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# Efficacy and safety of community-based moxibustion for primary hypertension: A randomized controlled trial with patient preference arms

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## Abstract

Moxibustion has been shown to have a potential antihypertensive effect, but its applicability for the primary care of hypertension is unclear. The authors conducted a multicenter randomized controlled trial (RCT) with patient preference arms to investigate the effect, safety, cost-effectiveness, and compliance of moxibustion in community patients with hypertension. Patients with primary hypertension were enrolled from seven communities randomly or nonrandomly assigned to receive self-administered moxibustion + the original hypertensive regimen or the original hypertensive regimen alone for 6 months. The authors mainly evaluated the effects of moxibustion on hypertensive outcomes and adverse events. As a result, a total of 160 and 240 patients were recruited into the randomized and nonrandomized arms, respectively, with 87.5% completing the follow-up. At month 6, there was a significantly greater reduction in systolic blood pressure (SBP) (difference: −10.57 mmHg), a higher proportion of responders (82.2% vs. 53.7%; odds ratio 4.00), and better improvements in hypertensive symptoms and quality of life (QoL) in the moxibustion group than in the control group in the randomized population, but there was no significant between-group difference in diastolic blood pressure (DBP). The nonrandomized findings showed the same effect direction for all outcomes, except for DBP. All moxibustion-related adverse events were mild. In conclusion, moxibustion can reduce SBP and improve hypertensive symptoms and QoL in community patients with hypertension, with good safety and low cost, although its effect on DBP remains uncertain. The findings suggest that moxibustion may be an appropriate technique for community primary care of hypertension.

KEYWORDS
community, moxibustion, patient preference trial, primary hypertension, randomized controlled trial

## 1 | INTRODUCTION

Hypertension is a primary preventable risk factor for cardiovascular morbidity and mortality.[1] Approximately 62% of strokes and 49% of myocardial infarction episodes are attributed to hypertension, suggesting hypertension being a primary preventable risk factor of cardiovascular morbidity and mortality.[1,2] However, the control rate of hypertension remains below 50%, even in developed countries with high medical investment.[3] This challenge is ascribed not only to the limited efficacy,[4] side effects,[5] and resistance[6] to drug therapy but also to other crucial barriers, including the low accessibility and high cost of hospital-based hypertension management, which is particularly pronounced in low- and middle-income countries.[7,8] Therefore, the exploration of a complementary community management model for hypertension based on appropriate antihypertensive techniques is necessary.

Moxibustion, an acupoint thermal stimulation therapy popular in East Asia, is receiving attention for its potential antihypertensive effects. Moxibustion produces thermal stimulation on acupoints by burning moxa wool made from dried moxa leaves and has been used for treating diseases for thousands of years.[9,10] Acupoint stimulation has been shown to produce biological effects related to blood pressure reductions, such as the regulation of vascular endothelial cell endocrine and oxidative stress.[11,12] Animal experiments have shown the hypotensive effect of moxibustion.[13,14] In addition to its efficacy, moxibustion does not require professional qualifications and is simple to learn, easy to operate, and low cost, making it suitable as a medical technique for the self-management of chronic diseases in the community setting.

Our previous systematic review of randomized controlled trials (RCTs) showed that moxibustion could reduce blood pressure in hypertension patients.[15] However, because the previous RCTs were conducted in hospital settings and suffered a moderate to high risk of bias, the findings of the systematic review cannot be generalized to demonstrate the applicability of self-administered moxibustion for hypertension treatment in the community. Therefore, we conducted a pragmatic RCT to assess the efficacy, safety, cost-effectiveness, and patient compliance of self-administered moxibustion for the treatment of primary hypertension in a community primary care setting and hypothesized that the addition of moxibustion to the original regimen would have better antihypertensive effects than the original regimen alone. To increase the sample size and validate the study, we also included nonrandomized arms in the trial.

## 2 | METHODS

### 2.1 | Study design and ethical approval

This is a multicenter, pragmatic, RCT with patient preference arms conducted from March 10, 2021 to December 9, 2021. The study protocol was approved by the Ethics Committee of the Affiliated Hospital to Jiangxi University of Chinese Medicine (no. JZFYKYLL20210301009) and registered at Clinicaltrials.gov (registration no. NCT04788563) and was previously published.[16] All patients provided written informed consent prior to participation with a full understanding of the study details and potential merits and harms. Patients can actively withdraw from the trial at any point for any reason. This report followed the Consolidated Standards of Reporting Trials (CONSORT) statement.[17]

### 2.2 | Participants

Participants were recruited from seven communities in Nanchang City, Jiangxi Province, China, through community physicians' inducement, leaflets, and posters. The study population included patients aged 18–80 years who had primary hypertension for more than 6 months, which was defined by the 2020 International Society of Hypertension Global Hypertension Practice Guidelines, namely, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.[18] Patients with a previous diagnosis of primary hypertension and regular use of antihypertensive drugs were also eligible. Patients could not have received acupoint stimulation therapy in the month prior to enrollment. In addition, patients included in the moxibustion group should be able to detect any heat-sensitive sensations (i.e., the expansion and deepening of sensory zones and the experience of nonthermal sensations such as soreness, swelling, aching, and ant-crawling sensations) on or near any main acupoints (as defined below). The exclusion criteria were uncontrolled hypertension indicated by systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg even with the use of antihypertensive drugs; secondary hypertension; lactation or pregnancy; an allergy to moxa or moxa smoke; contraindications to moxibustion such as acute cerebral hemorrhage, hypertensive crisis, or sensory impairment; cognitive impairment or severe psychiatric disorders; or enrollment in another study.

