al. (50)			C: 54	(8.60)	+ Neurotin		Tx				3.35 (1.52)			ST36
				C: 56.40	(0.1 g 2 times/d)						C: 6.25 (1.22)			
				(8.80)	+ HD						$\rightarrow 4.38 (1.19)$			
										DRKS	T: 10.96 (3.40)			
											$\rightarrow 5.46(2.17)$			
											C: 12.16 (9.55)			
											$\rightarrow$ 7.60 (2.63)			
-	·		upuncture (.	-										
-	RCT		T: 23		AI (2 times/W)		Conventional	12W	NA	NA	NA		NA	AI + A:
et al. (51)			C: 23		+ acupuncture		Tx					C: 19/23		LI11
					+ cetirizine									ST36
					(10 mg QHS)									SP10
0	RCT		T: 56	T: 29~78		Calcitrol (0.25		12 W	NA	NA	NA		NA	A:
et al. (52)			C: 54			ug 1 time/d or 1	Tx					C: 48/54		EM40
					times/W or 3	time/2ds) +								GB31
					times/2 Ws) +	HD								LI4
					HD									LI11 ST36
														S136 SP6
														SP0 SP9
														SP10
														AI:
														BI17
														BI23

•	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	(route,	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool		Effective rate l	Follow up duration	Acupoint
Acupoi	nt inject	ion + acuj	point massaş	ge (AI + A	M)									
Chen	RCT	HD	T: 30	T: 49.17	AI (2~3	HD	Conventional	8 W	NA	VAS	T: 7.50 (1.11) $\rightarrow$	T: 27/30	NA	AI:
et al. (53)			C: 30	(12.20)	times/W) + AM		Tx				5.23 (1.36)	C: 20/30		LI11
				C: 49.77	(2~3 times/W)						C: 7.33 (1.32)			ST36
				(1.24)	+ HD						→ 7.27 (1.36)			AM:
														DU14
														DU23
														EM1
														EM2
														HT7
														GB20
														LI4
														SP6
														SP10
														PC4
Acupoi	nt infrai	ed (AIF)												
i et al.	RCT	HD	T: 20	T: 56.37	AIR (2 times/W)	HD	Conventional	5 W	Ca, P, PTH,	VAS	$\text{T: 7.82 (1.69)} \rightarrow$	NA	NA	LI11
9)			C: 20	(4.22)	+ HD		Tx		albumin, BUN	,	4.17 (2.86)			SP6
				C: 56.89					Cr, Hb, WBC,		C: 7.49 (1.30)			SP10
				(4.19)					Plt,		$\rightarrow 6.02 (2.15)$			
										Sleep quality	$\text{T: 1.92} \; (0.78) \rightarrow$			
										score	0.72 (0.45)			
											C: 1.88 (0.85)			
											$\rightarrow$ 1.68 (0.91)			

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•	•	Inclusion criteria		Age (year- old)	(route, dosage, and	Control (route, dosage, and frequency)	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before → after), experimenta control		Follow up duration	Acupoint
Acupoi	nt massa	age (AM)												
Chen	RCT	High-flux	T: 31	T: 47.90	AM (3 times/W)	High-flux HD	Conventional	8 W	P, iPTH,	12-PSS	T: 18.40 (4.20)	NA	NA	LI11
et al. (54)		HD	C: 31	(13.40)	High-flux HD (3		Tx		hs-CRP		→ 11.60 (3.20)			
				C: 48.30	times/W)						C: 19.10 (6.30)			
				(11.20)							→ 13.80 (3.40)			
Karjalian	RCT	HD	T: 30	T: 55.31	AM (3 times/W)	C1 (Placebo	Conventional	4 W	Ca, P, Na, K,	NRS	$\mathrm{T:}8.37~(1.22)\rightarrow$	NA	5 W	SP6, SP10
et al. (7)			C1 (Placebo	(8.88)		massage, 3	Tx		PTH, BUN, Cr	,	2.87 (0.90)			ST36 LI11
			massage): 30	C1: 52.67		times/W) +			Hb		C1: 7.67 $\rightarrow$ 6.37			
			C2 (no	(10.89)		HD					C2: 7.73 $\rightarrow$ 7.33			
			intervention: 30	C1: 55.00		C2 (HD)								
				(11.14)										
Akca	RCT	HD	AM: 25	AM:	AM (3 times/W)	HD	Conventional	4 W	NA	VAS	AM:	NA	NA	ATENS: LI-11
et al. (14)			ATENS: 24	55.24	ATENS (3		Tx				$6.84~(1.70) \rightarrow$			
			C: 25	(10.13)	times/W)						3.36 (2.37)			
				TEAS:							ATENS:			
				48.08							7.37 (1.31) →			
				(9.05)							3.12 (2.15)			
				C: 45.84							C:			
				(10.40)							6.92 (1.41) →			
											5.08 (1.55)			
Jedras	RCT	HD	T: 30	T: 46.63	AM (3 times/W)	HD	Conventional	5 W	NA	frequency,	$\mathrm{T:8.53}~(2.31) \rightarrow$	NA	18 W	140 pressure
et al. (55)			C: 30	(12.41)			Tx			intensity	1.07 (1.91)			points (20 each
				C: 44.57						localization,	C: 7.70 (2.30)			on the head,
				(10.71)						influence on	→ 7.57 (2.03)			hands, trunk,
										wellbeing				legs)
										questionnaire				

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#### TABLE 1 (Continued)

Study (year)	•	Inclusion criteria		Age (year- old)	Treatment (route, dosage, and frequency)	(route, dosage, and	Concomitant treatment	Duration	Inspection data	Pruritus severity assessment tool	PS (before $\rightarrow$ after), experimenta control	rate	Follow up duration	Acupoint
Acupoi	nt sticki	ing therapy	v (AST)											
liu et al.	RCT	HD	T1 (HD): 20	T1: 45.20	AST (Difuzi,	HD, HPF, HF	Conventional	12 W	Ca, P, PTH,	VAS	T1 vs C1	NA	NA	Umbilicus
(56)			T2 (HD+HPF): 20	(1.90)	Tusizi, Mudanpi	,	Tx		Hb, BUN, Cr		T1: 5.95 (2.26)			
			T3 (HD+HF): 20	T2: 44.60	and Taoren/2ds)						$\rightarrow$ 5.20 (2.49)			
			C1 (HD): 20	(2.00)							C1: 6.65 (1.57)			
			C2 (HD+HPF): 20	T3: 45.30							$\rightarrow 5.05 (1.64)$			
			C3 (HD+HF): 20	(1.80)							T2 vs C2			
				C1: 45.30							T2: 6.85 (1.56)			
				(2.10)							$\rightarrow$ 3.20 (1.08)			
				C2: 44.70							C2: 6.40 (1.78)			
				(2.70)							$\rightarrow 3.75(1.12)$			
				C3: 45.1							T3 vs C3			
				(2.20)							T3: 6.90 (1.80)			
											$\rightarrow$ 1.80 (2.03)			
											C3: 5.85 (1.89)			
											$\rightarrow 2.30 (2.03)$			
Transc	utaneou	s electrical	acupoint stim	ulation (	TEAS)									
Akca	RCT	HD	AM: 25	AM:	AM (3 times/W)	HD	Conventional	4 W	NA	VAS	AM:	NA	NA	ATENS: LI-11
et al. (14)			TEAS: 24	55.24	ATENS (3		Tx				$6.84~(1.70) \rightarrow$			
			C: 25	(10.13)	times/W)						3.36 (2.37)			
				ATENS:							ATENS:			
				48.08							$7.37~(1.31) \rightarrow$			
				(9.05)							3.12 (2.15)			
				C: 45.84							C:			
				(10.40)							$6.92~(1.41) \rightarrow$			
											5.08 (1.55)			

RCT, randomized controlled trial; T, treatment group; C, control group; Tx, treatment; NA, not applicable; HD, hemodialysis; HDF, hemodiafiltration; HF, hemofiltration; HP, hemoperfusion; ND, nocturnal dialysis; AA, auricular acupressure; ATENS, Acupoint transcutaneous electrical nerve stimulation; W, week; d, day; 5DIS, 5-D itch scale; VAS, visual analog scale; DRKS, Dirk R. Kuypers scale; TCM syndrome score, traditional Chinese medicine syndrome score; PSQI, Pittsburgh Sleep Quality Index; 12-PSS, 12-Item Pruritus Severity Scale; PS, performance status.

 $^{\Delta} \mathrm{Difference}$  between two numbers.

<sup>†</sup>Median (interquartile range).

-		Experimental Mean SD To		Control SD 1	fotal Weigh	Mean Difference t IV, Random, 95% (	CI Year	Mean Difference IV. Random, 95% Cl
	1.2.1 Acupuncture Nahidi 2018 Zhu 2018 Zhang 2020 Jiang 2021	1.45 0.58 5.75 0.97 0 0.61	30 7 14 1	1.4 1.28 1.54 3.29	11 4.69 20 7.79 33 7.69 14 4.49	6 -3.79 [-4.41, -3.1 6 -1.25 [-1.88, -0.6 6 -1.00 [-2.75, 0.7	7] 2018 2] 2020 5] 2021	
	Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 2 Test for overall effect: Z 1.2.2 Aricular acuprese	.65; Chi² = 38.96 = 2.95 (P = 0.00		< 0.0000	78 24.3 1); I <sup>2</sup> = 92%	6 -2.58 [-4.29, -0.8]	(]	
	Yan 2015 He 2018	3.84 1.69 1.79 1.1		1.13	30 6.59 35 7.99	-1.50 [-2.03, -0.9	7] 2018	
	Yan 2020 Yan 2021 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	2.66 0.87 1 .00; Chi <sup>2</sup> = 0.17,	32 4.19 37 df = 3 (P =		39 7.39 34 8.19 138 29.89 = 0%	-1.53 [-1.96, -1.1	0] 2021	Ť
	1.2.3 Acupoint far infra Hsu 2009 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	10.71 1.17 licable	21	1.03	20 7.59 20 7.59			•
	1.2.4 Acupoint injection	1						
	Wang 2021 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	icable = 3.94 (P < 0.00	55 01)	1.19	54 7.99 54 7.99			•
	1.2.5 Acupoint injection Chen 2017 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	5.23 1.36 icable	30 7.27 30	1.36	30 7.59 30 7.59			•
	1.2.6 Acupoint infrared Yi 2018 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	4.17 2.86 icable	20	2.15	20 4.99 20 4.99	6 -1.85 [-3.42, -0.24 6 -1.85 [-3.42, -0.24	8] 2018 8]	
	1.2.7 Acupoint massag Akca 2016 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	3.36 2.37 icable	25	1.55	25 6.29 25 6.29			•
	1.2.8 Acupoint sticking Ju 2015 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	5.2 2.49 icable	20	1.64	20 5.69 20 5.69		6] 2015 6]	•
	1.2.9 Transcutaneous of Akca 2016 Subtotal (95% CI) Heterogeneity: Not appl Test for overall effect: Z	3.12 2.15 icable	24 5.08 24	ation 1.55	25 6.49 25 6.49		1] 2016 1]	•
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Test for subgroup differ	.84; Chi <sup>2</sup> = 96.06 = 6.09 (P < 0.00	001)	P < 0.000	01); I² = 85%		1] .	4 - 2 0 2 4 Favours [experimental] Favours [control]
E	5							
	Study or Subgroup		otal Mea		Total Wei		95% CI	Mean Difference IV. Random. 95% Cl
	Chou 2005 He 2018 Mai 2021	17.3 5.5 3.35 2.47 3.75 1.42		5 3.2 9 4.94 5 1.67	20 32. 35 33. 40 33.	4% -6.34 [-8.18	, -4.50]	
	Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 9 Test for overall effect: 2	58.31; Chi <sup>z</sup> = 16	94 7.93, df =		95 100.	0% -9.38 [-18.09,		-20 -10 0 10 20 Favours (experimental) Favours (control)
c	;							
	Ma 2014	Experimenta Mean SD T 4.35 4.74 21.23 4.84	l otal Mea 23 20.2 30 25.0 53	1 8.48	Total Wei 23 49. 33 51. 56 100.	0% -15.86 [-19.83, - 0% -3.86 [-6.13	<u>95% CI</u> -11.89] , -1.59]	Mean Difference N. Random, 95% Cl
	Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2		.42, df = 1	(P < 0.0(				-20 -10 0 10 20 Favours (experimental) Favours (control)
C	)							
	<u>Study or Subgroup</u> Pu 2017 Wang 2021	Experimenta Mean SD 10.4 3.4 5.46 2.17	<u>Fotal Me</u> 27 18	Contro an SD 3.9 4.1 7.6 2.63	Total We 27 49	Mean Differen ight IV, Random, 9 .0% -8.50 [-10.51, .0% -2.14 [-3.05,	5% CI -6.49]	Mean Difference IV. Random. 95% Cl
	Total (95% CI) Heterogeneity: Tau² = Test for overall effect: 2			(P < 0.0		).0% -5.25 [-11.49, 7%	0.98]	-20 -10 0 10 20 Favours [experimental] Favours [control]

