The efficacy and safety of self-administered acupressure on respiratory tract infection in chronic kidney disease: a randomized controlled trial

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Background: Respiratory tract infection (RTI) is associated with a higher risk of kidney failure in patients with chronic kidney disease (CKD), without effective precautions. Self-administered acupressure (SAA) has been shown to potentially prevent RTI, but still lack of clinical evidence in CKD. The present randomized controlled trial assessed the efficacy and safety of SAA in preventing RTI recurrence in patients with CKD.

Methods: Participants with CKD who had been diagnosed with RTI on more than 2 occasions in the preceding 12 months were enrolled between November 6, 2017, and August, 6, 2018. They were randomly assigned (1:1) to receive daily SAA combined with usual care (intervention) or usual care alone (control) for 24 months. The primary outcome was time to first RTI. Secondary outcomes were RTI rate, kidney function, proteinuria and serum immune indicators, detected by the clinical laboratory in the hospital. The study would be discontinued if the participant met the criteria of stopping the study. Kaplan-Meier method and multivariable Cox proportional hazards regression were used to compare the primary outcome between the two groups.

Results: Among the 540 patients screened, 114 participants were randomly assigned to the intervention group (n=57) or the control group (n=57). The median follow-up duration was 24.4 months. Compared with controls, participants in the intervention group did not have a significantly lower risk of RTI according to Kaplan-Meier analysis, but did have a significantly lower risk of RTI according to competing risk analysis (HR 0.65, 95% CI: 0.42–1.00; P=0.05), when considering endpoint (dialysis or death) and loss to follow-up as competing risks, and had a significantly lower rate of RTI [1.65 *vs.* 2.19 episodes per patient-year,

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respectively; incidence rate ratio (IRR) 0.75, 95% CI: 0.62–0.92; P=0.006]. Apart from lower study serum IgG levels in the intervention group at 24 months (mean difference 0.68 g/L; 95% CI: 0.07–1.29; P=0.029), all other secondary outcomes and overall adverse events were comparable between the 2 groups.

Conclusions: SAA is a promising effective and safe therapy for preventing RTI in patients with CKD. However, the efficacy of SAA in children and adolescents still needs further study.

Trial Registration: Chinese Clinical Trials Registry identifier: ChiCTR-IOR-17012654.

Keywords: Chronic kidney disease prevention (CKD prevention); randomized controlled trial; respiratory tract infection (RTI); self-administered acupressure (SAA)

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Introduction

Chronic kidney disease (CKD) has become a major public health concern throughout the globe and is associated with high health care costs, poor quality of life, and severely reduced life expectancy (1,2). Patients with CKD are susceptible to infections, especially respiratory tract infection (RTI) (3,4), due to experiencing significant immune dysregulation compared with the general population (5,6). Infections are an important cause of morbidity and mortality among patients at all stages of CKD and constitute the second most common cause of death (7). In those with advanced CKD, a single infection episode, mainly RTI, is associated with a 1.6- and 3.4-fold higher risk of kidney failure and mortality, respectively (8). Therefore, strategies to prevent RTI in patients with CKD are a high priority.

Unfortunately, the risk factors for RTI are not easily modified, such as advanced age, cause of kidney disease, high burden of comorbidities, and immune dysfunction. One potentially effective strategy to prevent RTI recurrence in patients with CKD is vaccination (6). However, patients with kidney dysfunction have been observed to have lower rates of vaccine response (9,10). Besides, the reported vaccination rate in the CKD populations is inadequate (11) due to the patient concerns about vaccine safety. Nutrient supplementation, such as vitamin C (12) and vitamin D supplementation (13), have been reported useful in the prevention of RTI in general people (14). However, the safety of long term vitamin C intake also has been concerned, such as the risk of renal cell carcinoma (15). And vitamin D supplementation has been used as conventional therapy in CKD patients (16,17), who still have high susceptible to infections.

As prevention RTI in CKD is full of challenges, more attention is being paid to non-drug therapies. Acupressure has been used for more than two thousand years in Asian countries as a therapeutic strategy to prevent infection (18). It uses the same points as acupuncture but applies manual pressure and usually employs the finger or thumb on these points as opposed to using the insertion of a needle. The noninvasive nature of acupressure and its ability to be self-administered at home has made it relatively popular with patients. According to the theory of Traditional Chinese medicine (TCM), acupressure works by releasing blocked energy in certain areas of the body, thereby facilitating host protection from exogenous pathogens. Previous studies have reported that the epigenetic effects of acupressure include the upregulation of immunity-related genes and the downregulation of inflammation-related genes (19,20). With respect to RTI treatment, several investigations have demonstrated that acupressure confers a number of potential benefits, including regulated respiration, increased oxygen saturation, and significantly decreased asthma assessment scores (21,22).

Patients with CKD are exposed to a proinflammatory environment and experience immune dysfunction due to oxidative stress, inflammation, and metabolic kidney dysregulation, which engender an increased susceptibility to infections and a poor vaccine response (4,5). However, to date, there has been very limited study of self-administered acupressure (SAA) in this setting, and consequently, SAA therapy for preventing RTI recurrence in patients with CKD still lack clinical evidence support. We hypothesized that SAA would be an effective strategy for preventing RTI in people with CKD.

In the present randomized controlled study, we

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aimed to evaluate whether SAA therapy could reduce the incidence risk of RTI over a period of 24 months in patients with nondialysis CKD. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2376/rc).

Methods

Trial design

This study was a prospective, open-label, parallel-arm, randomized controlled trial (RCT) conducted in the outpatient department of the CKD center at Guangdong Provincial Hospital of Chinese Medicine (GPHCM), a tertiary level TCM hospital in the south east of China. The allocation ratio is 1:1.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the study protocol was approved by the Ethics Committee of GPHCM (No. B2017-006-01). Each eligible patient provided written informed consent before randomization.