## 2.3 | Randomization

Seven communities were first randomized into a mandatory randomization cluster (three communities) and a patient preference cluster (four communities), where participants with a strong preference were allowed to select which group to participate in, and those with no preference were randomized (Figure 1). An independent statistician generated random sequences using the "blockrand" package of R 4.1.0 (Ross Ihaka, Robert Gentlemen, New Zealand). For the randomization of individuals, a blocked random sequence with a mixed block size of 4 or 6 and an allocation ratio of 1:1 was generated for each study site. The results of randomization were concealed on scratch cards, and patients scratched the coating on the cards to access the group assignment. During the trial, treatment assignment was open label to patients and physicians but was masked to the outcome assessors and data analysts. In the nonrandomized group, patients chose to enter the moxibustion group or the control group according to their preference, with a 1:1 allocation ratio.

## 2.4 | Interventions

Patients in both groups maintained their original antihypertensive regimen, namely, antihypertensive drugs (e.g., calcium channel blockers (CCBs), angiotensin receptor blockers or angiotensin-converting enzyme inhibitors (ARBs/ACEIs), diuretics, beta-blockers, etc.) or no interventions, for 6 months. Additionally, patients in the moxibustion group self-administered moxibustion treatment for 6 months. Prior to the initiation of the treatment, an acupuncturist helped the patient probe sensations near three main acupoints (Baihui (GV20), Shenque (CV8), and Yongquan (KI1)) and five secondary acupoints (Dazhui (GV14), Quchi (LI11), Hegu (LI4), Zusanli (ST36), and Taichong (LR3)) by a suspended moxibustion technique. One main and one secondary acupoint each with the strongest heat-sensitive sensation were selected for moxibustion treatment, where only the side with the stronger sensation was selected for symmetrically distributed acupoints (i.e., Yongquan, Quchi, Hegu, Taichong, and Zusanli). After being trained and mastering the manipulation of moxibustion, patients performed moxibustion by themselves or with the help of their family as the following steps: the operator first places a moxa column into a moxibustion jar and then ignites the moxa column and places it on the acupoints for moxibustion; the treatment ends when the heat-sensitive sensation disappears or when one column burns out (approximately 30 min) (see Supplementary Methods for details). The moxibustion materials (moxa columns) were purchased from Poai Biotechnology Co. Ltd., and the origin of the moxa was Shangrao City, Jiangxi Province, China. Driven by the pragmatic design, the recommended frequency of moxibustion for patients was no less than two sessions per week, ideally once a day.

All patients were advised to follow a low salt diet and increase their physical activity and were prohibited from receiving other acupoint stimulation therapies. Routine treatment for comorbidities was allowed. Patients were required to truthfully report cointerventions, and deviations from the protocol, if any, did not affect their continued participation.

## 2.5 | Outcomes

The primary outcome was the change in SBP from baseline to month 6; blood pressure was measured uniformly by an Omron HEM-7124 blood pressure monitor prior to morning dosing of antihypertensive drugs.

Secondary outcomes included the following: changes in SBP at the remaining time points; changes in DBP; the proportion of blood pressure responders with an SBP decrease $\geq$20 mmHg, a DBP decrease $\geq$10 mmHg, or an SBP/DBP that reached <130/80 mmHg (<140/90 mmHg in those aged $\geq$65 years); changes in the dose of antihypertensive drugs; changes in the severity of hypertensive symptoms assessed using a 24-item scale described in the Guidelines for Clinical Research on New Chinese Medicines (score range: 0–72 points, higher scores indicate worse symptoms); changes in quality of life (QoL) assessed by the Euro-QoL-5 Dimensions-5 Levels (EQ-5D-5L) scale, which provides an index score ranging from 0 to 1 and an overall health score ranging from 0 to 100 (higher indices or scores indicate better QoL); the incidence of new cardiovascular events; patient compliance with moxibustion; cost-effectiveness; and adverse events.

## 2.6 | Study procedures

After the baseline assessment, the patients were followed up each month for 6 months. There was a $\pm$3-day time window for each follow-up visit, beyond which the visit was dropped. At the baseline visit, we collected demographic information and medical history and measured blood pressure. At each follow-up visit, we measured or recorded blood pressure, medication dose, compliance, new-onset disease, medical costs, and adverse events. QoL and hypertensive symptoms were assessed again at months 3 and 6. Each study site was assigned a coordinator who had received standardized training to interact with patients and collect data. An independent data and safety monitoring committee was established to monitor the safety and quality of the trial.