FIGURE 3 Forest plot ( Kuypers scale in patients with ure variable; SD, standard deviation.

1.1.1 Acupuncture Gao 2002 33 34 24 34 6.7% 1.38 [1.10, 1.72] 2002 Zhang 2011 13 15 10 15 2.8% 1.30 [0.86, 1.96] 2011 Ma 2014 18 23 1 19 0.3% 1.487 [2.18, 10.14] 2014 Zhang 2017 9 16 2 17 0.5% 4.78 [1.21, 18.65] 2017 Zhu 2017 24 27 20 27 5.6% 1.20 [0.93, 1.56] 2017 Zhu 2018 19 20 13 20 3.6% 1.46 [1.04, 2.05] 2018 Subtotal (95% CI) 250 247 37.5% 1.48 [1.32, 1.66] Total avents 200 134 Heterogeneity. Chi <sup>#</sup> = 2.6 81, df = 7 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 4.6 ( $P < 0.00001$ ) 1.1.2 Aricular acupressure Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 Zha 2021 45 50 38 50 10.6% 1.21 [0.2, 1.47] 2020 Zha 2021 45 50 38 50 10.6% 1.21 [0.2, 1.47] 2020 Zha 2021 45 50 38 50 10.6% 1.21 [0.2, 1.47] 2020 Zha 2021 45 50 38 50 10.6% 1.21 [0.2, 1.44] 2021 Yu 2021 45 50 38 50 10.6% 1.21 [0.2, 1.44] 2021 Yu 2021 45 50 38 50 10.6% 1.27 [1.14, 1.41] Total avents 173 135 Heterogeneity. Chi <sup>#</sup> = 2.65, df = 4 ( $P = 0.05$ ); $P = 58\%$ Test for overall effect Z = 4.6 ( $P = 0.05$ ); $P = 58\%$ Test for overall effect Z = 4.5 ( $P < 0.0001$ ) 1.1.5 Acupoint injection and Acupuncture Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Total avents 73 67 Heterogeneity. Chi <sup>#</sup> = 0.53, df = 4 ( $P = 0.05$ ); $P = 58\%$ Test for overall effect Z = 1.0 ( $P = 0.27$ ); $P = 0\%$ Test for overall effect Z = 2.10 ( $P = 0.04$ ) Total events 77 20 Total avents 27 20 Heterogeneity. Chi <sup>#</sup> = 0.41, df = 1.5 ( $P < 0.0001$ ); $P = 68\%$ Test for overall effect Z = 2.10 ( $P = 0.04$ ) Total events 27 20 Heterogeneity. Chi <sup>#</sup> = 4.74, df = 1.5 ( $P < 0.0001$ ); $P = 68\%$ Test for overall effect Z = 2.10 ( $P = 0.04$ ) Total events 473 366 Heterogeneity. Chi <sup>#</sup> = 4.74, df = 1.5 ( $P < 0.0001$ ); $P = 82.8\%$	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Rul 2002 71 80 62 80 17.3% 1.15 [0.9, 1.32] 2002 Zhang 2011 13 15 10 15 2.8% 1.30 (0.6, 1.66) 2011 Ma 2014 18 23 1 19 0.3% 14.87 [2.18, 101.41] 2014 Zhang 2017 24 27 20 27 5.6% 4.78 [1.2, 1.86] 2017 Zhu 2017 24 27 20 27 5.6% 1.20 [0.9, 1.56] 2017 Zhu 2018 19 20 13 20 3.6% 1.46 [1.04, 2.05] 2018 Zhang 2020 13 35 2 36 0.6% 1.65 01 (5.6, 2.671) 2020 Subtolat [95% CI) 250 247 37.5% 1.48 [1.32, 1.66] Total events 200 134 Heterogeneity. Chi <sup>2</sup> = 2.86 1, df = 7 ( $P = 0.0002$ ), $P = 76\%$ . Test for overall effect Z = 6.61 ( $P < 0.00001$ ) 1.1.2 Ancular acupressure Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 Zha 2021 46 50 38 50 10.6% 1.31 [1.03, 1.47] 2020 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Zhai 2021 45 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Total events 173 135 Heterogeneity. Chi <sup>2</sup> = 0.56, df = 4 0.0001) 1.1.5 Acupoint injection and Acupoint massage Chen 2015 22 3 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% CI) 79 77 18.0% 1.06 [0.95, 1.16] Total events 73 67 Heterogeneity. Chi <sup>2</sup> = 0.90, df = 1 ( $P = 0.32$ ), $P = 6\%$ . Test for overall effect Z = 1.10 ( $P = 0.32$ ), $P = 0\%$ Total events 73 36 Total events 73 367 Heterogeneity. Chi <sup>2</sup> = 0.99, df = 1 ( $P = 0.32$ ), $P = 0\%$ . Test for overall effect Z = 1.10 ( $P = 0.32$ ), $P = 0\%$ . Total events 473 366 Heterogeneity. Chi <sup>2</sup> = 0.99, df = 1 ( $P = 0.32$ ), $P = 0\%$ . Total events 473 366 Heterogeneity. Chi <sup>2</sup> = 0.14, df = 1.5 ( $P < 0.0001$ ), $P = 82.8\%$ .									
Rui 2002 71 80 62 80 17.3% 115 [0.99, 1.32] 2002 Zhang 2011 13 15 10 15 2.8% 1.30 [0.96, 1.96] 2010 Ma 2014 18 23 1 19 0.3% 14.87 [2.18, 101.41] 2014 Zhang 2017 9 16 2 17 0.5% 4.78 [1.21, 18.85] 2017 Zhu 2017 24 27 20 7 5.6% 1.20 [0.33, 1.56] 2017 Zhu 2018 19 20 13 20 3.6% 1.46 [1.04, 2.05] 2018 Zhang 2020 13 35 2 25 0.6% 6.50 [1.50, 26.71] 2020 Subtotal (95% CI) 250 247 37.5% 1.48 [1.32, 1.66] Total events 200 134 Heterogeneity: Ch <sup>2</sup> = 2.6.1 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 6.81 ( $P = 0.0000$ ); $P = 76\%$ Test for overall effect Z = 4.45 ( $P = 0.05$ ); $P = 56\%$ Test for overall effect Z = 4.45 ( $P = 0.05$ ); $P = 56\%$ Test for overall effect Z = 1.10 ( $P = 0.32$ ); $P = 0\%$ Test for overall effect Z = 1.10 ( $P = 0.32$ ); $P = 0\%$ Total events 73 67 Heterogeneity: Ch <sup>2</sup> = 0.99, df = 1 ( $P = 0.32$ ); $P = 0\%$ Total events 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 <b>1.1.5 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 <b>1.1.6 Acupoint injection and Acupoint massage</b> Total events 27 20 Heterogeneity: Not applicable Test for overall effect Z = 2.10 ( $P = 0.04$ ) <b>1.1.6 (<math>0.96\%</math> CI)</b> 558 551 100.0% 1.31 [1.23, 1.40] Total events 473 356 Heterogeneity: Not applicable	territoria de la construcción de la constru	33	34	24	34	6.7%	1.38 [1.10, 1.72]	2002	
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			15		15				
Thang 2017 9 16 2 17 0.5% 4.76 [1,2], 18,85 2017 Pu 2017 24 27 20 27 5.8% 1.20 [0,3], 1.56 2017 The pu 2017 24 27 20 27 5.8% 1.46 [1.04, 2.05 2017 The pu 2017 25 247 37.5% 1.48 [1.32, 1.66] The pu 2017 250 247 37.5% 1.48 [1.32, 1.66] Total events 200 134 Heterogenetic, Ch <sup>2</sup> = 2.8, 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 5.61 ( $P < 0.0000$ ) Heterogenetic, Ch <sup>2</sup> = 2.8, 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 1.0 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 5.6, 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 5.6, 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 5.6, 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 1.67 ( $P = 0.0002$ ); $P = 76\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.22$ ); $P = 0\%$ Test for overall effect Z = 1.0 ( $P = 0.0001$ ); $P = 68\%$ Total events 27 20 Heterogenetic, Ch <sup>2</sup> = 47.41, df = 15 ( $P < 0.00001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.0001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.00001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.00001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.0001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.00001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.00001$ ); $P = 68\%$ Test for overall effect Z = 1.0 ( $P = 0.00001$ ); $P = 68\%$	_	18	23	1	19				
Pu 2017 24 27 20 27 $6.6\%$ 120 $0.31.66$ 2017 Zhu 2018 19 20 13 20 $3.6\%$ 146 $(10.42.05)$ 2018 Zhang 2020 13 35 2 35 $0.6\%$ 6.50 $(1.68, 26.71)$ 2020 Subtotal (95% CI) 250 2447 37.5% 1.48 $(1.32, 1.66]$ Total events 200 134 Heterogeneity. ChF = 2.8.61, df = 7 (P = 0.0002); P = 76% Test for overall effect Z = 6.61 (P < 0.00001) 1.1.2 Aricular acupressure Chi 2012 26 29 23 27 6.7% 1.05 $[0.86, 1.29]$ 2012 Li 2017 38 40 28 40 7.6% 1.36 $[1.09, 1.68]$ 2017 Chen 2020 20 30 8 30 2.2% 2.50 (1.31, 4.77) 2020 Zhai 2021 46 50 38 50 10.6% 1.21 $[1.02, 1.14]$ 2021 Vu 2021 43 50 38 50 10.6% 1.21 $[1.03, 1.37]$ 2020 Zhai 2021 46 50 38 50 10.6% 1.21 $[1.03, 1.37]$ 2020 Zhai 2021 46 50 38 50 10.6% 1.21 $[1.03, 1.37]$ 2020 Zhai 2021 47 35 38 50 10.6% 1.21 $[1.03, 1.37]$ 2021 Subtotal (95% CI) 199 197 38.0% 1.27 $[1.14, 1.41]$ Total events 173 135 Heterogeneity. ChF = 9.55, (ff = 4 (P = 0.05); P = 58% Test for overall effect Z = 4.45 (P < 0.00001) 1.1.5 Acupoint injection and Acupuicture Weng 2004 51 56 48 54 13.7% 1.02 $[0.90, 1.16]$ 2004 Deng 2015 22 23 19 23 5.3% 1.16 $[0.94, 1.42]$ 2015 Subtotal (95% CI) 79 77 19.0% Test for overall effect Z = 1.10 (P = 0.32); P = 0% Test for overall effect Z = 1.10 (P = 0.32); P = 0% Test for overall effect Z = 2.10 (P = 0.02); P = 08% Test for overall effect Z = 2.10 (P = 0.02); P = 08% Test for overall effect Z = 2.10 (P = 0.02); P = 08% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P < 0.0001); P = 682 % Test for overall effect Z = 1.00 (P < 0.0001); P = 82.8%		9	16	2	17				
