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## Original Article

# Acupressure reduces the severity of restless legs syndrome in hemodialysis patients: A cluster-randomized crossover pilot study

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## ABSTRACT

**Background:** Restless legs syndrome (RLS), a neurological disorder, often affects sleep quality in hemodialysis patients. This study aimed to evaluate acupressure's effect on the severity of RLS symptoms and sleep quality in hemodialysis patients with RLS.

**Methods:** This study is a cluster-randomized crossover pilot study. Patients were randomized to two sequences: acupressure for one month and observation for another month (AC); and observation for one month and acupressure for another month (CA). For the four-week acupressure intervention, patients received 36 min of acupressure three times weekly during their hemodialysis sessions. The acupoints were on the bilateral lower limbs, including Zusanli (ST36), Yanglingquan (GB34), Sanyinjiao (SP6), Xuanzhong (GB39), Chengshan (BL57), and Taichong (LR3). RLS severity and sleep quality (measured with the Pittsburgh sleep quality index, PSQI) were measured at baseline, month 1, and month 2.

**Results:** AC sequence (n = 14) was similar to the CA sequence (n = 9) in terms of gender, age, education, employment, marital status, comorbid disease, BMI, duration of dialysis, medication for RLS and insomnia, RLS severity, and PSQI. The general linear mixed model revealed no significant carryover effect on RLS severity, PSQI, and the seven subscales of PSQI. A significant treatment effect (acupressure) was only observed in RLS severity (p = 0.0013) but not in PSQI and the seven subscales. The significant period effect was observed in RLS severity (p = 0.0250) and the subscale of sleep disturbance (p = 0.0021).

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**Conclusion:** In hemodialysis patients with RLS, acupressure can alleviate the severity of RLS but cannot improve sleep quality.

### At a glance commentary

#### Scientific background on the subject

Restless legs syndrome (RLS) affects sleep quality in hemodialysis patients. Although medications can relieve RLS symptoms, they have side effects and rebounds of RLS symptoms. Whether acupressure can relieve RLS symptoms in hemodialysis patients has not been studied.

#### What this study adds to the field

This cluster-randomized crossover pilot study showed that the four-week acupressure intervention (36 min, three times weekly during hemodialysis sessions on the 12 acupoint points of bilateral lower limbs) could alleviate the severity of RLS in hemodialysis patients.

Restless legs syndrome (RLS), also known as the Will-Ekbom disease, is a neurological and sensorimotor disorder often characterized by abnormal sensations, such as numbness, swelling, tightness, soreness, itching, burning, pain, or infestation in the lower limbs. RLS typically occurs at night and thus disrupts sleep. Individuals with RLS are likely to experience these unpleasant sensations while resting, standing still, and sleeping, especially at night, thus having an irresistible urge to move their limbs to relieve such sensations [1,2]. The latest data from several countries revealed that the prevalence of RLS in hemodialysis patients is 5.2%–55% [3–12]. Hemodialysis patients who experience RLS have lower sleep quality than those without RLS [7–9,13–15]. Sleeping is a basic human need, and adequate sleep is vital for physical and mental well-being. Low sleep quality causes fatigue, inattention, anxiety, depression, and low life quality [16]. Hemodialysis patients with RLS are more likely to suffer from depression and to have a lower quality of life than those without RLS [6,14,15,17,18]. Patients with RLS also have a higher risk of developing new cardiovascular diseases and higher mortality than those without RLS [19–21].

RLS can be managed using different means: (1) pharmacotherapy, (2) non-pharmacotherapy, (3) change lifestyle, and (4) acupuncture or acupressure. (1) The medications for RLS include dopamine agonists (pramipexole and ropinirole), opiates (tramadol), antiepileptics (gabapentin), sedatives, and hypnotics. Despite effective relieving symptoms and increasing sleeping time, these medications have side effects, such as nausea, emesis, general weakness, headache, and drowsiness, which eventually cause the rebound and augmentation of RLS symptoms [22,23]. (2) Non-pharmacotherapy (such as exercise, massage, and vibration) has been reported to reduce RLS symptoms in hemodialysis patients. Exercise and massage raise the blood circulation and stimulate the release of endorphin and dopamine [24–29];

vibration therapy increases muscle blood flow, the sensitivity of neural receptors and nerve velocity, and decreases muscular viscosity [30]. (3) Reduced caffeine, alcohol, and tobacco consumption and maintaining a regular sleep pattern might reduce RLS severity for hemodialysis patients with RLS [24]. However, the working mechanisms behind non-pharmacotherapy and maintaining a good lifestyle are diverse. (4) Chinese medical acupuncture's curative effect on primary (idiopathic) RLS has shown encouraging results [31,32].