## 2.7 | Sample size estimation

Based on the results of our pilot study and experts' opinions, the between-group difference in mean SBP reductions at month 6 was assumed to be at least 5 mmHg, with a pooled standard deviation of 8 mmHg. Considering an $\alpha$ of 0.05, a $\beta$ of 0.20, and a 20% attrition rate, the superiority-design sample size estimation yielded a minimum of 102 patients in the randomized population (51 patients per group). To improve statistical power, we expanded the randomized sample size to 160. Considering the 6:1 ratio of patients with and without a

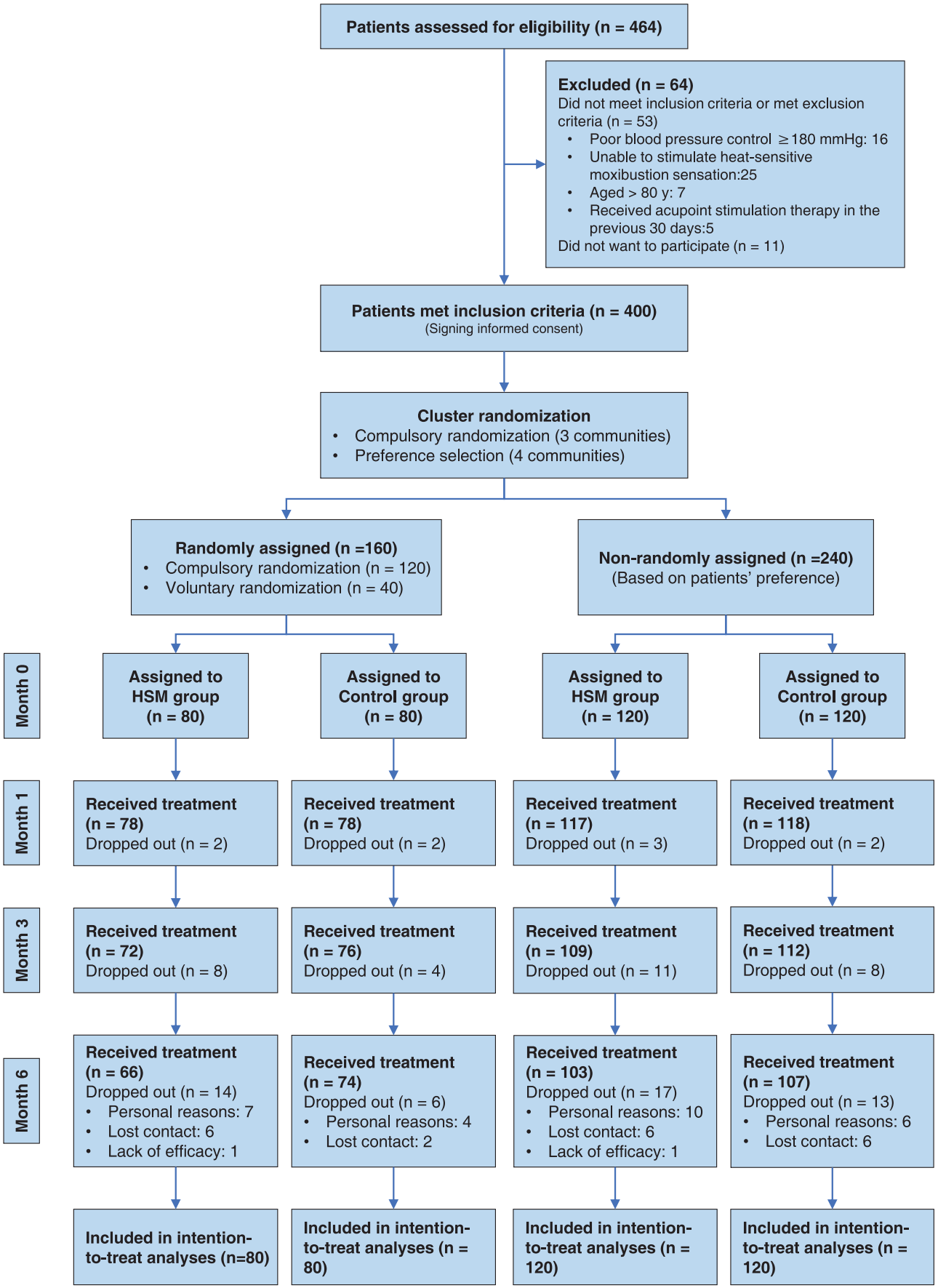


**FIGURE 1** Study flowchart.

preference in our pilot survey and funding constraints, we set a voluntary randomization population of 40 patients and a nonrandomized population of 240 patients, with 120 patients undergoing mandatory randomization (Figure 1).

### 2.8 | Statistical analysis

Data analysis was separately performed for randomized and nonrandomized populations using SAS version 9.4 (SAS Institute Inc.). Baseline characteristics, adverse events, and compliance between the groups were described and compared by *t* test, chi-square test, or rank sum test. Analyses of blood pressure outcomes were based on the full analysis set with the intention-to-treat principle. The per-protocol set—defined as the population with at least three follow-up visits who completed the last visit and completed at least two moxibustion sessions per week (in the moxibustion group)—was used for the analysis of other outcomes. The difference in effects for continuous outcomes was measured by least-square means and 95% confidence intervals (CIs), as estimated by a linear mixed-effects model for repeated measures. For dichotomous outcomes, effects were estimated by a logistic generalized linear mixed model for repeated measures and measured by odds ratios (ORs) and 95% CIs. The analyses of the randomized population were adjusted for visit, visit × group interactions, and study site; for the nonrandomized population, there were additional adjustments for baseline SBP, age, baseline BMI, hypertension course, antihypertensive drug use, Charlson comorbidity index, smoking status, and drinking status. All the covariates were considered fixed effects except for study site, which was considered a random effect. Two-sided *p* values less than .05 were considered statistically significant. Incremental cost-effectiveness ratios (ICERs) were calculated as the ratio of the between-group difference in the total per capita cost of hypertension treatment to the between-group difference in quality-adjusted life years (QALYs) yielded from the EQ-5D-5L index.