Participants

The study included adults aged ≥18 years old with CKD who had been diagnosed with RTI on more than 2 occasions in the 12-month period prior to enrollment. The exclusion criteria were any of the following: requirement for kidney replacement therapy; any other primary kidney disease with the mean decline of glomerular filtration rate within 12 weeks before enrolment being more than 30%; acute myocardial infarction, unstable angina, stroke, or any other cardiovascular or cerebrovascular accident requiring revascularization surgery within 12 weeks prior to enrolment, or a revascularization operation being urgently needed after recruitment; presence or history of arrhythmia or heart failure classified as New York Heart Association (NYHA) class III and IV cardiac disease; advanced hepatic disease (e.g., hepatic cirrhosis, decompensated cirrhosis); active malignancy within 5 years before enrolment; active infectious disease under treatment; pregnant or breastfeeding or planning to become pregnant or begin breastfeed during the study; inability to comply with treatment (e.g., mental disease); and participation in another clinical trial.

The study would be discontinued if the participant had renal replacement treatment (dialysis or renal transplantation); or was diagnosed as any of the following disease (active malignant tumors, myocardial infarction, cerebrovascular accident); or needed long term antibiotics treatment due to other infectious disease; or was pregnant during the study period.

Randomization

Randomization was performed by the Key Unit of Methodology in Clinical Research (KUMCR) of GPHCM. A computer generated randomization list created from PROC PLAN in SAS 9.2 (SAS Institute, Cary, NC, USA) was used. Randomization instructions were delivered via the Interactive Web Response System for Chinese Medicine Trials (IWRS-CMT), a validated web-based randomization system. The randomization was stratified according to the stage of CKD (stage 1–2 or stage 3–5) with confidential block size. Eligible participants were assigned to the intervention or control group in a 1:1 allocation ratio. The randomized sequence was generated by a central allocation management system, and researchers strictly followed the operating instruction and random distribution plan written by the KUMCR.

Intervention

Eligible participants were randomly assigned (1:1) to receive daily SAA combined with usual care (intervention) or usual care alone (control) for 24 months.

Training sessions

Participants in the intervention group were trained in SAA therapy, which involved the application of finger pressure at designated acupoints by licensed therapists. Face-to-face training sessions were delivered every 2 weeks in the first month. Each training session took 20 to 30 minutes. To ensure the SAA was delivered in a standardized way, two licensed therapists were employed as fixed trainer during the study, and were trained before the study recruitment to ensure that their teaching methods are consistent. In the first training session, the trainer taught participants the SAA therapy in detail, including acupoint location, time required, and the proper method of using the finger pulp to press the acupoints. A graphic booklet was given to participants for their reference. In the second training session 2 weeks later,

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Table 1 Details of self-administered acupressure therapy

Acupoint	Location	Acupressure therapy instruction	Frequency and duration
Yingxiang (LI20)	On the face, in the nasolabial sulcus, at the same level as the midpoint of the lateral border of the ala of the nose	Using the thumb pad, firmly massage the surrounding area of this acupoint unilaterally on the lateral border of the ala of the nose	2–3 cycles per second for 3 minutes (both sides at the same time)
Taiyang (EX-HN5)	The area on each side of the forehead above the cheek bones, lateral to and slightly superior to the outer canthus of the eye	Using the thumb pad, firmly massage the surrounding area of this acupoint unilaterally on the outer canthus of the eye	2–3 cycles per second for 3 minutes (both sides at the same time)
Fengchi (GB20)	In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of the sternocleidomastoid and the trapezius muscles	Using 2 thumbs, press on the points bilaterally while the other 4 fingers hold the back of the head naturally	2–3 cycles per second for 3 minutes (both sides at the same time)
Fengfu (GV16)	In the posterior region on the neck, directly inferior to the external occipital protuberance, in the depression between the trapezius muscles	Using one thumb, press on the points while the other 4 fingers hold the back of the head naturally	2–3 cycles per second for 3 minutes
Dazhui (GV14)	In the posterior region of the neck, in the depression inferior to the spinous process of the seventh cervical vertebra (C7), on the posterior median line	Massage and press with the pad of the middle finger	2–3 cycles per second for 3 minutes
Zusanli (ST36)	On the anterior aspect of the leg, on the line connecting ST35* with ST41#, 3 B-cun inferior to ST35	Using thumb pad, firmly massage the surrounding area of this acupoint unilaterally on the anterior aspect of the leg	2–3 cycles per second for 3 minutes each side (bilateral, 6 minutes in total)

*, ST35-Dubi is located on the anterior aspect of the knee in the depression lateral to the patellar ligament; #, ST41-Jiexi is located on the anterior aspect of the ankle in the depression at the center of the front surface of the ankle joint between the tendons of the extensor hallucis longus and the extensor digitorum longus.

participants were checked by the trainer whether they could operate the SAA correctly on site. Then the trainer repeated the instruction process, and helped them to solve problems concerning the acupressure manipulation. To guarantee the adherence of the SAA group during the follow up, a 30-day diary was provided to the participants to record their daily performance regarding the exact acupoints and their feelings, which were checked at each visit. Any drugs they took to treat their RTI, especially antibiotics were required to record in the diary.

SAA therapy

SAA was performed once daily between meals or before sleep. Acupoints Yingxiang (LI20), Taiyang (EX-HN5), Fengchi (GB20), Fengfu (GV16), Dazhui (DU14), and Zusanli (ST36) were selected for this study according to the traditional literature, previous acupressure RCTs, and expert opinion. When performing the SAA, participants were instructed to sit comfortably on a chair with back or on bed, relaxing all the muscles with several deep slow breaths. Then they applied their fingers on the point with moderate strength. They were also told to avoid pressing on the damaged skin. The detailed application of acupressure used in this study is listed in *Table 1* (23,24).

Usual care

All patients in the intervention and control groups were instructed to continue their routine medical therapy for CKD according to the guideline *Kidney Disease: Improving Global Outcomes (KDIGO) Guideline recommendations* (25). All participants were also provided with standard advice regarding lifestyle modification, including dietary and regular exercise regimens.

Follow-up

Participants underwent a follow-up visit every 30 days for assessment. A 30-day diary was delivered to participants at each visit and collected at the next visit. The diary was used to record RTI occurrence, symptoms, duration, and related medication. RTI symptoms included but were not limited to cough, sneezing, stuffy or runny nose, sore throat,

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headache, muscle ache, breathlessness or wheezing, chest congestion, fever, and chills. Patients in the intervention group were also asked to record their daily performance of SAA therapy.