In traditional Chinese medicine (TCM), there are 12 standard meridians and eight extraordinary vessels. The meridians and vessels are the paths through which the life-energy known as “Qi” is believed to flow. RLS is considered a deficiency of “Yin” and “Xue” (blood) of the legs because “Yin” and “Xue” are in effect at night and function to relax the mind and body. According to TCM, the activity and function of the legs are controlled by liver function, and, thus, the deficiency of “Yin” and “Xue” of the liver at night is the leading cause of RLS [31,33]. Acupuncture uses fine needles to insert specific points (acupoints) on the body. The stimulation of acupoints is believed to generate and smoothen the Qi, enhancing blood flow, dispelling blood congestion, harmonizing the “Yin” and “Yang,” and increasing the production of serotonin and endorphin [34,35].

The randomized control trial by Pan et al. (2015) reported that acupuncture reduces the abnormal leg activity of nocturnal activity and Epworth Sleepiness scale in RLS patients compared with the control group (using sham acupuncture). Study subjects were treated with either standard acupuncture (n = 15) or sham acupuncture (n = 16) in a single-blind manner, 30 min per session, three-session per week for six weeks. The 12 acupoints were Shenshu (BL23, bilateral), Mingmen (DU4), Xuehai (SP10, unilateral), Chengshan (BL57, unilateral), Taichong (LR3, bilateral), Zusanli (ST36, unilateral), Sanyinjiao (SP6, bilateral), and Taixi (KI3, bilateral) [31]. Raissi et al. (2017) did a single-blind randomized add-on trial on patients with primary RLS: the experimental group (acupuncture plus gabapentin, n = 17) and control group (gabapentin alone, n = 16). Both groups received a low dose of gabapentin (300 mg per day for four weeks). The experimental group received acupuncture for ten sessions, three times per week for four weeks. Each session lasted about 1 h. A total of 13 bilateral acupoints, namely, Shenshu (BL23), Ganshu (BL18), Chengjin (BL56), Chengshan (BL57), Jinggu (BL64), Zusanli (ST36), Liangqiu (ST34), Shangqiu (SP5), Xuehai (SP10), Sanyinjiao (SP6), Taixi (KI3), Yanglingquan (GB34), and Xuanzhong (GB39) were selected. The RLS symptoms were reduced, and sleep quality (Pittsburgh Sleep Quality Index, PSQI) was improved in the experimental group compared with the control group [32].

Although acupuncture might relieve RLS in primary RLS patients, acupuncture is not suitable to manage RLS for hemodialysis patients because of their problems with coagulopathy and immunity insufficiency. Comparing with stimulating

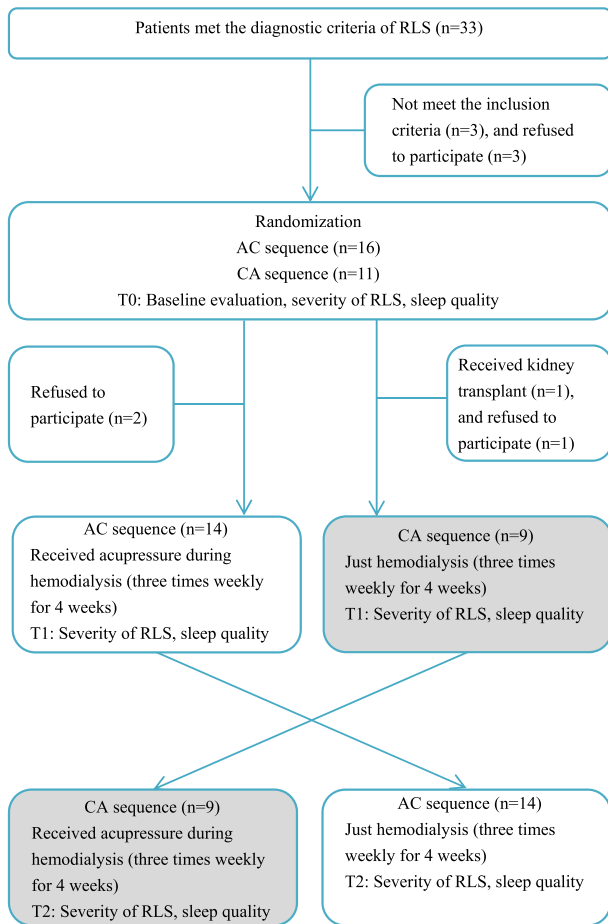


Fig. 1 Enrolling the patients and giving acupressure for the two sequences.