Regression-based multiple imputation was used to impute missing outcome values, considering all abovementioned covariates. For each analysis, 100 multiple imputations were performed, and the final effect estimate was yielded from an average of all imputed dataset estimates. Sensitivity analyses using the per-protocol set were performed to test the robustness of the estimates of blood pressure outcomes. Moreover, we performed a post hoc subgroup analysis stratified by background antihypertensive regimens (including subgroups of no drugs, CCBs, ARBs/ACEIs, and multiple drugs; the subgroup of other drugs was not analyzed due to insufficient sample size) for SBP and DBP. We combined randomized and nonrandomized samples for the subgroup analysis.

## 3 | RESULTS

### 3.1 | Participants

A total of 464 patients with primary hypertension were screened from March 10 to June 10, 2021, of whom 400 were ultimately enrolled. The randomized population included 77 men and 91 women, with an average age of 63.1 years (SD, 9.7); the nonrandomized population included 114 men and 126 women, with an average age of 62.9 years (SD, 9.5). As shown in Table 1, all baseline characteristics were balanced between the moxibustion and control groups in the randomized population; however, in the nonrandomized population, there were imbalances in age, baseline EQ-5D-5L VAS score, proportion of patients with comorbidities, and baseline Charlson comorbidity index between the two groups. Follow-ups ended on December 9, 2021, and 350 (87.5%) patients completed the last follow-up. There were 14 (17.5%), 6 (7.5%), 17 (14.2%), and 13 (10.8%) patients in the randomized trial group, randomized control group, nonrandomized trial group and nonrandomized control group, respectively, who withdrew from the study, mostly because of loss of contact, personal reasons, or dissatisfaction with the efficacy (Figure 1).

### 3.2 | Efficacy

In both the randomized and nonrandomized populations, SBP was significantly reduced at all visits in the moxibustion group compared to baseline, and the reduction was significantly greater than that in the control group at all visits (difference at month 6: −10.57 mmHg [95% CIs −14.98 to 6.16] in the randomized population; −15.89 mmHg [95% CIs −19.22 to −12.57] in the nonrandomized population) (Table 2 and Figure 2). Sensitivity analyses showed similar effect directions at month 6 (Table S1).

During the trial, DBP also showed a significant downward trend in the moxibustion group in both populations. In the randomized population, the reduction in DBP was significantly greater in the moxibustion group than in the control group from month 1 (difference: −3.32, 95% CIs −6.28 to −0.36) to month 4 (difference: −3.41, 95% CIs −6.51 to −0.31), but the advantage was not maintained thereafter. In the nonrandomized population, DBP decreased significantly more in the moxibustion group than in the control group at month 5 (difference: −3.18, 95% CIs −5.55 to −0.81) and month 6 (difference: −4.99, 95% CIs −7.29 to −2.69) (Table 2 and Figure 2). The sensitivity analysis of the randomized population showed an important change in that the moxibustion group had a significantly greater reduction in DBP than the control group at all visits (Table S1).

In the randomized population, the proportion of blood pressure responders was significantly higher in the moxibustion group than in the control group only at month 6 (82.2% vs. 53.7%; odds ratio 4.00, 95% CIs 1.81 to 8.83), whereas in the nonrandomized population, the moxibustion group had significantly more responders than the control group from month 2 onward, reaching rates of 86.0% vs. 37.0% at month 6 (odds ratio 10.50, 95% CIs 5.07 to 21.75) (Table 2 and Figure 2). Sensitivity analyses did not show important changes (Table S1).

In both the randomized and nonrandomized populations, patients in the moxibustion group showed significant or marginally significant improvement in hypertensive symptoms (randomized population: difference −2.50, 95% CIs −4.14 to −0.86; nonrandomized population:

**TABLE 1** Baseline characteristics of patients in the full analysis dataset.

| Characteristic | Randomized population | | Nonrandomized population | |
|---|---|---|---|---|
| | Moxibustion ($n = 80$) | Control ($n = 80$) | Moxibustion ($n = 120$) | Control ($n = 120$) |
| Gender, *n* (%) | | | | |
| Man | 34 (42.5) | 35 (43.8) | 52 (43.3) | 62 (51.7) |
| Woman | 46 (57.5) | 45 (56.3) | 68 (56.7) | 58 (48.3) |
| Mean age (SD), year | 63.4 (9.8) | 62.7 (9.6) | 64.5 (9.1) | 61.4 (9.7)* |
| Education | | | | |
| Middle school or lower | 51 (63.8) | 59 (73.8) | 105 (87.5) | 95 (79.2) |
| Junior college or higher | 29 (36.2) | 21 (26.2) | 15 (12.5) | 25 (20.8) |
| Current smoker, *n* (%) | 11 (13.8) | 13 (16.3) | 24 (20.0) | 31 (25.8) |
| Current drinker, *n* (%) | 20 (25.0) | 18 (22.5) | 31 (25.8) | 41 (34.1) |
| Mean body mass index (SD), kg/m$^2$ | 24.5 (2.5) | 24.2 (3.2) | 24.9 (3.1) | 24.4 (3.1) |
| Median course of hypertension (interquartile range), year | 9.0 (5.0, 12.5) | 7.0 (2.5, 12.0) | 6.0 (2.5, 14.5) | 7.5 (3.0, 13.0) |
| Mean systolic blood pressure (SD), mmHg | 137.4 (15.7) | 135.8 (17.4) | 142.1 (15.0) | 139.7 (14.4) |
| Mean diastolic blood pressure (SD), mmHg | 82.8 (9.2) | 81.7 (10.7) | 83.0 (10.2) | 84.3 (9.4) |
| Comorbidities, *n* (%) | | | | |
| None | 13 (16.3) | 16 (20.0) | 25 (20.8) | 39 (32.5)* |
| Diabetes | 19 (23.8) | 21 (26.3) | 21 (17.5) | 16 (13.3) |
| Dyslipidemia | 25 (31.3) | 27 (33.8) | 42 (35.0) | 42 (35.0) |
| Carotid artery plaque | 30 (37.5) | 27 (33.8) | 22 (18.3) | 17 (14.2) |
| Hyperuricemia/gout | 2 (2.5) | 3 (3.8) | 10 (8.3) | 12 (10.0) |
| Chronic renal disease | 1 (1.3) | 1 (1.3) | 1 (0.8) | 1 (0.8) |
| Median Charlson comorbidity index (interquartile range) (range: 0–6)[a] | 3 (2, 3) | 2 (2, 4) | 3 (2, 3) | 2 (1, 3)** |
| Mean hypertensive symptom score (SD) (range: 8–72)[a] | 11.9 (7.3) | 11.6 (5.9) | 12.1 (5.9) | 11.3 (7.4) |
| Mean EQ-5D-5L index score (SD) (range: 0–1)[b] | 0.79 (0.12) | 0.80 (0.14) | 0.80 (0.12) | 0.83 (0.14) |
| Mean EQ-5D-5L overall health score (SD) (range: 0–100)[b] | 71.0 (11.2) | 71.8 (12.9) | 68.3 (13.8) | 72.5 (11.1)** |
| Use of antihypertensive drugs, *n (%)* | | | | |
| None | 8 (10.0) | 7 (8.8) | 22 (18.3) | 22 (18.3) |
| Calcium channel blockers | 37 (46.3) | 44 (55.0) | 70 (58.3) | 63 (52.5) |
| ARBs/ACEIs | 9 (11.3) | 10 (12.5) | 12 (10.0) | 11 (9.2) |
| Other drugs | 3 (3.7) | 1 (1.2) | 1 (0.8) | 1 (0.8) |
| Combination of two drugs | 20 (25.0) | 15 (18.8) | 13 (10.8) | 21 (17.5) |
| Combination of three drugs | 3 (3.7) | 3 (3.7) | 2 (1.7) | 2 (1.7) |

Abbreviations: ARBs/ACEIs, angiotensin receptor blockers or angiotensin-converting enzyme inhibitors; EQ-5D-5L, EuroQol 5 Dimension 5 Level questionnaire; SD, standard deviation; VAS, visual analog scale.

[a]Higher scores on the Charlson comorbidity index and hypertensive symptom score indicate worse comorbidity or symptoms.

[b]Higher scores on the EQ-5D-5L index score and EQ-5D-5L overall health score indicate a better quality of life.

Moxibustion group vs. control group among the nonrandomized population: *$p < .05$; **$p < .01$.

difference −3.96, 95% CIs −5.21 to −2.72), EQ-5D-5L index scores (randomized population: difference 0.034, 95% CIs −0.001 to 0.069), and EQ-5D-5L overall health scores compared to the control group at month 6 (randomized population: difference 5.93, 95% CIs 2.26 to 9.59; non-randomized population: difference 9.68, 95% CIs 6.84 to 12.53) (Table 2); however, there was no significant between-group difference in changes in the dose of antihypertensive drugs (Table 2) and the incidence of new cardiovascular events (Table S2) at any visit.

### 3.3 | Results of subgroup analysis

In all subgroups of background antihypertensive regimens, the moxibustion group exhibited a significantly greater reduction in SBP compared to the control group at month 6 (difference: −12.74 mmHg [95% CI −20.26 to −5.22] in the no-drug subgroup; −14.57 mmHg [95% CI −17.88 to −11.25] in the CCB subgroup; −14.65 mmHg [95% CI −22.73 to −6.58] in the ARB/ACEI subgroup; and −10.45 mmHg