Serum samples and urine were collected every 3 months. All participants were requested to report adverse events (AEs) at each visit. The participants were followed up until either completion of 24 months of follow-up or initiation of renal replacement therapy (dialysis or renal transplantation).

Outcomes and definitions

The primary outcome was time to first RTI, defined as upper respiratory tract infection, acute tracheobronchitis, or pneumonia, whichever came first. Upper respiratory tract infection was defined as self-limited irritation and swelling of the upper airways with associated cough but no evidence of pneumonia or a separate condition to account for the patient's symptoms (26). Acute tracheobronchitis was defined as acute inflammation of the trachea and/or bronchial tree caused by various organisms like bacteria and viruses, and characterized by increased bronchial secretion and impaired mucociliary function (27). Pneumonia was defined as follows: (I) fever, productive cough, or abnormal white blood cell count; and (II) newly developed consolidation and/or ground-glass opacities on a chest radiograph or chest high-resolution computed tomography (HRCT) (28).

The secondary outcomes were RTI rate, change on estimated glomerular filtration rate (eGFR) (29), urine protein to creatinine ratio (UPCR), serum immunoglobulin A/G/M (IgA/G/M), 50% hemolytic complement (CH50) activity of serum, serum complement 3 and 4 (C3, C4), CD3/CD4/CD8 lymphocyte counts of serum. Safety outcomes included all AEs.

Other laboratory measurements performed included counts/level of white blood cells, neutrophils, monocytes, lymphocytes, eosinophils, red blood cells, hemoglobin, serum albumin, serum uric acid, blood urea nitrogen, triglycerides, total cholesterol, low-density lipoprotein, serum potassium, serum calcium, and serum phosphorus.

Sample size

In the absence of prior studies of SAA, the sample size estimation was based on 1 observational cohort study of RTI occurrence in 1,139,470 health care users participating in the Stockholm CREAtinine Measurements Project (30), which indicated that patients with CKD (eGFR less than 90 mL/min per 1.73 m^2) have a 25% higher incidence of RTI compared with people with normal kidney function. Assuming an incidence of 2 RTIs per year in the control group, a mean exposure time of 2 years, a 2-sided significance level of 5%, and a 15% dropout rate, it was estimated that a final sample size of 115 participants would provide 80% power to detect a 25% reduction in RTI rate in the intervention group.

Statistical analysis

Results are expressed as frequencies and percentages for categorical variables, mean ± SD for continuous normally distributed variables, and median [interquartile range (IQR)] for continuous variables that were not normally distributed. The primary and secondary outcomes were analyzed according to the intention-to-treat principle. The primary outcome of time to first RTI was analyzed using the Kaplan-Meier method and multivariable Cox proportional hazards regression. Survival curves were compared statistically using the log-rank test. As age, presence of diabetes mellitus, presence of hypertension, use of Chinese caterpillar fungus preparation, and use of calcium supplements had been reported to be the risk factors of RTI (31) or have the effect on the RTI prevention (13), these variables were included in the multivariable Cox models as covariates. Multivariable Cox proportional hazards survival analysis using a competing risks approach was also performed: endpoint (dialysis or death) and loss to follow-up were competing risks. The secondary outcome RTI rate was analyzed using a Poisson regression model. Incident rate ratios (IRRs) and 95% CIs from the model were reported. Within each group, RTI rates were calculated as the number of RTI episodes divided by the total time at risk and are expressed as episodes per patient-year at risk. The change in the eGFR from baseline to 24 months was analyzed with a linear mixed-model with fixed effects for treatment, time, the interaction of treatment with time, and baseline eGFR. Sensitivity analyses were conducted with the use of primary cause of kidney diseases and covariables (age, presence of diabetes mellitus, presence of hypertension, and use of Chinese caterpillar fungus preparation) in the model. Measurements of UPCR, blood pressure, serum immunologic testing indicators, and other serum laboratory indices over time were analyzed with a linear mixed-model, with treatment, time, and the interaction of treatment with time as fixed effects. Safety analyses were performed on

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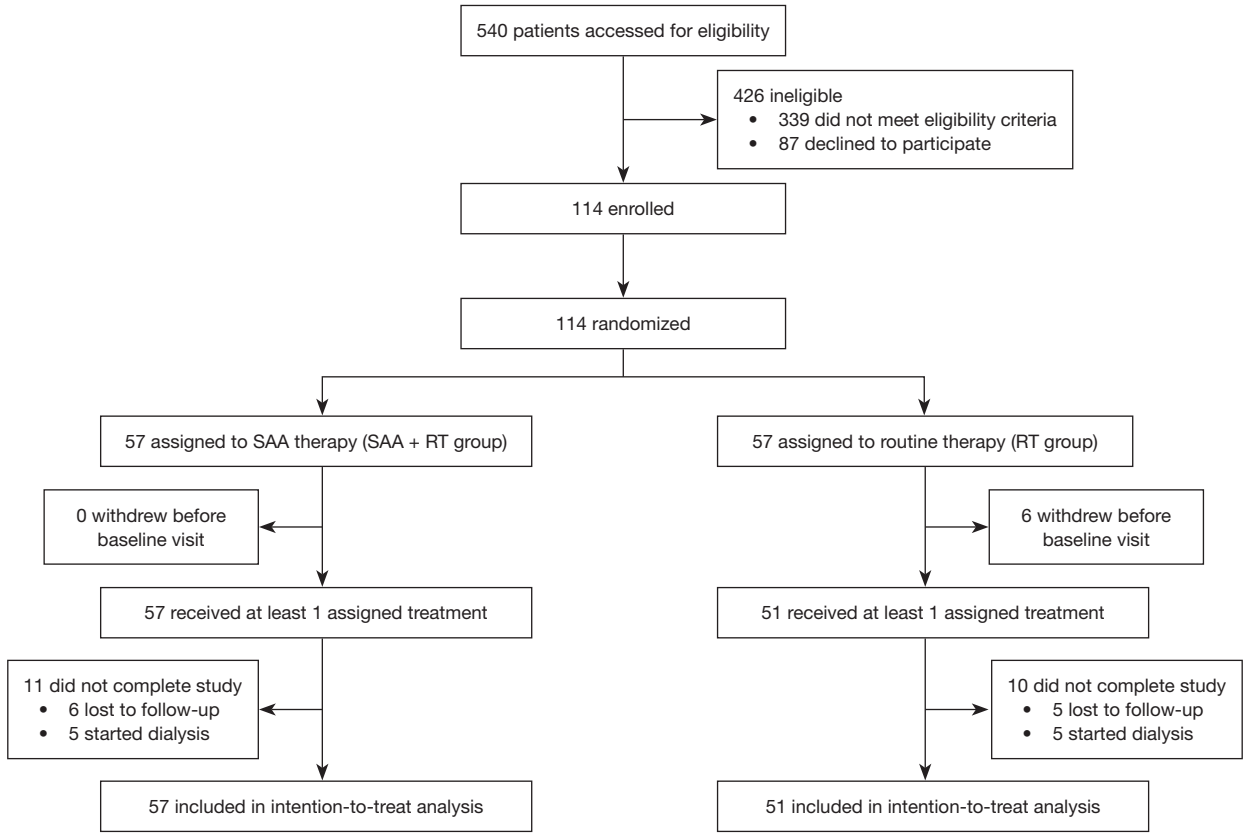