acupoints with needles (acupuncture), stimulating acupoints with pressure (acupressure) is considered safer [34]. On the other hand, acupuncture time for each acupoint is much longer than the acupressure time, because the administering difference between acupuncture (leaving the needle in the acupoint for a long time) and acupressure (apply pressure one acupoint a time by one acupressurist). The noninvasive nature of acupressure avoids the transmission of infectious diseases, reduces bleeding, and does not involve pain and fear of the needles [35,36]. Acupressure is inexpensive, seldom has adverse effects, is easy to perform, and does not require doctor's orders. Family members, clinical nurses, or even the patients themselves can do acupressure after training [34,35,37,38]. Our group's case report in 2016 showed promising results on a 50-year-old male hemodialysis patient with RLS. A clinical nurse did acupressure while the patient received routine hemodialysis, three sessions a week for four weeks. Acupressure was applied to 16 acupoints on the bilateral lower limbs for 3 min per acupoint and 48 min per session. The patient's wife was also trained to do acupressure and gave acupressure to the patient every day before bed. The patient reported a reduction in the severity of RLS symptoms and improved sleep quality (PSQI) [38].

To the best of our knowledge, the effect of acupressure on hemodialysis patients with RLS has not been studied, except

for one case report [38]. Thus, this study aimed to examine the effects of acupressure on the severity of RLS symptoms and sleep quality in hemodialysis patients with RLS.

## Material and methods

### Study design

This study is a cluster-randomized crossover pilot trial based on dialysis shifts (morning/afternoon vs. evening) to avoid treatment contamination [39]. The sample size of 30 (15 per group) was estimated based on: (1) the treatment effect of 5 units reduction of RLS severity with a SD = 4, or the treatment effect of 4 units improvement of PSQI with SD = 4 [32], (2) significant level = 0.05 and statistical power = 0.9, (3) simple crossover design [40]. Dialysis shifts were randomly allocated into two sequences: acupressure for four weeks followed by observation for another four weeks (AC sequence) and observation for four weeks followed by acupressure for another four weeks (CA sequence). The severity of RLS symptoms and sleep quality were assessed at baseline (T0), first month (T1), and second month (T2) (Fig. 1).

### Subjects

Patients who had RLS and received hemodialysis for more than 3 months at X Hospital, Northern Taiwan, from June 4, 2018, to August 5, 2018, were invited to participate in this study. RLS was diagnosed using the diagnostic criteria of the International Restless Legs Syndrome Study Group [1]. The following questions were asked to each subject: (1) During the past month, have you had any uncomfortable sensations or an urge to move your legs at rest? (2) During the past month, did uncomfortable sensations or an urge to move your legs occurred or worsened when you were sitting or lying down? (3) During the past month, was the urge to move your legs or uncomfortable sensations relieved by movement—by walking around, for example? (4) During the past month, did uncomfortable sensations or an urge to move your legs worsened in the evening or at night compared with that at daytime? RLS diagnosis was defined when a patient answered affirmatively to all these questions.

In addition to the diagnostic criteria for RLS, patients had to meet the following inclusion criteria: (1) at least 20 years old; (2) clear consciousness and able to communicate in Mandarin or Taiwanese; (3) no history of malignancy; (4) intact skin and no impairment in the lower extremities; and (5) stable vital signs and no bleeding tendency.

A total of 33 hemodialysis patients answered “Yes” to all four questions in the diagnostic questionnaire for RLS. Three out of the 33 patients did not meet the inclusion criteria, and another three patients refused to participate in the study. After baseline evaluation, two subjects in the AC sequence and one subject in the CA sequence refused to participate; one subject in the CA sequence received a kidney transplant. Hence, 14 subjects in the AC sequence and 9 subjects in the CA sequence were eligible for this study (Fig. 1). The Institutional Review Board of the hospital approved this study (201700554A3). All the subjects signed consent forms after the study purpose was explained.

### Acupressure intervention

We developed the acupressure protocol based on literature review (supplement) and consultation with three licensed traditional Chinese physicians who graduated from medical schools in Taiwan and have practiced acupuncture for more than ten years.

Acupoints were selected because of the following reasons: (1) According to the TCM philosophy of RLS [31–33], treatments should focus on the increase of both “Yin” and “Xue” (blood) of the legs [31,33]. (2) according to previous studies [31,32] for patients with primary (idiopathic) RLS and a case report [38] for hemodialysis patients with RLS, respectively. (3) Patients had leg discomfort and arteriovenous fistula on the hand and had to be in a supine position during hemodialysis. (4) According to the Yellow Emperor's Classic of Internal Medicine, Qi generates the blood, the blood generates Qi, Yin generates Yang, and Yang generates Yin.

Fig. 2 illustrates the acupoints use in this study to relieve cramps, pain, and numbness in the legs, promote blood circulation in the lower extremities, and promote sleep quality. A total of 12 acupoints of legs were selected, including Zusanli (ST36), Yanglingquan (GB34), Sanyinjiao (SP6), Xuanzhong (GB39), Chengshan (BL57), and Taichong (LR3) [31,41,42] (supplement).