Zhu 2018 19 20 13 20 36% 146 $[1.04] 2.05]$ 2018 Zhang 2020 13 35 2 35 0.6% $[6.50[1.58, 26.7]$ 2020 Subtotal (95% CI) 250 247 37.5% 1.46 $[1.32, 1.66]$ Total events 200 134 Heterogeneity: Ch <sup>2</sup> = 2.8.1, df = 7 (P = 0.00001) <b>1.1.2 Aricular acupressure</b> Chi 2012 26 29 23 27 6.7% 1.05 $[0.86, 1.29]$ 2012 Li 2017 38 40 22 40 7.8% 1.36 $[1.09, 1.68]$ 2017 Chen 2020 20 30 8 30 2.2% 2.50 $[1.31, 4.77]$ 2020 Zhang 2021 46 50 38 50 10.6% 1.21 $[1.02, 1.44]$ 2021 Yu 2021 43 50 38 50 10.6% 1.21 $[1.02, 1.44]$ 2021 Yu 2021 43 50 38 50 10.6% 1.21 $[1.02, 1.44]$ 2021 Yu 2021 43 50 38 50 10.6% 1.27 $[1.14, 1.41]$ Total events 173 135 Heterogeneity: Ch <sup>2</sup> = 0.55, df = 4 (P < 0.05); P = 58% Test for overall effect Z = 4.45 (P < 0.0001) <b>1.1.5 Acupoint injection and Acupuncture</b> Neng 2014 51 56 48 54 13.7% 1.02 $[0.90, 1.16]$ 2004 Deng 2015 22 23 19 23 5.3% 1.16 $[0.94, 1.42]$ 2015 Subtotal (95% CI) 79 77 19.0% 1.06 $[0.95, 1.18]$ Heterogeneity: Ch <sup>2</sup> = 0.90, df = 1 (P = 0.32); P = 0% Test for overall effect Z = 1.10 (P = 0.27) <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 $[1.02, 1.79]$ 2017 <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 $[1.02, 1.79]$ 2017 <b>1.1.6 Acupoint injection</b> Total events 73 67 Heterogeneity: Ch <sup>2</sup> = 0.90, df = 1 (P = 0.32); P = 0% Test for overall effect Z = 2.10 (P = 0.00); P = 68% Total events 27 20 Heterogeneity: Ch <sup>2</sup> = 4.7.41, df = 15 (P < 0.0001); P = 68% Total events 473 356 Heterogeneity: Ch <sup>2</sup> = 4.7.41, df = 15 (P < 0.0001); P = 68% Total events 473 356 Heterogeneity: Ch <sup>2</sup> = 4.7.41, df = 15 (P < 0.0001); P = 68% Total events 473 356 Heterogeneity: Ch <sup>2</sup> = 4.7.41, df = 15 (P < 0.0001); P = 82.8%. Total events 473 366 Heterogeneity: Ch <sup>2</sup> = 4.7.41, df = 15 (P < 0.0001); P = 82.8%. Total events 672 = 8.19 (P < 0.00001); P = 82.8%.	-	24	27	20	27	5.6%			
Subtorial (95% CI) 250 247 37.5% 1.48 [1.32, 1.66] Total events 200 134 Heterogeneity: Ch <sup>2</sup> = 28.61, df = 7 (P = 0.0002); P = 76% Testfor overall effect Z = 6.61 (P < 0.00001) <b>1.1.2 Aricular acupressure</b> Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 Li 2017 38 40 28 40 7.8% 1.36 [1.09, 1.68] 2017 Chen 2020 20 30 8 30 2.2% 2.50 [1.31, 4.77] 2020 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Total events 173 135 Heterogeneity: Chi <sup>P</sup> = 9.55, df = 4 (P = 0.05); P = 58% Test for overall effect Z = 4.45 (P < 0.0001) <b>1.1.5 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 Subtotal (95% CI) 79 77 19.0% Los (0.95, 1.18] Total events 73 67 Heterogeneity: Chi <sup>P</sup> = 0.99, df = 1 (P = 0.32); P = 0% Test for overall effect Z = 2.10 (P = 0.04) <b>Total events</b> 77 20 Heterogeneity: Chi <sup>P</sup> = 4.741, df = 15 (P < 0.0001); P = 88% Test for overall effect Z = 2.10 (P = 0.04) <b>Total events</b> 473 366 Heterogeneity: Chi <sup>P</sup> = 4.741, df = 15 (P < 0.0001); P = 88% Test for overall effect Z = 2.10 (P = 0.04) <b>Total events</b> 473 366 Heterogeneity: Chi <sup>P</sup> = 4.741, df = 15 (P < 0.0001); P = 82 8%. <b>Total events</b> 473 366 Heterogeneity: Chi <sup>P</sup> = 4.19 (P < 0.0001) <b>Total events</b> 473 366 Heterogeneity: Chi <sup>P</sup> = 4.741, df = 15 (P = 0.0001) <b>Total events</b> 473 366 Heterogeneity: Chi <sup>P</sup> = 4.19 (P < 0.0001); P = 88% Test for overall effect Z = 8.19 (P < 0.0001) Favours [control] Favours [experimental]	Zhu 2018	19	20	13	20	3.6%			
Heterogeneity: Chi <sup>2</sup> = 28.61, df = 7 (P = 0.0002); P = 76% Test for overall effect Z = 6.61 (P < 0.00001) <b>1.1.2 Arcicular acupressure</b> Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 1.2017 38 40 28 40 7.8% 1.36 [1.09, 1.68] 2017 Chen 2020 20 30 8 30 2.2% 2.50 [1.31, 4.77] 2020 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.27 [1.14, 1.41] Total events 173 135 Heterogeneity: Chi <sup>2</sup> = 9.55, df = 4 (P = 0.05); P = 58% Test for overall effect Z = 4.45 (P < 0.0001) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% Cl) 79 77 19.0% 1.06 [0.95, 1.18] Total events 73 67 Heterogeneity: Chi <sup>2</sup> = 0.98, df = 1 (P = 0.32); P = 0% Test for overall effect Z = 1.10 (P = 0.27) <b>1.1.6 Acupoint injection and Acupuncture</b> Heterogeneity: Chi <sup>2</sup> = 0.98, df = 1 (P = 0.32); P = 0% Test for overall effect Z = 2.10 (P = 0.04) Total events 73 66 Heterogeneity: Chi <sup>2</sup> = 4.741, df = 15 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.04) Total events 473 356 Heterogeneity: Chi <sup>2</sup> = 4.741, df = 15 (P < 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68% Test for overall effect Z = 2.10 (P = 0.0001); P = 68%		13		2				2020	•
Test for overall effect $Z = 6.61$ ( $P < 0.00001$ ) <b>1.1.2 Aricular acupressure</b> Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 Li 2017 38 40 28 40 7.8% 1.36 [1.09, 1.68] 2017 Chen 2020 20 30 8 30 2.2% 2.50 [1.31, 4.77] 2020 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.13 [0.33, 1.37] 2021 Subtotal (95% CI) 199 197 38.0% 1.27 [1.14, 1.41] Heterogeneity. Chi <sup>2</sup> = 9.56, df = 4 ( $P = 0.05$ ); $P = 58\%$ Test for overall effect $Z = 4.45$ ( $P < 0.00001$ ) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% CI) 79 77 19.0% 1.06 [0.95, 1.18] Total events 73 67 Heterogeneity. Chi <sup>2</sup> = 0.99, df = 1 ( $P = 0.32$ ); $P = 0\%$ Test for overall effect $Z = 1.10$ ( $P = 0.27$ ) <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] Total events 27 20 Heterogeneity. Not applicable Test for overall effect $Z = 2.10$ ( $P = 0.001$ ) Total events 473 356 Test for overall effect $Z = 2.10$ ( $P = 0.0001$ ) Total events 473 356 Test for overall effect $Z = 2.10$ ( $P = 0.0001$ ) Total events 473 356 Test for overall effect $Z = 2.10$ ( $P = 0.0001$ ) Total events 473 356 Test for overall effect $Z = 2.10$ ( $P = 0.0001$ ); $P = 68\%$ Test for overall effect $Z = 8.19$ ( $P < 0.00001$ ) Total events 473 356 Test for overall effect $Z = 8.19$ ( $P < 0.00001$ ) Test for overall effect $Z = 8.19$ ( $P < 0.00001$ ) Test for overall effect $Z = 8.19$ ( $P < 0.00001$ ) Test for subtromu differences: Ch <sup>2</sup> = 17 41 df = 3 ( $P = 0.0006$ ) $P = 82.8\%$	Total events	200		134					
Test for overall effect: $Z = 6.61$ (P < 0.00001) <b>1.1.2 Aricular acupressure</b> Chi 2012 26 29 23 27 6.7% 1.05 [0.86, 1.29] 2012 Li 2017 38 40 28 40 7.8% 1.36 [1.09, 1.68] 2017 Chen 2020 20 30 8 30 2.2% 2.50 [1.31, 4.77] 2020 Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.31 [0.33, 1.37] 2021 Subtotal (95% CI) 199 197 38.0% 1.27 [1.14, 1.41] Total events 173 135 Heterogeneity: Chi <sup>2</sup> 9.56, df - 4 (P = 0.05); iP = 56% Test for overall effect: Z = 4.45 (P < 0.00001) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% CI) 79 77 19.0% 1.06 [0.95, 1.18] Total events 73 67 Heterogeneity: Chi <sup>2</sup> 9.09, df = 1 (P = 0.32); iP = 0% Test for overall effect: Z = 1.10 (P = 0.27) <b>1.1.6 Acupoint injection and Acupunt massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] Total events 27 20 Heterogeneity: Chi <sup>2</sup> = 2.10 (P = 0.04) Total events 473 356 Test for overall effect: Z = 2.10 (P = 0.0001); P = 68% Test for overall effect: Z = 2.10 (P = 0.0001); P = 68% Test for overall effect: Z = 8.19 (P < 0.00001) Total events 473 356 Test for overall effect: Z = 8.19 (P < 0.00001) Total events 473 366 Test for overall effect: Z = 8.19 (P < 0.00001); P = 68% Test for overall effect: Z = 8.19 (P < 0.00001) Total events 473 366 Test for overall effect: Z = 8.19 (P < 0.00001); P = 68%	Heterogeneity: Chi <sup>2</sup> =	28.61, df=	7 (P = 1	0.0002); P	= 769	6			
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Zhai 2021 46 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.21 [1.02, 1.44] 2021 Yu 2021 43 50 38 50 10.6% 1.31 [0.33, 1.37] 2021 Subtotal (95% CI) 199 197 38.0% 1.27 [1.14, 1.41] Total events 173 135 Heterogeneity: Chi <sup>P</sup> = 9.55, df = 4 (P = 0.05); P = 58% Test for overall effect $Z = 4.45$ (P < 0.0001) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% CI) 79 77 19.0% Total events 73 67 Heterogeneity: Chi <sup>P</sup> = 0.99, df = 1 (P = 0.32); P = 0% Test for overall effect $Z = 1.10$ (P = 0.27) <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] Total events 27 20 Heterogeneity: Not applicable Test for overall effect $Z = 2.10$ (P = 0.04) Total events 27 20 Heterogeneity: Not applicable Test for overall effect $Z = 2.10$ (P = 0.04) Total events 473 356 Heterogeneity: Chi <sup>P</sup> = 47.41, df = 15 (P < 0.0001); P = 68% Test for overall effect $Z = 8.19$ (P < 0.0001) Total events 473 366 Heterogeneity: Chi <sup>P</sup> = 47.41, df = 15 (P < 0.0001); P = 68% Test for overall effect $Z = 8.19$ (P < 0.0001) Test for subtoround differences Chi <sup>P</sup> = 17.41 df = 3 (P = 0.0006) P = 82.8%	Li 2017	38	40	28	40	7.8%	1.36 [1.09, 1.68]	2017	