**TABLE 2** Primary and secondary outcomes based on the full analysis set.

| Outcome | Randomized population | | | Nonrandomized population | | |
|---|---|---|---|---|---|---|
| | Moxibustion ($n = 80$) | Control ($n = 80$) | Difference/Odd ratio (95% CI) | Moxibustion ($n = 120$) | Control ($n = 120$) | Difference/Odd ratio (95% CI) |
| **Change in systolic blood pressure (mmHg)** | | | | | | |
| Month 1 | −8.32 (−11.35, −5.28) | −3.35 (−6.37, −0.32) | −4.97 (−9.27, −0.67)* | −9.88 (−12.18, −7.57) | −5.66 (−7.93, −3.39) | −4.22 (−7.45, −0.99)* |
| Month 2 | −12.66 (−15.78, −9.54) | −5.04 (−8.05, −2.03) | −7.62 (−11.96, −3.28)*** | −12.98 (−15.37, −10.60) | −6.40 (−8.68, −4.11) | −6.59 (−9.89, −3.28)*** |
| Month 3 | −12.44 (−15.52, −9.36) | −4.60 (−7.65, −1.56) | −7.84 (−12.18, −3.50)*** | −15.67 (−18.01, −13.33) | −7.25 (−9.55, −4.94) | −8.43 (−11.72, −5.14)*** |
| Month 4 | −10.84 (−14.04, −7.63) | −4.50 (−7.57, −1.42) | −6.34 (−10.79, −1.88)** | −15.32 (−17.82, −12.82) | −6.16 (−8.56, −3.76) | −9.16 (−12.65, −5.66)*** |
| Month 5 | −10.04 (−13.26, −6.81) | −3.34 (−6.43, −0.26) | −6.70 (−11.15, −2.24)** | −16.80 (−19.26, −14.34) | −4.18 (−6.59, −1.77) | −12.62 (−16.03, −9.21)*** |
| Month 6 | −13.26 (−16.44, −10.09) | −2.70 (−5.74, 0.35) | −10.57 (−14.98, −6.16)*** | −19.25 (−21.60, −16.89) | −3.35 (−5.68, −1.03) | −15.89 (−19.22, −12.57)*** |
| **Change in diastolic blood pressure (mmHg)** | | | | | | |
| Month 1 | −3.87 (−5.96, −1.78) | −0.55 (−2.62, 1.53) | −3.32 (−6.28, −0.36)* | −2.37 (−3.96, −0.79) | −2.82 (−4.38, −1.26) | 0.45 (−1.77, 2.66) |
| Month 2 | −5.10 (−7.27, −2.93) | −1.44 (−3.50, 0.63) | −3.66 (−6.66, −0.67)* | −3.47 (−5.12, −1.82) | −2.69 (−4.26, −1.12) | −0.78 (−3.06, 1.50) |
| Month 3 | −5.83 (−7.95, −3.70) | −1.57 (−3.66, 0.53) | −4.26 (−7.26, −1.26)** | −6.04 (−7.65, −4.42) | −3.07 (−4.66, −1.49) | −2.96 (−5.23, −0.69)* |
| Month 4 | −5.31 (−7.56, −3.06) | −1.90 (−4.02, 0.22) | −3.41 (−6.51, −0.31)* | −4.53 (−6.27, −2.78) | −2.25 (−3.92, −0.58) | −2.27 (−4.72, 0.17) |
| Month 5 | −3.16 (−5.43, −0.90) | −0.55 (−2.68, 1.58) | −2.61 (−5.72, 0.49) | −3.81 (−5.53, −2.10) | −0.63 (−2.31, 1.05) | −3.18 (−5.55, −0.81)** |
| Month 6 | −4.07 (−6.29, −1.86) | −1.67 (−3.76, 0.42) | −2.40 (−5.46, 0.65) | −5.38 (−7.01, −3.75) | −0.38 (−1.99, 1.22) | −4.99 (−7.29, −2.69)*** |
| **Blood pressure responders (%)** | | | | | | |
| Month 1 | 68.1 (57.1, 79.1) | 54.7 (42.9, 66.5) | 1.76 (0.90, 3.46) | 61.9 (51.3, 72.4) | 55.1 (44.5, 65.7) | 1.32 (0.74, 2.38) |
| Month 2 | 75.5 (65.3, 85.8) | 66.5 (55.4, 77.7) | 1.56 (0.75, 3.23) | 74.8 (65.1, 84.6) | 57.7 (47.1, 68.3) | 2.19 (1.15, 4.17)* |
| Month 3 | 81.2 (71.7, 90.6) | 68.8 (57.8, 79.9) | 1.96 (0.89, 4.30) | 85.0 (77.6, 92.4) | 62.7 (52.4, 73.0) | 3.37 (1.68, 6.78)*** |
| Month 4 | 71.4 (60.0, 82.7) | 67.1 (55.8, 78.4) | 1.22 (0.58, 2.56) | 82.4 (73.2, 91.5) | 52.9 (41.5, 64.3) | 4.19 (1.95, 9.02)*** |
| Month 5 | 67.6 (55.6, 79.6) | 62.3 (50.5, 74.0) | 1.27 (0.61, 2.62) | 79.9 (70.6, 89.2) | 43.3 (32.3, 54.4) | 5.23 (2.58, 10.64)*** |
| Month 6 | 82.2 (72.7, 91.7) | 53.7 (41.9, 65.6) | 4.00 (1.81, 8.83)*** | 86.0 (78.7, 93.3) | 37.0 (26.5, 47.5) | 10.50 (5.07, 21.75)*** |

(Continues)