- Zusanli (ST36): The Leg Yang Ming Stomach Meridian—the point is located four finger widths (3 inches) down from the bottom of the lateral side of the leg below the knee and 2.5 inches lateral to the tibia (the anterior tibialis muscle).
- Yanglingquan (GB34): The Leg Shao Yang Gall Bladder Meridian—the point is located on the a fibular aspect of the leg, particularly in the depression anterior and distal to the fibula's head.

- Sanyinjiao (SP6): The Leg Tai Yin Spleen Meridian—the point is located on the inner side of the leg, three inches above the ankle and posterior to the medial crest of the tibia.
- Xuanzhong (GB39): The Leg Shao Yang Gall Bladder Meridian—the point is located 3 inches above the tip of the external malleolus, particularly at the fibula's anterior.
- Chengshan (BL57): The Leg Tai Yang Bladder Meridian—the point is located in the midline below the calf muscle, between the back of the knee and heel.
- Taichong (LR3): The Leg Jue Yin Liver Meridian—point is located on the dorsum of the foot, particularly at the midpoint of the depression located 1 inch distally to the joint and between the heads of the first and second metatarsal bones.

The acupressure schedule was as follows:

- (1) The acupressure intervention was incorporated into the patient's routine hemodialysis schedule. Acupressure started 30 min after the patients received hemodialysis when patients were usually calm and showed stable vital signs. A total of 36 min were required to complete each session, and there are three sessions a week for four weeks.
- (2) Acupressure was applied by fingertips rolling (about two or three rollings per second) to give constant pressure on the designated acupoints. Each acupoint was pressed for 5-s, was relieved for 1-s, and repeated for 3 min. Hence, each session took 36 min for 12 acupoints.
- (3) The acupressure sensation was confirmed after the subjects felt numbness, pressure, heaviness, soreness, and distention at the acupoint. This subjective sensation can be experienced differently by individuals and is referred to as “De Qi”.
- (4) The two trained clinical nurses were responsible for collecting the data and applying acupressure for the subjects.

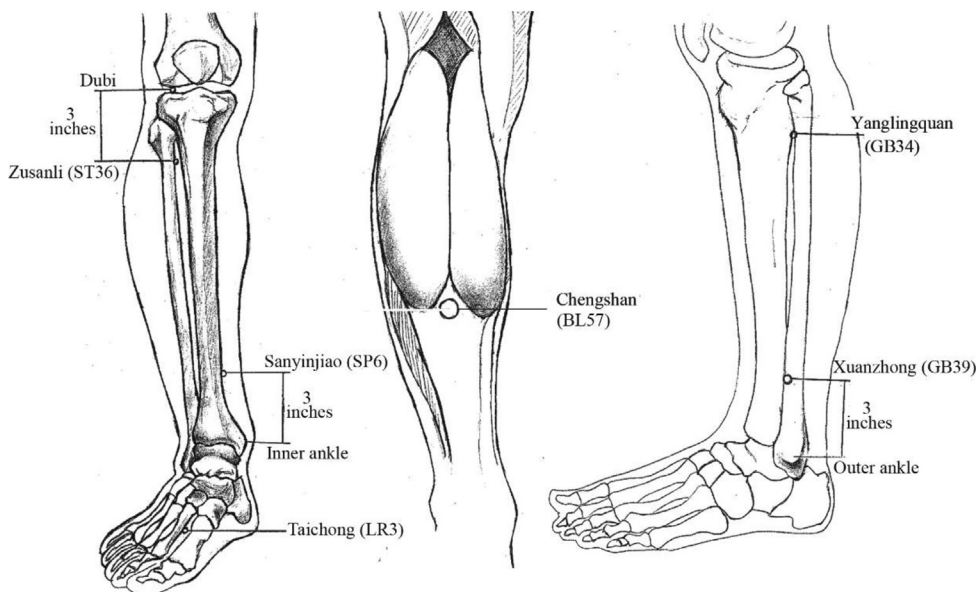


Fig. 2 Acupoints selected for restless legs syndrome in hemodialysis patients in the study.