Figure 1 Study flowchart. All participants who were randomized and received at least 1 assigned treatment, were included in the ITT analysis. SAA, self-administered acupressure; RT, routine treatment; ITT, intention-to-treat.

the safety population. Group comparisons were performed using the chi-square test. All analyses were performed using the Predictive Analytics Software (PASW) Statistics 18.0 software package (IBM Corporation, Armonk, NY, USA) and STATA software 15.0 (Stata Corp. College Station, TX, USA) with a 2-sided P value of less than 0.05 being considered significant.

Results

Overall, 540 patients were screened between November 6, 2017, and August 6, 2018. Of these, 114 were enrolled and randomly assigned to either the intervention (n=57) or control group (n=57). Six patients in the control group withdrew from the study immediately because they wanted to receive the intervention. The remaining 108 patients were included for intention-to-treat analysis. The median follow-up time was 24.4 months (IQR 24.0, 24.9 months). During the follow-up period, 11 (18%) participants in the intervention group and 10 (20%) participants in the control group were considered as discontinuing the assigned treatment due to loss to follow-up or dialysis (total attrition rate =18.42%). At study termination, 46 of the 57 (81%) patients in intervention group and 41 of the 51 (80%) patients in the control group completed the 24-month follow-up period (*Figure 1*).

The patients' baseline characteristics, with the exception of the age, body mass index (BMI), and the comorbidity of diabetes mellitus, were balanced between the assigned treatment groups (*Table 2* and Table S1). The mean (± SD) age was 55.55±13.49 in the control group and 48.82±13.29 in the intervention group. The mean (± SD) eGFR was 53.12±28.44 mL per minute per 1.73 m^2 in the control group and 54.86±33.15 in the intervention group, and the mean (± SD) UPCR was 1.15±1.98 g/g in the control group and 1.19±1.36 in the intervention group.

Primary outcome

During the study, 45 of 57 (79%) participants in the

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Table 2 Demographic and clinical characteristics of the patients at baseline

Characteristic	Intervention group (N=57)	Control group (N=51)	Total (N=108)
Age (years)[#], mean ± SD	48.82±13.29	55.55±13.49	52.00±13.74
Female, n (%)	27 (47.4)	21 (41.2)	48 (44.4)
Body mass index (kg/m^2)*[#], mean ± SD	21.52±3.06	23.49±3.21	22.45±3.27
Blood pressure (mmHg)[†], mean ± SD			
Systolic	122.58±18.00	126.75±16.00	124.55±17.13
Diastolic	72.70±12.81	74.31±10.52	73.46±11.76
Primary renal disease, n (%)			
Chronic glomerulonephritis	26 (45.6)	18 (35.3)	44 (40.7)
Nephrotic syndrome	5 (8.8)	4 (7.8)	9 (8.3)
IgA nephropathy	8 (14.0)	5 (9.8)	13 (12.0)
Hypertension	2 (3.5)	4 (7.8)	6 (5.6)
Diabetic nephrology	2 (3.5)	7 (13.7)	9 (8.3)
Other	14 (24.5)	13 (25.5)	27 (25)
Diabetes mellitus, n (%)[#]	3 (5.26)	11 (21.57)	14 (12.96)
Hypertension, n (%)	26 (45.61)	17 (33.33)	43 (39.81)
Hyperuricemia, n (%)	17 (29.82)	14 (27.45)	31 (28.70)
Receiving steroid or immunosuppressant therapy, n (%)	14 (24.56)	12 (23.53)	25 (23.15)
Receiving Chinese caterpillar fungus preparation, n (%)	4 (7.02)	8 (15.69)	12 (11.11)
Receiving calcium supplements, n (%)	11 (19.30)	10 (19.61)	21 (19.44)
CKD stage, n (%)			
Stage 1–2	19 (33.3)	22 (43.1)	41 (38.0)
Stage 3–5	38 (66.7)	29 (58.9)	67 (62.0)
Estimated GFR (mL/min/1.73 m^2), mean ± SD	54.86±33.15	53.12±28.44	54.03±30.88
Urinary protein to creatinine ratio (g/g), mean ± SD	1.19±1.36	1.15±1.98	1.17±1.67

[#], the P value of body mass index (kg/m^2), diabetes mellitus [n (%)], and age (years) was significantly different between the control group and SAA group (P=0.002, P=0.012, and P=0.011, respectively). [†], blood pressure was expressed in (mmHg). CKD, chronic kidney disease; GFR, glomerular filtration rate; SAA, self-administered acupressure.

intervention group and 46 of 51 (90%) in the control group experienced the primary outcome (first occurrence of RTI). The median RTI-free survival time in the intervention group was longer than that of the control group (intervention group: 2.27 months, 95% CI: 1.40–3.17; control group: 2.17 months, 95% CI: 0.93–3.90). Compared with controls, participants in the intervention group did not have a significantly different risk of RTI according to Kaplan-Meier analysis [hazard ratio (HR) 0.76, 95% CI: 0.50–1.14; P=0.19; *Figure 2* and *Table 3*] but did have a significantly lower hazard of RTI according to competing risk survival analysis (HR 0.65, 95% CI: 0.42–1.00; P=0.05; *Table 3*), when considering endpoint (dialysis or death) and loss to follow-up as competing risks, because the occurrence of these competing risks stopped the follow up of the participant and would preclude the occurrence of RTI event.