Yu 2021       43       50       38       50       10.6%       1.13 [0.93, 1.37]       2021         Subtotal (95% CI)       199       197       38.0%       1.27 [1.14, 1.41]         Total events       173       135         Heterogeneify: Chi <sup>2</sup> = 9.55, df = 4 (P = 0.05); P = 59%       59%         Test for overall effect: $Z = 4.45$ (P < 0.00001)       1.15 (0.90, 1.16)       2004         1.15 Acupoint injection and Acupuncture       Weng 2004       51       56       48       54       13.7%       1.02 [0.90, 1.16]       2004         Deng 2015       22       23       19       23       5.3%       1.16 [0.94, 1.42]       2015         Subtotal (95% CI)       79       77       19.0%       1.06 [0.95, 1.18]       70       70         Total events       73       67         Heterogeneity: Chi <sup>2</sup> = 0.99, df = 1 (P = 0.32); P = 0%       70%       1.35 [1.02, 1.79]       2017         Total events       27       20       30       5.6%       1.35 [1.02, 1.79]       2017         Total events       27       20       70       70       1.31 [1.23, 1.40]       70       70       70       70         Total events       473       356       558       551	Chen 2020		30	8	30		2.50 [1.31, 4.77]	2020	
Subtotal (95% CI) 199 197 38.0% 1.27 [1.14, 1.41] Total events 173 135 Heterogeneity: Ch <sup>2</sup> = 9.55, df = 4 (P = 0.05); P = 58% Test for overall effect $Z = 4.45$ (P < 0.0001) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtotal (95% CI) 79 77 19.0% 1.06 [0.95, 1.18] Total events 73 67 Heterogeneity: Ch <sup>2</sup> = 0.9 df = 1 (P = 0.32); P = 0% Test for overall effect $Z = 1.10$ (P = 0.27) <b>1.1.6 Acupoint injection and Acupoint massage</b> Chen 2017 27 30 20 30 5.6% 1.35 [1.02, 1.79] 2017 Subtotal (95% CI) 30 30 5.6% 1.35 [1.02, 1.79] Total events 27 20 Heterogeneity: Not applicable Test for overall effect $Z = 2.10$ (P = 0.04) Total events 473 356 Heterogeneity: Ch <sup>2</sup> = 47.41, df = 15 (P < 0.0001); P = 68% Test for overall effect $Z = 8.19$ (P < 0.00001) Test for subaround differences: Ch <sup>2</sup> = 17.41 df = 3 (P = 0.0006); P = 82.8%									+
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Heterogeneity: $Ch^{\mu} = 9.55$ , $df = 4$ (P = 0.05); $ ^{\mu} = 58\%$ Test for overall effect: $Z = 4.45$ (P < 0.0001) <b>1.1.5 Acupoint injection and Acupuncture</b> Weng 2004 51 56 48 54 13.7% 1.02 [0.90, 1.16] 2004 Deng 2015 22 23 19 23 5.3% 1.16 [0.94, 1.42] 2015 Subtoal (95% CI) 79 77 19.0% 1.06 [0.95, 1.18] Total events 73 67 Heterogeneity: $Ch^{\mu} = 0.99$ , $df = 1$ (P = 0.32); $ ^{\mu} = 0\%$ Test for overall effect: $Z = 1.10$ (P = 0.32); $ ^{\mu} = 0\%$ Test for overall effect: $Z = 1.10$ (P = 0.32); $ ^{\mu} = 0\%$ Test for overall effect: $Z = 1.10$ (P = 0.32); $ ^{\mu} = 0\%$ Test for overall effect: $Z = 2.10$ (P = 0.32) Total events 27 20 Heterogeneity: Not applicable Test for overall effect: $Z = 2.10$ (P = 0.04) Total events 473 356 Heterogeneity: $Ch^{\mu} = 47.41$ , $df = 15$ (P < 0.0001); $ ^{\mu} = 68\%$ Heterogeneity: $Ch^{\mu} = 47.41$ , $df = 15$ (P < 0.0001) Test for overall effect: $Z = 8.19$ (P < 0.00001) Test for subarroup differences: $Ch^{\mu} = 1741$ $df = 3$ (P = 0.0006)  ^{\mu} = 82.8\%			199		197	38.0%	1.27 [1.14, 1.41]		•
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Subtotal (95% Cl)       79       77       19.0%       1.06 $[0.95], 1.18]$ Total events       73       67         Heterogeneity: Chi <sup>2</sup> = 0.99, df = 1 (P = 0.32); P = 0%       79       77       10.06 $[0.95], 1.18]$ Total events       73       67         Heterogeneity: Chi <sup>2</sup> = 0.99, df = 1 (P = 0.32); P = 0%       79       70         Test for overall effect: Z = 1.10 (P = 0.27)       1.16 Acupoint injection and Acupoint massage         Chen 2017       27       30       20       30       5.6%       1.35 [1.02, 1.79]       2017         Subtotal (95% Cl)       30       30       5.6%       1.35 [1.02, 1.79]       2017         Total events       27       20       20       1.35 [1.02, 1.79]       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.00       1.01       1.01       1.00       1.00       Favours [control]       Favours [control]       Favours [experimental]         Total events       47.3       356       551       100.0%       1.31 [1.23, 1.40]       1.01       0.01       0.11       1.01       1.00       1.00         Total events <td< td=""><td>1.1.5 Acupoint injecti</td><td>on and Ac</td><td>upuncti</td><td>ire</td><td></td><td>10.70</td><td></td><td></td><td></td></td<>	1.1.5 Acupoint injecti	on and Ac	upuncti	ire		10.70			
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Subtotal (95% CI)       30       30       5.6%       1.35 [1.02, 1.79]         Total events       27       20         Heterogeneity: Not applicable       Test for overall effect: $Z = 2.10$ (P = 0.04)         Total (95% CI)       558       551       100.0%       1.31 [1.23, 1.40]         Total events       473       356         Heterogeneity: Chi <sup>2</sup> = 47.41, df = 15 (P < 0.0001); I <sup>2</sup> = 68%       0.01       0.1       1       10       100         Test for overall effect: Z = 8.19 (P < 0.00001)	1.1.5 Acupoint injecti Weng 2004 Deng 2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	on and Act 51 22 73 0.99, df = 1 Z = 1.10 (F	upunctu 56 23 79 1 (P = 0. 2 = 0.27)	48 48 19 67 32); I <sup>2</sup> = 0	23 77	5.3%	1.16 [0.94, 1.42]		
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Total (95% Cl)       558       551       100.0%       1.31 [1.23, 1.40]         Total events       473       356         Heterogeneity: Chi <sup>2</sup> = 47.41, df = 15 (P < 0.0001); I <sup>2</sup> = 68%       0.01       0.1       1       10       100         Test for overall effect: Z = 8.19 (P < 0.00001)	1.1.5 Acupoint injecti Weng 2004 Deng 2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 1.1.6 Acupoint injecti Chen 2017 Subtotal (95% CI) Total events	on and Act 51 22 73 0.99, df = 1 Z = 1.10 (F on and Act 27 27	upunctu 56 23 <b>79</b> 1 (P = 0. 2 = 0.27) upoint r 30	17e 48 19 67 32); I² = 0 ) massage 20	23 77 % 30	5.3% <b>19.0%</b> 5.6%	1.16 [0.94, 1.42] <b>1.06 [0.95, 1.18]</b> 1.35 [1.02, 1.79]	2015	<b>★</b>
Total events         473         356           Heterogeneity: Chi <sup>2</sup> = 47.41, df = 15 (P < 0.0001); I <sup>2</sup> = 68%         0.01         0.1         1         10         100           Test for overall effect: Z = 8.19 (P < 0.00001)	1.1.5 Acupoint injecti Weng 2004 Deng 2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 1.1.6 Acupoint injecti Chen 2017 Subtotal (95% CI) Total events Heterogeneity: Not ap	on and Act 51 22 73 0.99, df = 1 Z = 1.10 (F on and Act 27 27 27 plicable	upunctu 56 23 79 (P = 0. = 0.27) upoint r 30 30	re 48 19 67 32); I²= 0 ) nassage 20 20	23 77 % 30	5.3% <b>19.0%</b> 5.6%	1.16 [0.94, 1.42] <b>1.06 [0.95, 1.18]</b> 1.35 [1.02, 1.79]	2015	•
Total events         473         356           Heterogeneity: Chi <sup>2</sup> = 47.41, df = 15 (P < 0.0001); I <sup>2</sup> = 68%         0.01         0.1         1         10         100           Test for overall effect: Z = 8.19 (P < 0.00001)	1.1.5 Acupoint injecti Weng 2004 Deng 2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 1.1.6 Acupoint injecti Chen 2017 Subtotal (95% CI) Total events Heterogeneity: Not ap	on and Act 51 22 73 0.99, df = 1 Z = 1.10 (F on and Act 27 27 27 plicable	upunctu 56 23 79 (P = 0. = 0.27) upoint r 30 30	re 48 19 67 32); I²= 0 ) nassage 20 20	23 77 % 30	5.3% <b>19.0%</b> 5.6%	1.16 [0.94, 1.42] <b>1.06 [0.95, 1.18]</b> 1.35 [1.02, 1.79]	2015	•
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and TEAS (MD -1.96; 95% CI: -3.01, -0.91; p = 0.0003). No statistically significant improvement was evident for AFIR (MD 0.01, 95% CI: -0.66, 0.68; p = 0.98) or AST (MD -0.42; 95% CI: -0.96, 0.13; p = 0.13). Nonetheless, for all 15 studies combined, a significant decline in VAS score was evident in the experimental vs. control group (MD -1.64; 95% CI: -2.16, -1.11; p < 0.00001), with significant heterogeneity among the studies ( $I^2$  86%; p < 0.0001).