Locating the designated acupoints and applying the constant pressure to achieve “De Qi” is essential for the trial. Before the trial, LML (a nursing professor who taught the class of Traditional Chinese Medicine Nursing (TCMN), third co-author) taught the two clinical nurses (who had taken classes of TCMN previously) how to perform acupressure on the acupoints, how to select the designated acupoints, and what they should and should not do during acupressure. First of all, the two clinical nurses were instructed to apply 1–5 kg of pressure using fingers on a scale and then use similar pressure to the subject. Next, the two clinical nurses practiced acupressure on two nursing students (one male and one female) with the guidance of the instructor (LML). The instructor ensured the correctness of the designated acupoints and the recipient students achieving the acupressure sensation of “De Qi” for all the 12 designated

acupoints. During the trial, most patients reported experiencing a “De Qi” sensation when pressure was maintained at 1.8–3.9 kg. The instructor randomly audited the two clinical nurses' acupressure performance (locating the designated 12 acupoints, the force of pressure, and acupressure sensation of “De Qi”) in hemodialysis patients with RLS.

## Measures

### Demographics and disease characteristics

Face-to-face interviews with the subjects were made to collect their demographic characteristics (sex, age, educational status, employment status, marital status, comorbidities, and BMI) and disease characteristics (dialysis duration and any medication for RLS or insomnia).

**Table 1** Demographic, comorbidity and dialysis characteristics between two sequences (AC and CA) among hemodialysis patients with restless leg syndrome (RLS).

Variables	Total (n = 23)	AC (n = 14)	CA (n = 9)	p
Gender				0.6570 <sup>a</sup>
Male	16 (69.57%)	9 (64.29%)	7 (77.78%)	
Female	7 (30.43%)	5 (35.71%)	2 (22.22%)	
Age (years)				0.7407 <sup>a</sup>
35–64	17 (73.91)	10 (71.43)	7 (77.78)	
≥65	6 (26.09%)	4 (28.57%)	2 (22.22%)	
Education				0.6551 <sup>a</sup>
Illiterate and below senior high	14 (60.87)	8 (57.14)	6 (66.67)	
College or above	9 (39.13%)	6 (42.86%)	3 (33.33%)	
Employment				0.6570 <sup>a</sup>
No	15 (65.22%)	10 (71.43%)	5 (55.56%)	
Yes	8 (34.78%)	4 (28.57%)	4 (44.44%)	
Marital status				1.0000 <sup>a</sup>
Single	2 (8.70%)	1 (7.14%)	1 (11.11%)	
Married	21 (91.30%)	13 (92.86%)	8 (88.89%)	
Diabetes				0.3826 <sup>a</sup>
No	14 (60.87%)	10 (71.43%)	4 (44.44%)	
Yes	9 (39.13%)	4 (28.57%)	5 (55.56%)	
Hypertension				0.6693 <sup>a</sup>
No	10 (43.48%)	7 (50.00%)	3 (33.33%)	
Yes	13 (56.52%)	7 (50.00%)	6 (66.67%)	
Heart Disease				0.3630 <sup>a</sup>
No	16 (69.57%)	11 (78.57%)	5 (55.56%)	
Yes	7 (30.43%)	3 (21.43%)	4 (44.44%)	
Liver Disease				1.0000 <sup>a</sup>
No	21 (91.30%)	13 (92.86%)	8 (88.89%)	
Yes	2 (8.70%)	1 (7.14%)	1 (11.11%)	
Hepatitis B or C				0.3700 <sup>a</sup>
No	19 (82.61%)	12 (85.71%)	7 (77.78%)	
Yes	4 (17.39%)	2 (14.29%)	2 (22.22%)	
BMI (kg/m <sup>2</sup> )	23.22 ±4.34	22.67±4.77	24.08±3.69	0.3135 <sup>b</sup>
Dialysis duration (years)	10.74 ±7.46	10.5±6.6	11.11±9.06	0.8994 <sup>b</sup>
<5	5 (21.74%)	2 (14.29%)	3 (33.33%)	0.3428 <sup>a</sup>
≥5	18 (78.26%)	12 (85.71%)	6 (66.67%)	
Medication for RLS				0.1616 <sup>a</sup>
No	17 (73.91%)	12 (85.71%)	5 (55.56%)	
Yes	6 (26.09%)	2 (14.29%)	4 (44.44%)	
Medication for insomnia				0.1616 <sup>a</sup>
No	17 (73.91%)	12 (85.71%)	5 (55.56%)	
Yes	6 (26.09%)	2 (14.29%)	4 (44.44%)	

Footnote: AC acupressure for one month followed by observation for another month; CA, observation for one month and then acupressure for another month.

<sup>a</sup> Fisher's Exact Test.

<sup>b</sup> Wilcoxon rank-sum test.

### Severity of RLS

We used the International Restless Legs Syndrome Rating Scale (IRLSRS) to rate RLS severity. The questionnaire consisted of 10 items, each of which had a scale ranging from 0 (no impact) to 4 (very severe impact). RLS severity was defined as mild (0–10 points), moderate (11–20 points), severe (21–30 points), or very severe (31–40 points) [43].