**TABLE 2** (Continued)

| Outcome | Randomized population | | | Nonrandomized population | | |
|---|---|---|---|---|---|---|
| | Moxibustion ($n = 80$) | Control ($n = 80$) | Difference/Odd ratio (95% CI) | Moxibustion ($n = 120$) | Control ($n = 120$) | Difference/Odd ratio (95% CI) |
| **Change in dose of antihypertensive drugs (%)** | | | | | | |
| Month 1 | −4.40 (−7.73, −1.08) | −1.74 (−5.05, 1.57) | −2.66 (−7.36, 2.03) | 0.02 (−2.62, 2.67) | 0.79 (−1.81, 3.39) | −0.76 (−4.47, 2.95) |
| Month 2 | −3.44 (−6.84, −0.04) | −1.52 (−4.85, 1.80) | −1.92 (−6.67, 2.84) | 0.56 (−2.14, 3.26) | 1.73 (−0.90, 4.36) | −1.17 (−4.94, 2.60) |
| Month 3 | −2.24 (−5.67, 1.18) | −3.07 (−6.42, 0.29) | 0.82 (−3.97, 5.61) | 1.94 (−0.73, 4.60) | 0.95 (−1.68, 3.58) | 0.99 (−2.76, 4.73) |
| Month 4 | −2.61 (−6.13, 0.91) | −2.46 (−5.86, 0.93) | −0.14 (−5.03, 4.74) | 2.16 (−0.64, 4.96) | 1.16 (−1.60, 3.92) | 1.00 (−2.94, 4.93) |
| Month 5 | 0.26 (−3.33, 3.85) | −0.22 (−3.64, 3.21) | 0.47 (−4.49, 5.43) | 1.18 (−1.60, 3.96) | 1.84 (−0.93, 4.61) | −0.66 (−4.58, 3.27) |
| Month 6 | −1.13 (−4.63, 2.37) | 0.80 (−2.56, 4.17) | −1.94 (−6.79, 2.92) | 0.93 (−1.78, 3.64) | 1.61 (−1.06, 4.28) | −0.68 (−4.49, 3.12) |
| **Change in hypertensive symptom score**[a] | | | | | | |
| Month 3 | −4.25 (−5.50, −3.01) | −3.40 (−4.49, −2.32) | −0.85 (−2.50, 0.80) | −4.15 (−5.05, −3.26) | −1.92 (−2.77, −1.06) | −2.24 (−3.48, −1.00)*** |
| Month 6 | −4.67 (−5.92, −3.43) | −2.18 (−3.25, −1.10) | −2.50 (−4.14, −0.86)** | −6.14 (−7.04, −5.24) | −2.18 (−3.04, −1.32) | −3.96 (−5.21, −2.72)*** |
| **Change in EQ-5D-5L index score**[b] | | | | | | |
| Month 3 | 0.011 (−0.015, 0.038) | 0.0001 (−0.023, 0.023) | 0.011 (−0.024, 0.046) | 0.044 (0.025, 0.063) | 0.002 (−0.017, 0.020) | 0.042 (0.016, 0.069)** |
| Month 6 | 0.029 (0.003, 0.056) | −0.005 (−0.028, 0.018) | 0.034 (−0.001, 0.069) | 0.055 (0.036, 0.075) | 0.013 (−0.005, 0.032) | 0.042 (0.015, 0.069)** |
| **Change in EQ-5D-5L overall health score**[b] | | | | | | |
| Month 3 | 5.42 (2.64, 8.20) | 2.36 (−0.05, 4.78) | 3.14 (−0.53, 6.81) | 5.16 (3.11, 7.21) | 1.07 (−0.90, 3.03) | 4.10 (1.26, 6.94)** |
| Month 6 | 5.87 (3.09, 8.65) | −0.05 (−2.45, 2.34) | 5.93 (2.26, 9.59)** | 10.42 (8.36, 12.48) | 0.74 (−1.22, 2.70) | 9.68 (6.84, 12.53)*** |

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQoL 5 dimensions 5 level questionnaire.

Descriptive statistics are presented as adjusted least-square means or proportions with 95% CIs; between-group comparison: $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Analyses of the randomized population were adjusted for visits, visits × group, and study sites by a linear mixed-effects model for repeated measures (for continuous outcomes) or a logistic generalized linear mixed model for repeated measures (for dichotomous outcomes) with multiple imputation.

Analyses of the nonrandomized population were adjusted for visits, visits × group, study sites, age, baseline systolic blood pressure, baseline body mass index, duration of hypertension, use of antihypertensive drugs, Charlson comorbidity index, smoking, and drinking by a linear mixed-effects model for repeated measures (for continuous outcomes) or a logistic generalized linear mixed model for repeated measures (for dichotomous outcomes) with multiple imputation.

[a]Higher scores on the hypertensive symptom score (range: 0–72) indicate worse comorbidity or symptoms.

[b]Higher scores on the EQ-5D-5L index score (range: 0–1) and EQ-5D-5L overall health score (range: 0–100) indicate a better quality of life.