Secondary outcomes

There were 175 episodes of RTI in 45 patients in the

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intervention group and 200 episodes in 46 patients in the control group. The mean RTI rates in the intervention and control groups were 1.65 (95% CI: 1.41–1.90) and 2.19 (95% CI: 1.89–2.50) episodes per patient-year, respectively. Compared with controls, patients in the intervention group had a significantly lower rate of RTI (0.75; 95% CI: 0.62–0.92; P=0.006; *Table 4*).

Change in eGFR did not differ significantly between the intervention and control groups (intervention group: –2.47 mL per minute per 1.73 m^2 per year, 95% CI: –3.53 to –1.41; control group: –1.71 mL per minute per 1.73 m^2 per year, 95% CI: –2.85 to –0.58; mean difference 0.76 mL per minute per 1.73 m^2 per year, 95% CI: –0.80 to 2.31; P=0.339; *Figure 3A*). Sensitivity analyses showed similar results (*Table 5*).

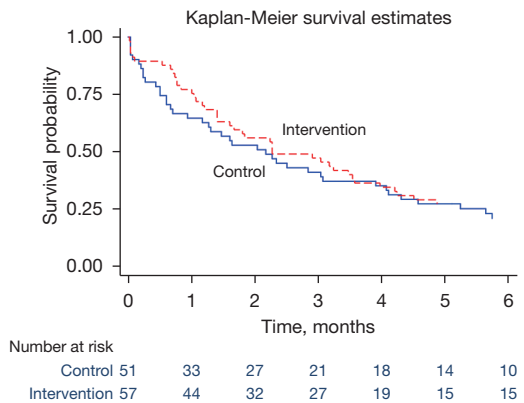

Figure 2 Kaplan-Meier analysis of the first RTI event curves for patients in the intervention group and control group. RTI, respiratory tract infection.

The mean UPCR adjusted for baseline decreased in the intervention group to 0.87 (95% CI: 0.47–1.27) at 12 months and remained at a lower level up to 24 months (1.02; 95% CI: 0.61–1.42) compared the control group (*Figure 3B*), whose mean UPCR was 1.07 (95% CI: 0.64–1.50) at 12 months and 1.25 (95% CI: 0.82–1.67) at 24 months. The mean difference in the UPCR level between groups, with adjustment for baseline values, was –0.24 (95% CI: –0.58 to 0.09) at 12 months and –0.27 (95% CI: –0.61 to 0.07) at 24 months, but this difference was not statistically significant.

All serum immunologic indicators varied within the normal range during the follow-up period. Compared with the control group, the mean serum IgG level at the end of the 24-month study period was significantly lower in the intervention group. The mean difference between groups was 0.68 g/L (95% CI: 0.07–1.29; P=0.029), with adjustment for baseline values. No significant between-group differences were observed for any other immunologic indicators (*Table 6*).

No significant differences were noted between the intervention and control groups with respect to systolic blood pressure (mean difference 1.82 mmHg; 95% CI: –4.04 to 7.67), diastolic blood pressure (mean difference 2.12 mmHg; 95% CI: –2.14 to 6.38; Figure S1), or other serum laboratory indices (complete blood count, lipid profile, serum electrolytes, serum albumin, serum urate) at 24 months,

Table 3 Effect of SAA on the primary outcome

Primary outcome※	Intervention [no./total (%)]	Control [no./total (%)]	HR (95% CI)	Adjusted HR† (95% CI)	Sub-HR* (95% CI)
The first RTI	45/57 (79.0)	46/51 (90.1)	0.76 (0.50–1.14)	0.65 (0.41–1.02)	0.65# (0.42–1.00)

※, the primary outcome was time to the first RTI (defined as upper respiratory tract infection, acute bronchitis, or pneumonia). †, adjusted HR in Cox regression and Sub-HR† in competing risk analysis were adjusted for age, presence of diabetes mellitus, presence of hypertension, receiving Chinese caterpillar fungus preparation, and receiving calcium supplements. *, lost to follow-up and end point (defined as receipt of dialysis for at least 30 days or kidney transplantation) were competing risks in the competing risk models. #, P=0.05. SAA, self-administered acupressure; HR, hazard ratio; CI, confidence interval.

Table 4 Incidence rate of RTI in the intervention and control groups

Outcome	Intervention		Control		Incidence rate ratio (95% CI)	P value
	Number of events	Event rate* (episodes per patient-year) (95% CI)	Number of events	Event rate* (episodes per patient-year) (95% CI)		
RTI	175	1.65 (1.41 to 1.90)	200	2.19 (1.89 to 2.50)	0.75 (0.62 to 0.92)	0.006

*, event rate includes the initial as well as subsequent events. RTI, respiratory tract infection; CI, confidence interval.