### Pauli-Magnus scale (PMS) score

Significant experimental-control group decreases in PMS scores (Figure 3B) were also noticed in three studies that included a total of 189 patients with UP (overall MD -9.38;

95% CI: –18.09, –0.66; p = 0.03), with significant heterogeneity among the studies ( $I^2$ 99%; p < 0.00001).

#### Modified Duo's (MDuo) pruritus score

Two studies in a total of 109 patients with UP showed no statistically significant overall improvement in mDuo score (Figure 3C) in the experimental vs. control group (MD -9.75; 95% CI: -21.50, +2.01;  $I^2$  96%; p = 0.10).

#### Dirk R. Kuypers scale (DRKS) score

Two studies in a total of 163 patients with UP showed no statistically significant overall improvement in DRKS score

(Figure 3D) in the experimental vs. control group (MD -5.25; 95% CI: -11.49, +0.98;  $I^2$  97%; p = 0.10).

#### Effective rate

Nine studies recorded the number of patients that became better after the therapies. For acupuncture, three individual studies showed statistically significantly higher efficacy in the treatment vs. the control group [risk ratio (RR) 4.78–14.87; Figure 4]. Overall results for acupuncture (RR 1.48; 95% CI: 1.32, 1.66), AA (RR 1.27; 95% CI: 1.14, 1.41), and AI+AM (RR 1.35; 95% CI: 1.02, 1.79) all showed increased efficacy relative to control; among these complementary therapies, improvements were statistically significant for acupuncture (p < 0.00001), AA (p < 0.0001) and AI+AM (p = 0.04). Although AI + acupuncture showed no significant improvement in efficacy relative to control, the complementary therapies evaluated demonstrated significantly improved overall efficacy vs. control (RR 1.31; 95% CI: 1.23, 1.40; p < 0.00001).

#### Laboratory parameters

The table of serum data from the collected studies was attached in the Supplementary material. Statistically significant overall improvement vs. control were noted, and with mild to high heterogeneity, for the complementary therapies evaluated, regarding BUN (MD -0.85; 95% CI: -1.46, -0.24; p = 0.006; Figure 5), PTH (MD -29.18; 95% CI: -48.19, -10.18; p = 0.003), and histamine levels (MD -1.18; 95% CI: -1.62, -0.73; p < 0.0001). Changes in serum creatinine, phosphate, calcium,  $\beta$ 2-microglobulin, C-reactive protein, hemoglobin, white blood cell count, and alkaline phosphatase were not statistically significant (p>0.05 for each; moderate to high heterogeneity).

## Discussion

In our review, acupoint acupuncture, AA, AI, AM, AIR, TEAS, and AI+AM statistically significantly improved mean VAS scores for pruritus in patients with UP (9, 12, 14, 27, 29, 34, 40, 42-44, 50, 53). Decreased mean PMS scores for treatment vs. control were noted in three studies: one study about acupuncture, and two about AA (5, 39, 44). Sixteen studies recorded effective rates for acupuncture, AA, acupuncture + AI, and AI+AM: results revealed significantly greater efficacy than control for acupuncture (RR 1.48; 95% CI: 1.32, 1.66), AA (RR 1.32; 95% CI: 1.00, 1.46), and AI+AM (RR 1.35; 95% CI: 1.02, 1.79) (25, 29, 30, 33, 34, 36-38, 41, 46, 48, 51, 53). In large populations, especially, small changes may be statistically significant, but can be irrelevant clinically. The minimal clinically important difference (MCID) is defined as the smallest change in any scale scoring that can be noticed by the patient (57). Several methods exist for determining MCID; however, currently no universal rule is established. Reich et al.

suggested that the MCID for clinical improvement in itch, as rated on the VAS and NRS, ranks between a decrease of 2-3points (57). Claudia et al. found MCID of 192 patients that the very severe baseline pruritus (>9) had to be reduced by at least 4.56 points, and the severe pruritus (7 to <9) by at least 3.65 (58). In our article, improvement of VAS is modest to minor, although statistically significant after pooling to meta-analyze the expanded study population.

Traditionally, acupuncture has been reported as a safe and effective treatment for pruritus, and has been used in China for many years (59). Yan et al. reported that acupuncture significantly reduced pruritus scores in hemodialysis patients with UP (60). Generally, the most frequently used method was manual acupuncture, although TEAS and auricular acupuncture have also been used for UP (14).

In our acupuncture group, the most common acupoint choices were SP10 (eight studies), LI11 (seven studies), SP6, and ST36 (each of these acupoints used in six studies) (5, 22, 25-34, 37, 38). EA at LI11 and SP10 could improve pruritus due to reducing the expression of TLR2, TLR4, MyD88 and NF- $\kappa B$  which increased in the morphine-induced pruritus model mice (61). Cold stimulation (20°C) at LI11 in compound 40/80-induced mice showed decreased c-fos expression in the dorsal horn at C2-C7 and decreased scratching bouts (62). The treatment frequency was about two to three times per week and decreased VAS, PMS, and DRKS scores confirmed the efficacy of the acupuncture. Overall, VAS scores showed significant improvements vs. control for acupuncture, AA, AI, AM, AIR, ATENS, and AI+AM (9, 12, 14, 27, 29, 34, 40, 42-44, 50, 53). Three studies revealed a significant decline in PMS scores, but with significant heterogeneity among the studies ( $I^2$  99%; p <0.00001) (5, 39, 44). Ma et al., Zhang et al., and Chang et al. all reported improved effective rates after acupuncture therapies compared with control (25, 31, 33). Regarding complications, Che et al. used acupuncture at SP6, SP10, ST36, and LI11 in 40 patients and could report that 2 patients (one in acupuncture group, another in control group) complained about elbow soreness and 3 patients in the control group complained about minimal bleeding induced by acupuncture (5). Phan et al. performed 216 times (12× in 18 patients) in patients undergoing hemodialysis who received heparin. Bleeding was observed in 13 patients after the needle was removed from the spot, and the bleeding was mild and could be controlled with the use of cotton and the application of pressure. No serious cases of bleeding occurred. Hematoma, which occurred after bleeding, was observed in four (1.85%) patients. However, the hematoma disappeared without any therapy within 3-10 days (28).

Auricular acupoints affect the functioning of the visceral organs and meridians, skeleton, and limbs, and AA proved to be a useful treatment for UP in patients with end-stage renal disease (60). Indeed, in patients undergoing hemodialysis, AA had a beneficial effect on conditions such as sleep disorders, depression, pruritus, and xerostomia (63). Karjalian et al. reported improved pruritus in a study that evaluated AM as