### The Chinese version of the pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is a widely used instrument for measuring subjective sleep quality and patterns in clinical practice and research [44]. The PSQI was used for the self-assessment of sleep quality in the preceding one month period. The PSQI can be divided into seven subscales, namely, sleep quality (S1), sleep latency (S2), sleep duration (S3), habitual sleep efficiency (S4), sleep disturbances (S5), use of sleeping medications (S6), and daytime dysfunction (S7). PSQI scoring was based on a 0–3 scale for each question, and a score of 3 reflects the negative extreme on the Likert scale. The seven subscales sum up the total PSQI score, which ranges from 0 to 21. A total PSQI score of >5 indicates a poor sleep. Higher scores indicate worse overall sleep quality and patterns [45].

### Statistical analysis

Frequency, percentage, mean, and standard deviation (SD) were used to describe the patients' demographic and disease characteristics, sleep quality, and RLS severity. Fisher's exact test or Wilcoxon rank-sum test was performed to compare the baseline characteristics between the two sequences. A general linear mixed model (GLMM) with a grand mean, a random effect of the subjects, fixed effects of treatment, period, sequence, and carryover was used in obtaining treatment effect (acupressure), period effect, and carryover effect [46]. SAS 9.4 was used in statistical analysis. The significant level of this study was 0.05.

## Results

About 70% were male, and 26% were  $\geq 65$  years old. About 39% had college degrees or above. One-third of the subjects were

employed. Most subjects (91.3%) were married, and two (8.7%) were single. Hypertension was the most common disease of the patients (56.5%), followed by diabetes (39.1%), heart disease (30.4%), hepatitis B or hepatitis C (17.4%), and liver disease (8.7%). The mean BMI was  $23.22 \pm 4.34$  kg/cm<sup>2</sup>. No significant difference in age, sex, comorbidities, or BMI was observed between the two sequences. The mean dialysis duration was 10.7 years, and 78.3% of the subjects had dialysis durations of more than five years. Six subjects (26.1%) received medication for RLS and their sleep problem. No significant difference in dialysis characteristics was observed between the two sequences (Table 1).

At baseline, the mean RLS severity was  $26.48 \pm 7.52$ , and the mean sleep quality (PSQI) was  $12 \pm 3.93$ . The mean of each sleep component was between 0.87 and 2.39. No significant difference in RLS severity, PSQI, or sleep components was observed between the two sequences, except sleep efficiency (S4;  $p = 0.0165$ ; Table 2)

The GLMM revealed no significant carryover effect on RLS severity, PSQI, and the seven sleep components. A significant treatment effect (acupressure) was only observed in RLS severity ( $p = 0.0013$ ). The significant period effect was observed in RLS severity ( $p = 0.0250$ ) and sleep disturbance (S5;  $p = 0.0021$ ; Table 3).

## Discussion

In this cluster-randomized crossover pilot study, we observed the 4-week acupressure in hemodialysis patients relieved the severity of RLS symptoms but did not improve sleep quality. To the best of our knowledge, we are the first team to examine the effect of acupressure on hemodialysis patients with RLS in a case report [38] and this trial ( $n = 23$ ). The two acupuncture trials on patients with primary RLS showed a significant reduction in the severity of primary RLS syndromes and improved sleep quality [31,32].

The selected acupoints in this study and the other three relevant studies are very similar [31,32,38] (Appendix), indicating our acupoints' appropriateness for hemodialysis patients with RLS. In this trial, we selected more Yang acupoints than Yin acupoints. According to the Yellow Emperor's Classic

**Table 2 RLS severity and sleep quality at baseline between two sequences (AC and CA) among hemodialysis patients with restless leg syndrome (RLS).**

Variables	Total (n = 23)		AC (n = 14)		CA (n = 9)		p <sup>a</sup>
	Mean	SD	Mean	SD	Mean	SD	
RLS severity	26.48	$\pm 7.52$	26.86	$\pm 7.23$	25.89	$\pm 8.37$	0.6581
Quality of sleep							
Total PSQI	12	$\pm 3.93$	13	$\pm 3.88$	10.44	$\pm 3.68$	0.1364
Sleep quality (S1)	2	$\pm 0.95$	2.07	$\pm 0.92$	1.89	$\pm 1.05$	0.7140
Sleep latency (S2)	2.39	$\pm 0.84$	2.5	$\pm 0.76$	2.22	$\pm 0.97$	0.5392
Sleep duration (S3)	2.04	$\pm 0.93$	2.29	$\pm 0.91$	1.67	$\pm 0.87$	0.0799
Sleep efficiency (S4)	1.57	$\pm 1.34$	2.07	$\pm 1.33$	0.78	$\pm 0.97$	0.0165*
Sleep disturbance (S5)	1.74	$\pm 0.45$	1.79	$\pm 0.43$	1.67	$\pm 0.5$	0.5624
Sleep medication (S6)	0.87	$\pm 1.32$	0.57	$\pm 1.09$	1.33	$\pm 1.58$	0.3113
Daytime function (S7)	1.39	$\pm 1.08$	1.71	$\pm 0.99$	0.89	$\pm 1.05$	0.0653

Footnote: AC, acupressure for one month followed by observation for another month; CA, observation for one month and then acupressure for another month.