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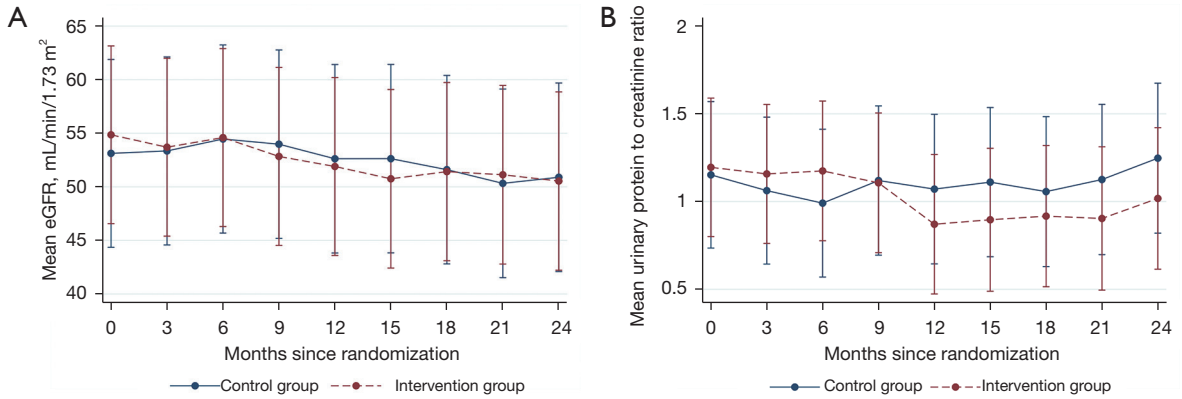

Figure 3 Effect of SAA therapy on eGFR and the UPCR. The effects of SAA on eGFR (A) and UPCR (B) are shown. Error bars indicate 95% CIs. eGFR, estimated glomerular filtration rate; SAA, self-administered acupressure; UPCR, urinary protein to creatinine ratio; CI, confidence interval.

Table 5 Effect of SAA on the secondary outcome of change in eGFR

Outcome eGFR	Change in eGFR (mL/min/1.73 m²/year) (95% CI)		Difference (intervention-control) (95% CI)
	Intervention	Control	
Adjusted for baseline eGFR	–2.47 (–3.53 to –1.41)	–1.71 (–3.53 to –1.41)	–0.76 (–2.31 to 0.80)
Adjusted for baseline eGFR and primary cause of kidney disease	–2.47 (–3.54 to –1.41)	–1.72 (–2.86 to –0.58)	–0.75 (–2.31 to 0.80)
Adjusted for baseline eGFR and minimization variables[†]	–2.47 (–3.54 to –1.41)	–1.71 (–2.85 to –0.58)	–0.76 (–2.31 to 0.80)

eGFR was calculated by the chronic kidney disease epidemiology creatinine equation. [†], adjusted for age, presence of diabetes mellitus, presence of hypertension, receiving Chinese caterpillar fungus preparation, and receiving calcium supplements. eGFR, estimated glomerular filtration rate.

Table 6 Secondary outcome laboratory indices at 24 months by treatment group (adjusted for baseline values)

Outcome	Intervention (N=57) (95% CI)	Control (N=51) (95% CI)	Difference (intervention-control) (95% CI)	P value
eGFR	50.54 (42.22–58.86)	50.89 (42.10–59.69)	–2.09 (–4.79–0.61)	0.130
UPCR	1.02 (0.61–1.42)	1.25 (0.82–1.67)	–0.27 (–0.61–0.07)	0.118
IgA	2.78 (2.53–3.03)	2.71 (2.45–2.98)	0.03 (–0.12–0.19)	0.631
IgG	12.55 (11.66–13.43)	12.97 (12.03–13.91)	–0.70 (–1.31—0.08)	0.026
IgM	1.00 (0.87–1.11)	0.91 (0.78–1.03)	0.00 (–0.06–0.06)	0.968
C3	1.02 (0.97–1.08)	1.11 (1.05–1.17)	–0.02 (–0.08–0.04)	0.570
C4	0.25 (0.22–0.27)	0.27 (0.25–0.29)	0.00 (–0.03–0.03)	0.860
CH50	37.92 (36.11–39.73)	39.57 (37.65–41.50)	–0.45 (–2.63–1.72)	0.682
CD3	68.15 (65.39–70.91)	66.96 (64.05–69.88)	1.40 (–0.72–3.48)	0.197
CD3CD4	36.17 (34.03–38.31)	38.20 (35.93–40.47)	–1.41 (–3.32–0.50)	0.148
CD3CD8	28.36 (26.22–30.50)	24.95 (22.69–27.21)	0.46 (–0.86–1.77)	0.496
CD3CD4/CD3CD8	1.43 (1.24–1.62)	1.75 (1.54–1.95)	–0.08 (–0.19–0.03)	0.173

eGFR, estimated glomerular filtration rate; UPCR, urinary protein to creatinine ratio; IgA/G/M, serum immunoglobulin A/G/M; CH50, 50% hemolytic complement activity of serum; C3/4, serum complement 3/4; CD3/CD4/CD8, CD3/CD4/CD8 lymphocyte counts of serum. CI, confidence interval.

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Table 7 Nonserious adverse reactions

Adverse reaction	Intervention (n=57)	Control (n=51)	Total (n=108)
Skin lesion	1 (2%)	0	1 (1%)
Bleeding	3 (5%)	0	3 (3%)
Headache	6 (11%)	5 (10%)	11 (10%)
Lower back pain	9 (16%)	12 (24%)	21(19%)
Arthralgia	8 (14%)	8 (16%)	16 (15%)
Sleep disorder	5 (9%)	6 (12%)	11 (10%)
Palpitation	5 (9%)	4 (8%)	9 (8%)
Nausea	0	3 (6%)	3 (3%)
Total	37 (65%)	35 (69%)	72 (67%)

with adjustments made for baseline values (Table S2).

Analysis of AEs

No cardiovascular events, deaths, or serious AEs occurred during the study period. AEs were reported in 37 of 57 (65%) patients in the intervention group and in 35 of 51 (69%) patients in the control group (*Table* 7). Four events in the intervention group were judged to be related or possibly related to the study. These related events were skin trauma and bleeding that were likely caused by incorrect use of fingernails on the acupoints and were mild in severity. No patients withdrew from the study due to experiencing AEs.

Discussion

The results of this study showed that, compared with usual care, SAA therapy combined with usual care resulted in a lower risk of RTI and a lower rate of RTI, suggesting that SAA therapy is a promising complementary and alternative medicine (CAM) therapy for preventing RTI in patients with CKD. SAA was also found to be safe with no significant difference in overall AEs between the intervention and control groups, and only 4 cases of minor skin trauma that might have been related to the treatment occurred. SAA had no significant effect on kidney function, proteinuria, blood pressure, or laboratory indices apart from lower serum IgG levels in the SAA group.