## Α

tudy or Subarous	Mean	eriment SD		Co Mean	ntrol SD 1	otel	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
tudy or Subgroup hi 2012	10	4	30	11	5	30	7.1%	-1.00 [-3.29, 1.29]	
u 2015-a	24.68	2.36			1.81	20	21.9%	-1.33 [-2.63, -0.03]	
u 2015-b	20.83	1.56	20	21.31	1.7	20	36.4%	-0.48 [-1.49, 0.53]	
u 2015-c	20.85	2.47		21.95		20	15.4%	-0.40 [-1.96, 1.16]	
arjalia 2020	55.25	12		56.43		30	0.6%	-1.18 [-8.83, 6.47]	
no 2015	19.1	5	20	20.6	6.5	23	3.1%	-1.50 [-4.94, 1.94]	
2018		2.94			3.05	20	10.8%	-1.38 [-3.24, 0.48]	
		7.13	30		6.76				
hang 2020 hu 2018	26.12 24.84			27.56 24.85		33 20	3.2% 1.4%	-1.44 [-4.88, 2.00] -0.01 [-5.18, 5.16]	
10 2018	24.04	0.20	20	24.05	0.42	20	1.4 %	-0.01 [-3.16, 3.10]	
otal (95% Cl) eterogeneity: Tau <sup>2</sup> : est for overall effect				: 8 (P = (			100.0%	-0.85 [-1.46, -0.24] _	-10 -5 0 5 10 Favours [control]
	-	rimenta			Control			Mean Difference	Mean Difference
udy or Subgroup	Mean	SD	Total	Mea	n s	SD T	otal Wei	ght IV, Random, 95%	CI IV, Random, 95% CI
ien 2021	971.8	124.2	31	962			31 12.		
ni 2012	316	59	30	31		60	30 15.		
su 2009	431.57	94.11	21	240.6				1% 190.93 [134.60, 247.2	
2015	850.35	34.58	20	800.7			20 16.		
rjalia 2020	894	140	30	88		80	30 10.		
10 2015	353.6	79.56	24	371.2		3.4	23 13.		
2018	868.2	287.5	20		2 274.			5% 6.00 [-168.23, 180.2	
ang 2020 u 2018	1,066.27 877.18		30 20		2 282.			1% -71.15 [-195.34, 53.0 9% -6.54 [-133.83, 120.7	
4.2010	077.10	200.30	20	003.7	z 202.	55	20 0.	-0.54 [153.05, 120.7	
tal (95% CI)			226				227 100.	0% 27.22 [-16.31, 70.7	<sup>75]</sup>
eterogeneity: Tau² = 2 st for overall effect: Z			08, df:	= 8 (P < 0	.00001)	; l² = 8	3%		-200 -100 0 100 200 Favours [experimental] Favours [control]
		rimenta			ntrol			Mean Difference	Mean Difference
udy or Subgroup	Mean	5 0 x 3 x 3 x 3		Mean				IV, Random, 95% CI	IV, Random, 95% Cl
hen 2020		0.41	30		0.36	30	6.5%	0.33 [0.13, 0.53]	
hi 2012	2.27	0.48	30		0.49	30	5.1%	0.01 [-0.24, 0.26]	
su 2009		0.03	21		0.04	20	12.0%	0.08 [0.06, 0.10]	
ang 2021	2.2	0.13	14	2.23	0.1	14	10.4%	-0.03 [-0.12, 0.06]	
	2.01	0.23	20	1.97	0.19	20	8.7%	0.04 [-0.09, 0.17]	
2015		0.20	30	1.9	0.34	30	7.7%	-0.17 [-0.33, -0.01]	
i 2015 arjalia 2020	1.73	0.23			0.00	40	2.6%	-0.10 [-0.50, 0.30]	
		0.96	40	2.5	0.88	40	2.0 /0	0.10[0.00]0.00]	
arjalia 2020	1.73		40 24		0.88 0.18	23	10.5%	-0.07 [-0.15, 0.01]	
arjalia 2020 u 2019	1.73 2.4 2.38	0.96							
arjalia 2020 u 2019 no 2015	1.73 2.4 2.38	0.96 0.1	24	2.45	0.18 0.3	23	10.5%	-0.07 [-0.15, 0.01]	
arjalia 2020 u 2019 no 2015 ang 2021	1.73 2.4 2.38 2.35 2.53	0.96 0.1 0.31	24 55	2.45 2.34 2.42	0.18 0.3	23 54	10.5% 9.3% 7.6%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27]	
arjalia 2020 u 2019 no 2015 ang 2021 an 2015 2018	1.73 2.4 2.38 2.35 2.53 2.06	0.96 0.1 0.31 0.37	24 55 32	2.45 2.34 2.42	0.18 0.3 0.28 0.16	23 54 30	10.5% 9.3%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11]	 
arjalia 2020 u 2019 no 2015 ang 2021 an 2015	1.73 2.4 2.38 2.35 2.53 2.06	0.96 0.1 0.31 0.37 0.13	24 55 32 20	2.45 2.34 2.42 2.26	0.18 0.3 0.28 0.16	23 54 30 20	10.5% 9.3% 7.6% 10.2%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27]	
arjalia 2020 u 2019 no 2015 ang 2021 an 2015 2018 nang 2020 otal (95% CI)	1.73 2.4 2.38 2.35 2.53 2.06 2.25	0.96 0.1 0.31 0.37 0.13 0.19	24 55 32 20 30 <b>346</b>	2.45 2.34 2.42 2.26 2.27	0.18 0.3 0.28 0.16 0.26	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11]	
arjalia 2020 u 2019 no 2015 ang 2021 un 2015 2018 aang 2020 otal (95% CI) eterogeneity: Tau <sup>2</sup> =	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; Cf	0.96 0.1 0.31 0.37 0.13 0.19	24 55 32 20 30 <b>346</b> 25, df	2.45 2.34 2.42 2.26 2.27	0.18 0.3 0.28 0.16 0.26	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07]	
arjalia 2020 u 2019 no 2015 ang 2021 an 2015 2018 nang 2020 otal (95% CI)	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; Cf	0.96 0.1 0.31 0.37 0.13 0.19	24 55 32 20 30 <b>346</b> 25, df	2.45 2.34 2.42 2.26 2.27	0.18 0.3 0.28 0.16 0.26	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09]	
arjalia 2020 u 2019 no 2015 ang 2021 un 2015 2018 aang 2020 otal (95% CI) eterogeneity: Tau <sup>2</sup> =	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; Cf	0.96 0.1 0.31 0.37 0.13 0.19	24 55 32 20 30 <b>346</b> 25, df	2.45 2.34 2.42 2.26 2.27	0.18 0.3 0.28 0.16 0.26	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07]	
arjalia 2020 u 2019 no 2015 ang 2021 un 2015 2018 aang 2020 otal (95% CI) eterogeneity: Tau <sup>2</sup> =	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; CP t Z = 0.11	0.96 0.1 0.31 0.37 0.13 0.19 hi <sup>2</sup> = 66. (P = 0.9	24 55 32 20 30 <b>346</b> 25, df	2.45 2.34 2.42 2.26 2.27 = 11 (P	0.18 0.3 0.28 0.16 0.26	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07]	
arjalia 2020 u 2019 no 2015 ang 2021 un 2015 2018 aang 2020 otal (95% CI) eterogeneity: Tau <sup>2</sup> =	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; CP t Z = 0.11	0.96 0.1 0.31 0.37 0.13 0.19 ni <sup>2</sup> = 66. (P = 0.9	24 55 32 20 30 <b>346</b> 25, df	2.45 2.34 2.42 2.26 2.27 = 11 (P	0.18 0.3 0.28 0.16 0.26 ≺ 0.000	23 54 30 20 33 <b>344</b>	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1	Favours [experimental] Favours [control]
arjalia 2020 u 2019 no 2015 ang 2021 an 2015 2018 nang 2020 otal (95% CI) eterogeneity: Tau <sup>#</sup> = est for overall effect	1.73 2.4 2.38 2.53 2.06 2.25 = 0.01; CF : Z = 0.11	0.96 0.1 0.31 0.37 0.13 0.19 mi <sup>z</sup> = 66. (P = 0.9 crimenta SD	24 55 32 20 30 <b>346</b> 25, df 31)	2.45 2.34 2.42 2.26 2.27 = 11 (P	0.18 0.3 0.28 0.16 0.26 ≺ 0.000 ntrol <u>SD T</u>	23 54 30 20 33 <b>344</b> 01); P	10.5% 9.3% 7.6% 10.2% 9.4% 100.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1 Mean Difference	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 no 2015 ang 2021 ang 2021 ang 2020 otal (95% CI) eterogeneity: Tau <sup>2</sup> = set for overall effect udy or Subgroup nen 2020	1.73 2.4 2.38 2.35 2.05 2.25 = 0.01; CF : Z = 0.11 Expe <u>Mean</u> 1.52	0.96 0.1 0.31 0.37 0.13 0.19 $hi^2 = 66.$ (P = 0.9 erimenta <u>SD</u> 0.23	24 55 32 20 30 <b>346</b> 25, df 31) al <u>Total</u> 30	2.45 2.34 2.42 2.26 2.27 = 11 (P - Co <u>Mean</u> 1.84	0.18 0.3 0.28 0.16 0.26 × 0.000 ntrol <u>SD T</u> 0.32	23 54 30 20 33 <b>344</b> 01); <sup>17</sup> <u>otal</u> 30	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% *= 83% Weight 7.1%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1 Mean Difference <u>IV, Random, 95% C1</u> -0.32 [-0.46, -0.18]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 no 2015 ang 2021 ang 2021 ang 2020 ytal (95% Cl) eterogeneity: Tau <sup>=</sup> = est for overall effect udy or Subgroup nen 2020 nen 2021	1.73 2.4 2.38 2.35 2.05 2.25 = 0.01; CF : Z = 0.11 Expe Mean 1.52 1.67	0.96 0.1 0.31 0.37 0.13 0.19 $hi^2 = 66.$ (P = 0.9 erimenta <u>SD</u> 0.23 0.32	24 55 32 20 30 <b>346</b> 25, df 31) al Total 30 31	2.45 2.34 2.42 2.26 2.27 = 11 (P - Co <u>Mean</u> 1.84 1.69	0.18 0.3 0.28 0.16 0.26 × 0.000 <b>ntrol</b> <u>SD T</u> 0.32 0.43	23 54 30 20 33 <b>344</b> 01); P <u>otal</u> 30 31	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% = 83% Weight 7.1% 6.2%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1 Mean Difference IV. Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 tal (95% CI) sterogeneity: Tau <sup>#</sup> = set for overall effect <u>udy or Subgroup</u> nen 2020 nen 2021 ni 2012	1.73 2.4 2.38 2.63 2.63 2.25 = 0.01; CF : Z = 0.11 Expe <u>Mean</u> 1.62 1.67 1.5	0.96 0.1 0.31 0.37 0.13 0.13 0.19 mi <sup>2</sup> = 66. ( $P = 0.9$ crimenta <u>sp</u> 0.23 0.32 0.4	24 55 32 20 30 <b>346</b> 25, df 31) <b>al</b> <b>Total</b> 30 31 30	2.45 2.34 2.42 2.26 2.27 = 11 (P · <u>Co</u> <u>Mean</u> 1.84 1.69 1.6	0.18 0.3 0.28 0.16 0.26 × 0.000 ntrol <u>SD T</u> 0.32 0.43 0.4	23 54 30 20 33 <b>344</b> 01); P	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% = 83% Weight 7.1% 6.2% 6.0%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H -1 Mean Difference <u>IV, Random, 95% C1</u> -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 otal (95% CI) sterogeneity: Tau <sup>2</sup> = set for overall effect udy or Subgroup hen 2020 hen 2021 hi 2012 su 2009	1.73 2.4 2.38 2.35 2.53 2.06 2.25 = 0.01; Ct : Z = 0.11 Expe <u>Mean</u> 1.52 1.67 1.52	0.96 0.1 0.31 0.37 0.13 0.19 mi <sup>2</sup> = 66. ( $P = 0.9$ crimenta <u>SD</u> 0.23 0.32 0.4 0.09	24 55 32 20 <b>346</b> 25, df 31) <b>346</b> 25, df 31) 30 31 30 21	2.45 2.34 2.42 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52	0.18 0.3 0.28 0.16 0.26 × 0.000 ntrol <u>SD T</u> 0.32 0.43 0.4 0.11	23 54 30 20 33 <b>344</b> 01); P <u>otal</u> 30 31 30 20	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% <sup>2</sup> = 83% <u>Weight</u> 7.1% 6.2% 8.0% 8.2%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1 Mean Difference IV, Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 no 2015 ang 2021 ang 2021 ang 2020 vtal (95% Cl) eterogeneity: Tau <sup>2</sup> = set for overall effect <u>udy or Subgroup</u> nen 2020 nen 2021 ni 2012 su 2009 ang 2021	1.73 2.4 2.38 2.35 2.63 2.25 = 0.01; Cf : Z = 0.11 Expe <u>Mean</u> 1.52 1.67 1.5 1.62 2.22	0.96 0.1 0.31 0.37 0.13 0.19 $hi^2 = 66.$ (P = 0.9 erimenta <u>SD</u> 0.23 0.32 0.4 0.09 0.13	24 55 32 20 30 <b>346</b> 25, df 70 1) <b>31</b> 30 31 30 31 30 21 14	2.45 2.34 2.26 2.27 = 11 (P - Co <u>Mean</u> 1.84 1.6 1.52 2.23	0.18 0.3 0.28 0.16 0.26 × 0.0000 ntrol <u>SD T</u> 0.32 0.43 0.43 0.41 0.1	23 54 30 20 33 <b>344</b> 01); P <u>otal</u> 30 31 30 20 14	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% <sup>2</sup> = 83% <sup>3</sup> <sup>2</sup> = 83% <sup>3</sup> 7.1% 6.2% 6.2% 6.2% 6.2% 7.9%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H -1 Mean Difference IV. Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 tal (95% CI) seterogeneity: Tau <sup>#</sup> = set for overall effect <u>udv or Subgroup</u> nen 2020 nen 2020 nen 2021 ni 2012 su 2009 ang 2021 1,2015	1.73 2.4 2.38 2.35 2.06 2.25 = 0.01; CF : Z = 0.11 <b>Expe</b> <u>Mean</u> 1.55 1.67 1.5 1.62 2.22 2.97	$0.96 \\ 0.1 \\ 0.31 \\ 0.37 \\ 0.13 \\ 0.19 \\ 0.19 \\ 0.19 \\ 0.13 \\ 0.23 \\ 0.23 \\ 0.23 \\ 0.23 \\ 0.23 \\ 0.4 \\ 0.09 \\ 0.13 \\ 0.09 \\ 0.13 \\ 0.09 \\ 0.09 \\ 0.13 \\ 0.09 \\ 0.09 \\ 0.09 \\ 0.00 \\ 0.$	24 55 32 20 30 <b>346</b> 25, df 31) <b>31</b> 30 31 30 31 30 21 14 20	2.45 2.34 2.26 2.27 = 11 (P <u>Mean</u> 1.84 1.69 1.69 1.52 2.23 1.88	0.18 0.3 0.28 0.16 0.26 × 0.0000 ntrol <u>SD T</u> 0.32 0.43 0.4 0.11 0.1 0.22	23 54 30 20 33 <b>344</b> 01); F <u>otal</u> 30 31 30 20 14 20	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% = 83% Weight 7.1% 6.2% 6.0% 8.2% 6.0% 8.2% 7.7%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H Mean Difference IV, Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [-0.40, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 otal (95% CI) eterogeneity: Tau <sup>≠</sup> = est for overall effect udv or Subgroup nen 2020 nen 2021 ni 2012 su 2009 ang 2021 1 2015 arjalia 2020	1.73 2.4 2.38 2.55 2.53 2.06 2.25 = 0.01; CH t: Z = 0.11 <b>Expe</b> Mean 1.52 1.67 1.55 1.62 2.22 1.97 2.39	$\begin{array}{c} 0.96\\ 0.1\\ 0.31\\ 0.31\\ 0.13\\ 0.19\\ 0.19\\ 0.19\\ rimenta\\ sp\\ 0.23\\ 0.32\\ 0.4\\ 0.09\\ 0.13\\ 0.09\\ 0.23\\ \end{array}$	24 55 32 20 30 <b>346</b> 25, df 31) 30 31 30 31 30 21 14 20 30	2.45 2.34 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52 2.23 1.88 2.8	0.18 0.3 0.28 0.16 0.26 < 0.000 ntrol <u>SD T</u> 0.32 0.43 0.4 0.11 0.1 0.22 0.21	23 54 30 20 33 <b>344</b> 01); F <u>otal</u> 30 31 30 20 14 20 30	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% *= 83% ************************************	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H -1 Mean Difference IV, Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 no 2015 ang 2021 ang 2021 ang 2020 vtal (95% CI) eterogeneity: Tau <sup>2</sup> = set for overall effect udy or Subgroup hen 2020 hen 2021 hen 2021 i 2015 ang 2021 i 2015 arjalia 2020 h 2018	1.73 2.4 2.35 2.53 2.06 2.25 = 0.01; Ct : Z = 0.11 Expe <u>Mean</u> 1.52 1.67 1.52 1.67 1.62 2.22 1.97 2.39 1.33	$0.96 \\ 0.1 \\ 0.37 \\ 0.13 \\ 0.19 \\ 0.19 \\ (P = 0.9 \\ rimenta \\ sp \\ 0.23 \\ 0.32 \\ 0.4 \\ 0.09 \\ 0.13 \\ 0.09 \\ 0.23 \\ 0.12$	24 55 32 20 30 <b>346</b> 25, df 31) 30 31 30 31 30 21 14 20 30 30	2.45 2.34 2.42 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.52 2.23 1.88 2.8 1.45	0.18 0.3 0.28 0.16 0.26 0.26 0.26 0.26 0.32 0.43 0.4 0.11 0.12 0.22 0.21 0.12	23 54 30 20 33 <b>344</b> 01); F 6 01); F 7 01); F 7 01 30 30 30 30 30	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% <sup>2</sup> = 83% <u>Weight</u> 7.1% 6.2% 6.0% 8.2% 7.9% 7.6% 8.2%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -1 Mean Difference IV. Random, 95% CI -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30] -0.12 [-0.18, -0.06]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 tal (95% Cl) sterogeneity: Tau <sup>#</sup> = est for overall effect udy or Subgroup hen 2020 hen 2020 hi 2012 su 2009 ang 2021 1 2015 1 2018 u 2019	1.73 2.4 2.38 2.63 2.65 2.25 = 0.01; CF : Z = 0.11 Expe Mean 1.62 1.67 1.5 1.62 2.22 1.97 2.39 1.33 1.75	0.96 0.1 0.31 0.37 0.13 0.13 0.13 0.19 rimenta <u>SD</u> 0.23 0.32 0.4 0.09 0.13 0.9 0.4 0.09 0.13 0.4 0.9 0.4 0.32 0.4 0.32 0.4 0.32 0.4 0.32 0.13 0.13 0.13 0.13 0.19 0.23 0.23 0.32 0.13 0.23 0.32 0.32 0.43 0.44 0.43 0.44 0.43 0.43 0.44 0.43 0.43 0.44 0.43 0.44 0.43 0.43 0.44 0.43 0.43 0.44 0.43 0.44 0.43 0.44 0	24 55 32 20 30 <b>346</b> 25, df 21) 31 30 31 30 21 14 20 30 30 40	2.45 2.34 2.42 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52 2.23 1.88 2.88 2.45 1.73	0.18 0.3 0.28 0.16 0.26 ntrol <u>\$0,000</u> 0.40 0.4 0.4 0.11 0.22 0.21 0.22 0.21 0.22	23 54 30 20 33 <b>344</b> 01); F 6 01); F 7 01); F 7 01); F 01 30 30 30 30 30 40	10.5% 9.3% 7.6% 10.2% 9.4% = 83% = 83% Weight 7.1% 6.2% 6.0% 8.2% 7.9% 7.7% 7.6% 8.2% 3.4%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H Mean Difference IV, Random, 95% CI -0.32 [-0.46, -0.18] -0.32 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [-0.30, 0.10] 0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30] -0.12 [-0.18, -0.06] 0.02 [-0.37, 0.41]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2020 tal (95% CI) sterogeneity: Tau <sup>2</sup> = set for overall effect udv or Subgroup nen 2020 nen 2020 ni 2012 su 2009 ang 2021 1 2015 arjalia 2020 n 2018 u 2019 no 2015	1.73 2.4 2.38 2.55 2.53 2.26 2.25 = 0.01; CH : Z = 0.11 Expe Mean 1.52 1.67 1.55 1.62 2.22 1.97 2.39 1.33 1.75 2.3	0.96 0.1 0.31 0.37 0.13 0.19 ni <sup>#</sup> = 66. (P = 0.1 0.23 0.32 0.32 0.32 0.4 0.09 0.13 0.09 0.13 0.09 0.12 0.087 0.5	24 55 32 20 30 <b>346</b> 25, df 25, df 21) 30 31 30 31 30 21 14 20 30 30 30 40 24	2.45 2.34 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52 2.23 1.88 2.8 1.45 1.73 2.3	0.18 0.3 0.28 0.16 0.26 ≤ 0.000 sD T 0.32 0.43 0.4 0.11 0.12 0.21 0.12 0.88 0.6	23 54 30 20 33 <b>344</b> 01); F 01); F 01]; F 01	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% 5=83% 5=83% 5=83% 5=83% 6.0% 8.2% 7.7% 7.6% 8.2% 7.7.6% 8.2% 3.4% 3.4%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H -0.02 [-0.14, 0.08] -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30] -0.12 [-0.18, -0.06] 0.02 [-0.37, 0.41] 0.00 [-0.32, 0.32]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 no 2015 ang 2021 ang 2021 ang 2020 vtal (95% CI) eterogeneity: Tau <sup>2</sup> = eterogeneity: Tau <sup>2</sup> = eterogeneity: Tau <sup>2</sup> = eterogeneity: Tau <sup>2</sup> = udv or Subgroup hen 2020 hen 2020 hen 2021 su 2009 ang 2021 i 2015 ang 2020 ho 2015 ang 2021	1.73 2.4 2.38 2.25 2.53 2.06 2.25 = 0.01; Ct : Z = 0.11 Expe Mean 1.52 1.67 1.55 1.62 2.22 1.97 2.39 1.33 1.75 2.3 3 2.13	0.96 0.1 0.31 0.37 0.13 0.19 n <sup>17</sup> = 66. (P = 0.4 (P = 0.4 0.23 0.32 0.4 0.9 0.13 0.23 0.4 0.09 0.23 0.23 0.4	24 55 32 20 30 <b>346</b> 25, df 31) 30 31 30 21 14 20 30 21 14 20 30 30 21 55	2.45 2.34 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52 2.23 1.88 2.8 1.45 1.23 2.21	0.18 0.3 0.28 0.16 0.26 ≤ 0.000 mtrol <u>\$0 1</u> 0.32 0.43 0.43 0.43 0.41 0.22 0.22 0.21 0.22 0.89 0.6 0.6	23 54 30 20 33 <b>344</b> 01); P 01); P 01	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% 2= 83% 2= 83% 7.1% 6.0% 8.2% 7.9% 7.6% 8.2% 3.4% 4.2% 3.4% 4.2%	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -0.00 [-0.08, 0.07] -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.32, 0.32] -0.08 [-0.23, 0.07]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 tal (95% CI) sterogeneity: Tau <sup>#</sup> = est for overall effect udy of Subgroup hen 2020 hen 2020 hen 2021 hi 2012 su 2009 ang 2021 u 2015 ang 2021 hi 2015	1.73 2.4 2.38 2.35 2.63 2.06 2.25 = 0.01; Ch : Z = 0.11 <b>Expe</b> Mean 1.52 1.67 1.5 1.62 2.22 1.97 2.39 1.75 2.3 2.13 3.1.75 2.3 2.13 2.04	0.96 0.1 0.37 0.13 0.19 ni <sup>#</sup> = 66. (P = 0.9 riment. <u>SD</u> 0.23 0.23 0.23 0.23 0.4 0.09 0.13 0.09 0.13 0.23 0.4 0.4 0.4 0.4	24 55 32 20 30 <b>346</b> 25, df 31) <b>31</b> 30 31 30 31 30 21 14 20 30 21 14 20 30 21 55 32	2.45 2.34 2.42 2.26 2.27 = 11 (P · Co <u>Mean</u> 1.84 1.69 1.62 2.23 1.88 1.62 2.23 1.88 1.45 1.73 2.3 2.21 2.2	0.18 0.3 0.28 0.16 0.26 ≤ 0.000 0.26 × 0.000 0.32 0.43 0.44 0.45 0.43 0.43 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.42 0.42 0.43 0.42 0.42 0.43 0.43 0.42 0.42 0.43 0.42 0.43 0.52 0.63 0.63 0.63 0.63 0.63 0.63 0.64 0.65 0.55	23 54 30 20 33 <b>344</b> 01); F 50 10 10 10 10 10 20 14 20 30 20 14 20 30 40 23 54 30	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% = 83% *= 83%*= 83%*= 83% *= 83%*= 83%*= 83%*= 83% *= 83%*= 83%*= 83% *= 83%*= 83%*= 83%*= 83% *= 83%*= 83%*= 83%*= 83% *= 83%*= 83%*= 83%*= 83%*= 83%*= 83%*= 83%*= 83%*= 8	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] H -0.02 [-0.10, 0.08] -0.32 [-0.46, -0.18] -0.32 [-0.46, -0.18] -0.32 [-0.46, -0.18] -0.32 [-0.41, 0.10] 0.10 [-0.30, 0.10] 0.11 [-0.18, -0.06] 0.09 [-0.01, 0.19] -0.12 [-0.18, -0.06] 0.02 [-0.37, 0.41] 0.008 [-0.23, 0.02] -0.08 [-0.23, 0.02] -0.08 [-0.23, 0.02] -0.08 [-0.24, 0.12]	Favours [experimental] Favours [control] Mean Difference
arjalia 2020 u 2019 to 2015 ang 2021 ang 2021 ang 2020 tal (95% CI) sterogeneity: Tau <sup>2</sup> = est for overall effect udv or Subgroup nen 2020 nen 2020 ni 2012 su 2009 ang 2021 1 2015 arjalia 2020 n 2015 ang 2021 u 2019 no 2015 ang 2021 u 2019 no 2015 ang 2021 u 2015 ang 2021 ang 2021	1.73 2.4 2.38 2.25 2.53 2.06 2.25 = 0.01; Ct : Z = 0.11 Expe Mean 1.52 1.67 1.55 1.62 2.22 1.97 2.39 1.33 1.75 2.3 3 2.13	0.96 0.1 0.37 0.13 0.19 ni <sup>#</sup> = 66. (P = 0.9 riment. <u>SD</u> 0.23 0.23 0.23 0.23 0.4 0.09 0.13 0.09 0.13 0.23 0.4 0.4 0.4 0.4	24 55 32 20 30 <b>346</b> 25, df 31) 30 31 30 21 14 20 30 21 14 20 30 30 21 55	2.45 2.34 2.26 2.27 = 11 (P <u>Co</u> <u>Mean</u> 1.84 1.69 1.6 1.52 2.23 1.88 2.8 1.45 1.23 2.21	0.18 0.3 0.28 0.16 0.26 ≤ 0.000 0.26 × 0.000 0.32 0.43 0.44 0.45 0.43 0.43 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.42 0.42 0.43 0.42 0.42 0.42 0.42 0.42 0.43 0.42 0.42 0.43 0.43 0.42 0.42 0.43 0.42 0.43 0.52 0.63 0.63 0.63 0.63 0.63 0.63 0.64 0.65 0.55	23 54 30 20 33 <b>344</b> 01); P 01); P 01	10.5% 9.3% 7.6% 10.2% 9.4% 100.0% 2 = 83% 2 = 83%2 = 83% 2 = 83% 2 = 83% 2 = 83%2 = 83% 2 = 83% 2 = 83%2 = 83% 2 = 83% 2 = 83%2 = 83%2 = 83% 2 = 83%2 = 83%2 = 83%2 = 83% 2 = 83%2 = 83%2 = 83% 2 = 83%2 = 83%2 = 83%2 = 83% 2 = 83% 2 = 83% 2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 = 83%2 =	-0.07 [-0.15, 0.01] 0.01 [-0.10, 0.12] 0.11 [-0.05, 0.27] -0.20 [-0.29, -0.11] -0.02 [-0.13, 0.09] -0.00 [-0.08, 0.07] -0.00 [-0.08, 0.07] -0.32 [-0.46, -0.18] -0.02 [-0.21, 0.17] -0.10 [-0.30, 0.10] 0.10 [0.04, 0.16] -0.01 [-0.10, 0.08] 0.09 [-0.01, 0.19] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.52, -0.30] -0.41 [-0.32, 0.32] -0.08 [-0.23, 0.07]	Favours [experimental] Favours [control] Mean Difference
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FIGURE 5 (Continued)