<sup>a</sup> Wilcoxon rank-sum test. \* $p < 0.05$ .

**Table 3 RLS severity and sleep quality at baseline (T0), first month (T1), and second month (T2) of two sequences (AC and CA) among hemodialysis patients with restless leg syndrome (RLS).**

Variables		T0		T1		T2		Acupressure effect	Period effect	Carryover effect
		Mean	±SD	Mean	±SD	Mean	±SD	(95% CI)	(95% CI)	(95% CI)
RLS severity	AC	26.86	±7.23	23.71	±6.11	25.00	±5.23	3.70 (1.62–5.78)* p = 0.0013	2.41 (0.33–4.49)* p = 0.0250	4.60 (–6.30–15.51) p = 0.3900
	CA	25.89	±8.37	25.11	±8.21	19.00	±7.35			
Quality of sleep										
Total PSQI	AC	13.00	±3.88	12.43	±4.03	11.64	±3.88	0.05 (–0.85–0.95)	0.05 (–0.85–0.95)	0.29 (–6.69–7.27)
	CA	10.44	±3.68	12.33	±4.18	11.44	±4.48	p = 0.9055	p = 0.0661	p = 0.9311
Sleep quality (S1)	AC	2.07	±0.92	1.79	±0.98	1.93	±0.73	0.18 (–0.22–0.59)	0.04 (–0.36–0.44)	–0.06 (–1.41–1.29)
	CA	1.89	±1.05	1.78	±0.83	2.00	±1.00	p = 0.3568	p = 0.8397	0.9230
Sleep latency (S2)	AC	2.50	±0.76	2.36	±0.84	2.50	±0.76	0.24 (–0.03–0.51)	0.10 (–0.17–0.36)	–0.14 (–1.45–1.17)
	CA	2.22	±0.97	2.67	±0.71	2.33	±0.87	p = 0.0801	p = 0.4701	p = 0.8229
Sleep duration (S3)	AC	2.29	±0.91	2.21	±0.80	2.00	±1.04	–0.05 (–0.38–0.27)	0.16 (–0.16–0.49)	–0.34 (–1.75–1.06)
	CA	1.67	±0.87	2.33	±0.50	2.22	±0.97	p = 0.7447	p = 0.3098	p = 0.6190
Sleep efficiency (S4)	AC	2.07	±1.33	2.07	±1.27	1.86	±1.23	–0.33 (–0.84–0.18)	–0.12 (–0.62–0.39)	1.93 (–0.04–3.90)
	CA	0.78	±0.97	0.78	±1.30	1.22	±1.39	p = 0.1910	p = 0.6412	p = 0.0542
Sleep disturbance (S5)	AC	1.79	±0.43	1.79	±0.58	1.36	±0.50	–0.05 (–0.27–0.18)	0.38 (0.16–0.61)*	0.37 (–0.44–1.17)
	CA	1.67	±0.50	1.56	±0.53	1.22	±0.44	p = 0.6656	p = 0.0021	p = 0.3568
Sleep medication (S6)	AC	0.57	±1.09	0.64	±1.15	0.50	±1.09	0.10 (–0.42–0.61)	0.24 (–0.27–0.75)	–1.86 (–3.96–0.25)
	CA	1.33	±1.58	1.67	±1.58	1.33	±1.58	p = 0.7019	p = 0.3430	p = 0.0806
Daytime function (S7)	AC	1.71	±0.99	1.57	±1.09	1.50	±0.52	–0.04 (–0.57–0.50)	0.04 (–0.50–0.57)	0.40 (–1.03–1.84)
	CA	0.89	±1.05	1.33	±1.32	1.33	±1.12	p = 0.8917	p = 0.8917	p = 0.5643

Footnote: AC, acupressure for one month followed by observation for another month, n = 14; CA, observation for one month and then acupressure for another month, n = 9; CI, for confidence interval.

PSQI: Pittsburgh sleep quality index.