During the course of the global COVID-19 pandemic, acupressure was singled out as the most frequently used intervention recommended in Chinese guidelines for discharged COVID-19 patients to improve their clinical symptoms and physical and mental health (32). An increasing number of clinical trials have been registered that evaluate the effects of acupressure for COVID-19 (33,34), indicating that the use of acupressure in RTI has been receiving increased attention.

Patients with CKD are susceptible to RTI due to significant immune dysregulation caused by inflammation, malnutrition, dietary restriction, or immunosuppressive drugs (5). Data from previous studies have been collected to clarify the poorly understood mechanisms through which acupoints affect immune responses. An increase in the release of endogenous opioid peptides is generally accepted to be a keystone pathway that affects the immune system after acupoints are stimulated (35,36). The anti-inflammatory actions of acupressure and acupuncture are mediated by efferent vagus nerve activation and inflammatory macrophage deactivation (37). Findings reported by Garcia *et al.* have supported a role for the vagus nerve-dependent anti-inflammatory effect of acupressure in kidney disease (38).

Moreover, specific acupoints may also play their own unique role in the prevention or treatment of RTI. Acupoints used in this study included Yingxiang (LI20), Taiyang (EX-HN5), Fengchi (GB20), Fengfu (GV16), Dazhui (DU14), and Zusanli (ST36). Yingxiang (LI20) acupressure has been reported to provide relief from nasal congestion by stimulation of the branches of the infraorbital nerves, which regulate the sensation of nasal airflow and control of sneezing (39). For allergic rhinitis, stimulation at Yingxiang (LI20) effectively reduces inflammatory parameters by regulating the expression of substance P (SP), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY),

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interleukin 4 (IL-4), interferon-γ (IFN-γ), Toll-like receptor 2 (TLR2), and TLR4 (40,41). Taiyang (EX-HN5), Fengchi (GB20), Fengfu (GV16), and Dazhui (DU14) are often selected as the treatment acupoints to treat common cold, influenza, acute tonsillitis, and acute bronchitis, with their stimulation being associated with a simultaneous increase in the percentage of T lymphocytes (42-44). Dazhui (DU14) has also been used for the prevention of chronic cough in treating winter disease in the summer (45). Stimulating these acupoints was reported to eliminate the serum proinflammatory factors (IL-1β, IL-6, TNF-α, and COX-2), and regulate humoral immunity and cellular immunity in patients by decreasing immunoglobulin G/A/M/E, complement 3 (C3), complement 4 (C4), and regulating levels of $CD3^+$, $CD4^+$, and $CD8^+$ (46,47). Previous studies (48-50) have reported that stimulation at Zusanli (ST36) might be effective in preventing the common cold and recurrent RTI in middle-aged and older adults or children. Pretreatment at Zusanli (ST36) has been reported to be an effective anti-inflammatory treatment in animal models of respiratory impairment via significant attenuation of inflammatory cytokine production, such as TNF-α, IL-1β, and IL-6, and inactivated TLR4/nuclear factor kappa-B (NF-κB) signaling (49,50).

Consistent with these previous investigations, our study found that acupressure at the above acupoints appeared to reduce the risk and rate of RTI in patients with CKD. Its simplicity and lack of requirement for additional equipment make it convenient for patients. However, among the serum humoral immunity and cellular immunity indicators examined in the present study (IgG, IgA, and IgM; C3, C4, and CH50; and $CD3^+$, $CD4^+$, and $CD8^+$), we only found a significant between-group difference in serum IgG levels.

Interestingly, no significant difference in change in eGFR from baseline to month 24 was observed between the 2 groups. Therefore, even though SAA therapy decreased the risk and the incident rate of RTI in patients with CKD, no significant effect on kidney function was subsequently observed.

Our study had several limitations. First, the study had an open-label design, such that the possibilities of detection and performance biases could not be excluded. Second, participant selection was limited to patients with more than 2 RTI episodes in the preceding year, which meant that enrolled patients had a higher susceptibility to RTI. Therefore, the incidence rate of RTI in our study was higher than that reported in the cohort studies by McDonald *et al.* (31) and Xu *et al.* (30), such that the results of this study may not be generalizable to nonsusceptible populations. Third, changes in the types and dosages of medications were not recorded during the study, so the possible impacts of pharmaceutical cointerventions could not be evaluated. However, the proportions of participants using these drugs at baseline were balanced between the groups. At last, antibiotic treatment related RTI during the follow up was allowed, which may influence the outcomes of inflammation and immune indicators.

Conclusions

Daily SAA therapy over 24 months significantly reduced the risk of RTI in adult patients with CKD, suggesting that SAA is a promising effective and safe therapy for preventing RTI in patients with CKD. However, the efficacy of SAA in children and adolescents, or non-susceptible populations still needs further study.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2376/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2376/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2376/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2376/coif). XL reports receiving funding from Program of the State Key Laboratory of Dampness Syndrome of Chinese Medicine (No. SZ2021ZZ43) without any payment. LZ reports receiving funding from Guangzhou Science and Technology Project (No. 2016201604030085) and funding from Program of the State Key Laboratory of Dampness

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Syndrome of Chinese Medicine (No. SZ2021ZZ16) without any payment. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (No. B2017-006-01). Each eligible patient provided written informed consent before randomization.