Forest plot comparison of serum levels of (A) blood urea nitrogen, (B) creatinine, (C) calcium, (D) phosphate, (E) parathyroid hormone, (F)  $\beta$ 2-microglobulin, (G) C-reactive protein, (H) histamine, (I) hemoglobin, (J) white blood cells, and (K) alkaline phosphatase in patients with uremic pruritus treated with acupuncture or other related complementary therapies. CI, confidence interval; IV, independent variable; SD, standard deviation.

a treatment for UP (7), and PMS scores improved after AA in studies conducted by Mai et al. and He et al. (39, 44). For AA, the treatment frequency in studies in our review was about three to eight times per day, and the meridians used included lung, kidney, heart, stomach, endocrine, subcortical, supracortical, adrenal, and TF4. One study used auricular acupoint scraping therapy for UP patients (35). Scraping stimulation makes subcutaneous capillaries expand or break, creating skin eruptions with flush or purple-red skin, miliary and papuloid spots, patchy and stripy plaques, and local hot sensation or mild pain. Skin eruptions can improve blood circulation, promote cell metabolism, and strengthen immunity to cure diseases and promote recovery (64). Overall, AA produced significant relief of symptoms, and significantly improved effective rates, relative to control (39, 44).

AI uses a syringe needle instead of an acupuncture needle at acupoints (50). AI achieved the same or higher plasma concentrations than the intravenous injection of carbamyl  $\beta$ -methylcholine chloride injection at ST36 and femoral vein (65). There was a significantly increased phylloquinone plasma concentration found in a study of AI at SP6 as the trigger point (66). Several clinical studies have shown that AI has definite advantages and reliable curative effects for the treatment of pruritis in patients with CKD (51–53, 67).

AM stimulates the meridian points by pressure applied with the fingertips, palms, small beads, or special devices (68). The pressure on acupoints could promote blood circulation and neurotransmitter secretion (7). Chen et al. combined AI with AM for patients with UP and reported improved efficacy relative to a control group (53).

Thermal (including infrared and far infrared) therapy has been used to treat pain, depression, dysmenorrhea, and coronary vascular endothelial dysfunction (49). Far infrared radiation has a wavelength of  $4-1,000 \,\mu$ m and can penetrate the subcutaneous tissues; as such, it may improve blood flow and endothelial and nervous-system function (49). Infrared rays can provide local warmth around acupoints and can have a similar effect to acupuncture; such rays may improve skin blood flow and the functioning of the cutaneous nervous system (69). Yi et al. found that AIR is effective in the treatment of UP, as evident from improvements in VAS and sleep quality scores (9).

Umbilical AST may increase immune function and amplify the effect of Traditional Chinese Medicine (TCM) (56). Indeed, for medications applied at the umbilical acupoint, bioavailability may be increased up to 6-fold (56). Jiu et al. used several Chinese medications with antioxidant and antiallergic properties and reported significantly improved VAS scores after AST (p <0.01) (56).

Akca et al. assessed acupressure and TEAS applied at acupoint LI11 (14); TEAS provides a faint electrical current and causes a small amount of pressure at the acupoint. The researchers reported a significant decrease in pruritus severity, as evident from a significant improvement in the mean VAS score (p = 0.0003) (14).

Patients with UP have higher serum levels of iPTH, hemoglobin, BUN, and high-sensitivity C-reactive protein rather than patients without UP (70). In our results, there were significant decreases in serum BUN, phosphate, PTH, and histamine levels in patients with UP compared with controls. Increased calcium and phosphate levels increase the stimulation of peripheral nerves in the skin; indeed, Sunita et al. found that calcium phosphate-induced pruritus was mediated by interleukin-6, Bruton's tyrosine kinase, and extracellular signalregulated kinase signaling in a murine model (71). PTH has also been associated with mast cell activation, leading to histamine release and pruritus (72). In an experimental study, Chinese herbal medicine (CHM) and acupoint thread implantation reduced serum PTH concentration in rats with CKD (73). Stockenhuber et al. observed increased histamine levels in patients with pruritus and CKD (74), and in another study, antihistamine therapy significantly improved the mean VAS score, indicating improved control of UP (75). Importantly, increased levels of calcium, phosphate, PTH, and histamine might cause a pruritic sensation in patients with UP.

A previous meta-analysis collected data from six studies of acupuncture in UP and showed, albeit with insufficient evidence, that acupuncture and acupressure were effective in UP; the researchers included articles in English, and only three trials recorded VAS scores (68). Importantly, our analysis collected data from a total of 36 studies, without language limits, and included ten different acupuncture techniques, several pruritus scores, and overall effective rates. However, the studies included in our analysis had considerable heterogeneity because of various clinical factors: the durations of each acupuncture method varied; some inter-study discrepancies in control groups existed, and overall effective rates were measured using different pruritus scores.

There were some limitations to our analysis: first, sample sizes of the included RCTs were small; second, all the selected articles lacked long-term follow-up; and third, the therapeutic mechanisms of effect for the different acupuncture techniques in UP were unclear. Nonetheless, our analysis is one of the first to endorse the therapeutic benefit of acupuncture and related techniques in the treatment of UP in patients with CKD.

# Conclusion

In summary, our meta-analysis found that acupuncture and related techniques have clinical benefits, as evident from various pruritus scores, in patients with UP. Further investigations in larger study populations and well-designed studies focusing on the dosage, frequency, and long-term effects are now warranted.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

## Author contributions

Po-HL designed the study and critically revised the manuscript. Po-HL, C-HC, H-EC, and I-HL contributed to the literature search, data extraction, quality assessment, and writing the first draft of the article. Pi-HL and C-HC performed statistical analysis and interpreted the results. All authors contributed to this article. All authors have read and agreed to the published version of the manuscript.

# Funding

This work was supported by grants from the Buddhist Tzu Chi Medical Foundation, Taiwan (TCMF-CM1-111-03 and TCMF-P 111-16) and Taipei Tzu Chi Hospital (TCRD-TPE-111-45).

## Acknowledgments

We thank all our colleagues at Mackay Memorial Hospital and Taipei Tzu Chi Hospital for helping with this study.

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We greatly appreciate technical support from the Core Laboratory of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fmed.2022.1036072/full#supplementary-material

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