\*p < 0.05.

of Internal Medicine, Qi generates the blood, the blood generates Qi, Yin generates Yang, and Yang generates Yin; acupoint specificity is an essential principle, and thus therapeutic efficacy results mainly from the correct selection of acupoints, and the effects of acupuncture are entirely related to appropriate acupoint selection during treatment [31]. Chengshan (BL57) can relieve cramps, pain, and numbness in the legs and promotes blood circulation in the lower extremities; Xuanzhong (GB39) can relieve numbness and soreness in the legs; and Taichong (LR3), Zusanli (ST36), and Sanyinjiao (SP6) increase “Yin” and “Xue” (blood) of the body. Yanglingquan (GB34) and Zusanli (ST36) can relieve soreness in the legs [31]. Noted that we selected the acupoints in the lower limbs because patients experienced leg discomfort and arteriovenous fistula on the hand, and had to be in a supine position during hemodialysis.

Our acupressure intervention in this study did not improve sleep quality in hemodialysis patients with RLS. This result contradicts our previous case report [38] and two acupuncture studies [31,32]. Acupressure may improve sleep quality by releasing neural mediators that regulate physical processes and relaxing the body [47]. Previous studies have consistently reported improved sleep quality after using acupressure in hemodialysis patients, but whether having RLS was not mentioned [34,48–50]. Major sleep problems are observed in more than 85% of hemodialysis patients with end-stage renal disease [50]. Hemodialysis patients who experience RLS have lower sleep quality than those without RLS [7–9,13–15]. Neither the selected acupoints nor the acupressure schedule explains the difference because they are very similar between ours and the other three studies [31,32,38]. We suspected that the insignificant improvement in sleep quality for the acupressure session in this study was due to the insufficient duration of the

acupressure (only given for one month, and each session lasted 36 min), the assessment period of PSQI (the past month) is the same as the duration of giving acupressure (one month). The low statistical power of treatment (acupressure) effect in PSQI was another explanation of the insignificant finding in PSQI. In this study, the statistical power of treatment (acupressure) effect in PSQI was only 0.05, based on 0.05 unit improvement in PSQI with the SD = 2.6 unit and significant level = 0.05. Furthermore, the patient's wife applied acupressure to the patient before bedtime every day in our previous case report [38]. Therefore, instructing patients' relatives to perform acupressure at home every day is recommended.

Regarding the reduction of RLS severity, our acupressure protocol for hemodialysis patients with RLS is appropriate. In this study, the statistical power of the treatment (acupressure) effect was 0.81 based on 3.7 unit reduction in RLS severity with the SD = 4.8 unit, significant level = 0.05. Furthermore, most patients were well-tolerated acupressure because no side effects, such as dizziness, nausea, skin eruption, were reported. From our clinical observation, we noticed that most patients are willing to receive acupressure when the acupressure is incorporated into the patient's routine hemodialysis schedule.

Although our study had a relatively small sample size, including only 14 patients in AC and nine patients in CA sequences, the crossover design allowed the comparison within the subjects. Thus, the standard errors of the estimates of treatment (acupressure) differences were small [46]. Hence, we were able to observe a significant reduction in the severity of RLS after acupressure.

Our study has some limitations: (1) No washout period was given between the two sequences. (2) The acupressure was only given for one month because of limited manpower. (3)

The sample size of this study was relatively small. (4) Despite that the two clinical nurses were well trained and had practiced before the trial, technical differences might have affected the results. Unfortunately, we could not further evaluate these between-nurses technical differences because we did not record the acupressure procedure in each session and we did not record which nurse applied acupressure on which patients. (5) We were unable to rule out the placebo effect because the control sequence did not receive any management. We suggest that sham acupressure should be given to the control sequence to rule out the placebo effect in the future study. (6) We worry some subjects who had RLS due to diabetic neuropathy because 39.1% of the subjects had DM. The diagnostic criteria of International Restless Legs Syndrome Study Group is unlikely to recruit patients with RLS due to diabetic neuropathy because patients with diabetic neuropathy cannot relieve their RLS by moving around or changing their body position.

Future studies may consider at least a month of washout period, increasing the number of acupoints, increasing the time to stimulate an acupoint (longer time per session, more sessions, or extended intervention period), increasing the sample size, recording the acupressure provider for each session. Besides, sham interventions is suggested to rule out the placebo effect. Finally, training patients or caregivers could be a solution for limited human resources, and daily sessions at home may produce good outcomes.

## Conclusions

Acupressure at the acupoints of the bilateral lower limbs, namely, Zusanli (ST36), Yanglingquan (GB34), Sanyinjiao (SP6), Xuanzhong (GB39), Chengshan (BL57), and Taichong (LR3), reduced the severity of RLS symptoms in hemodialysis patients with RLS. Acupressure is safe, feasible, inexpensive, and complication-free, and does not require doctors' orders. We suggest including acupressure as a part of nursing care, especially for patients at dialysis centers, and training patients or caregivers to perform acupressure at home during non-dialysis days.

## Conflicts of interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bj.2021.05.005>.

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