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Supplementary

Table S1 The laboratory measurements of the patients at baseline

Characteristic	Intervention (N=57)	Control (N=51)	Total (N=108)
White blood cell count (×10^3/μL)	6.63±2.41	7.18±3.41	6.44±2.40
Neutrophil count (×10^3/μL)	4.14±2.41	4.35±2.80	3.94±2.07
Monocyte count (×10^3/μL)	0.42±0.17	0.48±0.22	0.44±0.22
Lymphocyte count (×10^3/μL) #	1.67±0.50	2.11±0.95	1.81±0.64
Eosinophil count (×10^3/μL)	0.19±0.07	0.20±0.17	0.20±0.19
Red blood cells count (×10^6/μL)	4.41±0.65	4.34±0.65	4.38±0.65
Hemoglobin (g/dL)	12.84±2.05	12.94±1.94	12.89±1.99
Serum albumin (g/dL)	4.54±0.37	4.51±0.51	4.54±0.41
Triglyceride (mg/dL)	131.09±62.00	152.35±96.55	142.60±103.63
Total cholesterol (mg/dL)	189.48±49.11	209.20±83.53	191.42±53.36
Low-density lipoprotein (mg/dL)	121.42±41.00	138.44±72.31	125.68±45.63
IgA (g/L)	2.82±1.09	2.71±1.05	2.67±0.98
IgG (g/L)	13.02±4.32	12.74±3.23	12.65±3.41
IgM (g/L)	1.05±0.49	0.97±0.46	0.98±0.46
C3 (g/L) #	1.01±0.15	1.07±0.19	1.04±0.17
C4 (g/L)	0.26±0.06	0.27±0.06	0.26±0.06
CH50 (g/L)	34.53±6.67	35.73±7.05	35.10±6.84
CD3 (%)	69.86±9.69	67.26±10.98	67.82±10.44
CD3CD4 (%)	37.43±7.61	38.05±7.81	37.72±7.67
CD3CD8 (%)	28.64±7.79	25.69±8.68	27.25±8.31
CD3CD4/ CD3CD8	1.45±0.63	1.69±0.77	1.56±0.70

Conversion factors for units: triglyceride in mg/dL to mmol/L, ×0.01129; total cholesterol and low-density lipoprotein in mg/dL to mmol/L, ×0.02586. # The *P* value of lymphocytes and C3 was significantly different between the control and intervention groups (P<0.01 and P=0.04, respectively). IgA/G/M, serum immunoglobulin A/G/M; C3/4, serum complement 3/4; CH50, 50% hemolytic complement activity of serum; CD3/CD4/CD8, CD3/CD4/CD8 lymphocyte counts of serum.

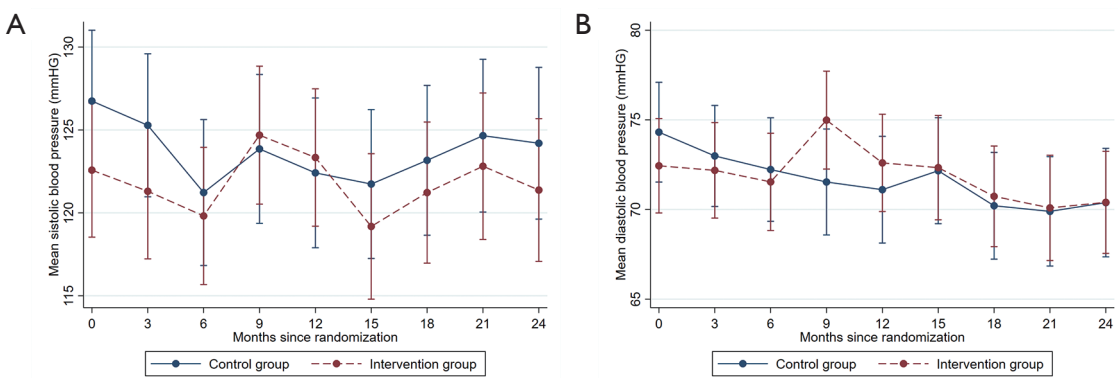

Figure S1 Effect of SAA on blood pressure. Error bars indicate 95% CIs. (A) Systolic blood pressure. (B) Diastolic blood pressure

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Table S2 The secondary laboratory outcomes at 24 months by intervention group (adjusted for baseline values)

Outcome	Intervention (N=57)	Control (N=51)	Difference (intervention-control) [95% CI]	P value
White blood cell count ($\times10^3$/μL)	6.26 [5.61–6.90]	6.79 [6.11–7.48]	0.18 [–0.52–0.89]	0.6
Neutrophil count ($\times10^3$/μL)	3.86 [3.30–4.43]	4.07 [3.47–4.68]	0.00 [–0.69–0.70]	0.9
Monocyte count ($\times10^3$/μL)	0.44 [0.37–0.50]	0.45 [0.38–0.51]	0.05 [–0.04–0.13]	0.3
Lymphocyte count ($\times10^3$/μL)	1.66 [1.49–1.83]	1.92 [1.74–2.10]	0.17 [–0.01–0.36]	0.07
Eosinophil count ($\times10^3$/μL)	0.17 [0.12–0.22]	0.22 [0.16–0.28]	–0.03 [–0.09–0.03]	0.3
Red blood cell count ($\times10^6$/μL)	4.22 [4.05–4.40]	4.29 [4.11–4.48]	–0.13 [–0.27–0.00]	0.06
Hemoglobin (g/dL)	12.56 [12.00–13.12]	12.92 [12.33–13.51]	–0.27 [–0.67–0.14]	0.2
Serum albumin (g/dL)	4.45 [4.34–4.56]	4.41 [4.29–4.52]	0.01 [–0.12–0.13]	0.9
Serum uric acid (mg/dL)	6.67 [6.25–7.09]	6.70 [6.25–7.14]	–0.03 [–0.61–0.55]	0.9
Triglyceride (mg/dL)	136.40 [108.95–163.86]	163.86 [134.63–193.09]	–6.20 [–40.74–27.46]	0.7
Total cholesterol (mg/dL)	189.87 [175.56–204.18]	199.54 [184.45–214.62]	10.05 [–6.19–26.30]	0.2
Low-density lipoprotein (mg/dL)	124.13 [111.76–136.50]	130.32 [117.17–143.46]	10.83 [–3.48–25.14]	0.1
Serum potassium (mEq/L)	8.76 [8.50–9.02]	8.98 [8.70–9.26]	–0.12 [–0.40–0.16]	0.4
Serum calcium (mEq/L)	4.70 [4.62–4.80]	4.88 [4.78–4.98]	–0.10 [–0.26–0.08]	0.3
Serum phosphorus (mEq/L)	2.60 [2.46–2.74]	2.50 [2.36–2.66]	0.06 [–0.08–0.20]	0.4

Conversion factors for units: serum uric acid in mg/dL to μmol/L, ×59.48; triglyceride in mg/dL to mmol/L, ×0.01129; total cholesterol and low-density lipoprotein in mg/dL to mmol/L, ×0.02586; serum potassium, serum calcium, and serum phosphorus in mEq/L to mmol/L, ×0.5.

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