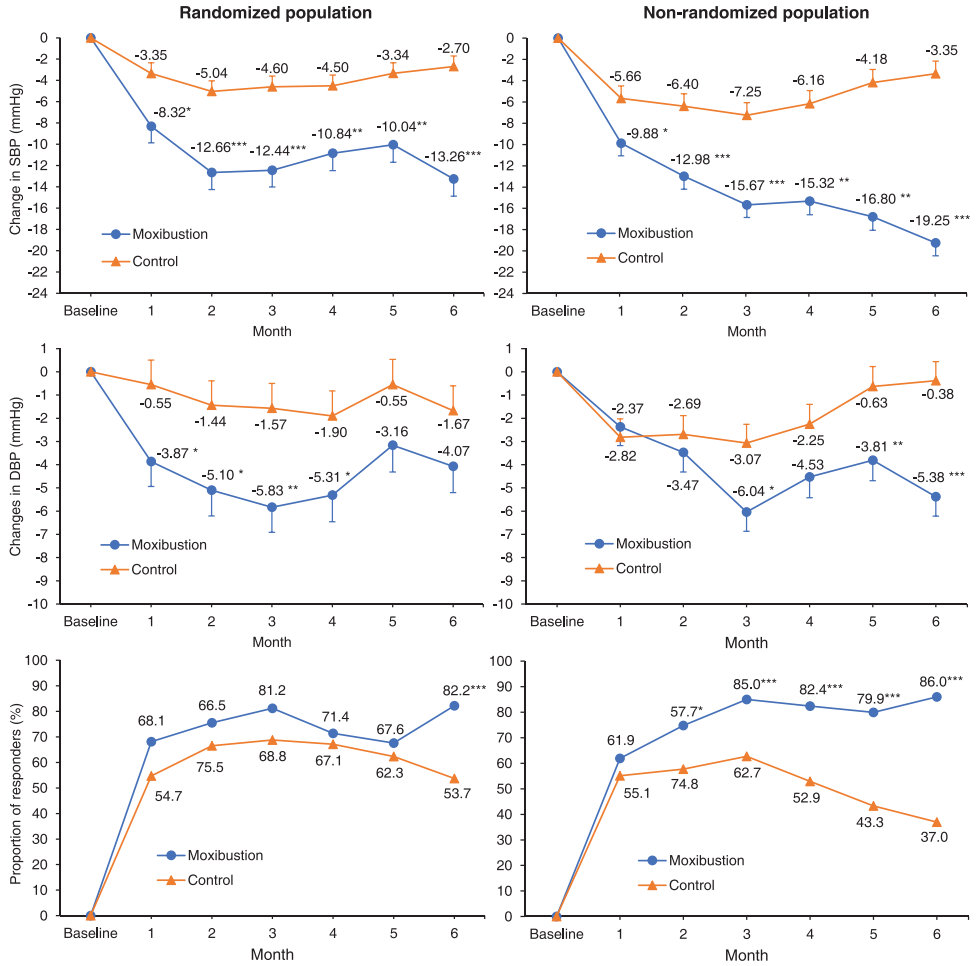


**FIGURE 2** Changes in blood pressure and proportions of responders over time. DBP, diastolic blood pressure; SBP, systolic blood pressure. Data are presented as adjusted least-square means and standard errors (error bars) The moxibustion group versus the control group: $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

[95% CI −17.14 to −3.76] in the multiple-drug subgroup). However, only in the CCB subgroup was the reduction in DBP in the moxibustion group significantly greater than that in the control group at month 6 (difference: −4.66 mmHg [95% CI −7.04 to −2.27]). Further details of the subgroup analysis can be found in Table S3.

## 3.4 | Cost effectiveness

Mean costs and QALYs by group at 3 and 6 months are shown in Table S4. The ICERs at month 6 were $155 and $399 per QALY in the randomized and nonrandomized populations, respectively.

## 3.5 | Compliance

In both randomized and nonrandomized populations, a significant proportion of patients (approximately 75% to 100%) in the moxibustion group successfully completed a minimum of 2 sessions of moxibustion per week during the six visits. On average, the two populations completed 3.8 and 4.2 sessions per week, respectively. The proportion of patients with poor compliance (<2 sessions/week) was higher in the randomized population than in the nonrandomized population. The mean dose of moxibustion per session was similar in both populations. During months 1–3, the voluntary randomized group showed better compliance to moxibustion than the mandatory randomized group, whereas during months 4 to 6, adherence was comparable between the two randomized groups (Table S5).

## 3.6 | Safety

During the trial, 29 adverse events were reported in the moxibustion group. Of these adverse events, 12 cases of burn blisters and eight cases of skin itching on the moxibustion area were considered definitely related to moxibustion use, and seven cases (two dizziness, one constipation, one eye swelling, one sore feet, one dry mouth, and one abdominal pain) were considered to be likely related to moxibustion use (Table S6). All adverse events were mild and transient, without withdrawals due to adverse events.

## 4 | DISCUSSION

Our RCT showed that adjuvant treatment with moxibustion significantly reduced SBP and increased the proportion of blood pressure responders who were in goals for both SBP and DBP but failed to reduce DBP and the antihypertensive drug dose at month 6. Moxibustion also helped improve hypertensive symptoms and QoL. Analysis of nonrandomized data validated all findings of the RCT, except for the inconsistency in DBP.

Elevated SBP is a major risk factor of coronary heart disease and cerebrovascular accidents[19]; its pathophysiology is mainly related to decreased vascular elasticity and compliance due to atherosclerosis and, secondarily, to water-sodium retention.[20,21] There is evidence that the stimulation of acupoints can reduce vascular inflammation by repairing vascular endothelial cells and water-sodium retention by improving renal hemodynamics[22,23]; therefore, we expected that moxibustion would have an SBP-lowering effect and selected SBP as the primary outcome. The effect direction of moxibustion on SBP in our RCT is consistent with the previous systematic review,[15] with a greater mean reduction in SBP in this study (−10.57 mmHg) than in the systematic review (−7.85 mmHg). Mechanistically, stimulation at acupoints with heat-sensitive sensation can better activate silent C nociceptors within the skin, which produces stronger effects than traditional suspended moxibustion, such as analgesia and regulation of the cardiovascular system.[24] Therefore, the greater SBP-lowering effect in our RCT may be due to the mechanistic advantage of the acupoint selection. Other possibilities for the difference in efficacy include the lack of rigorous randomization and appropriate data analysis in the RCTs included in the systematic review, as well as the different settings of moxibustion administration in communities and hospitals.

The finding that moxibustion is effective for SBP but not for DBP reductions is interesting. Physiologically, the increase in SBP is primarily associated with increased contraction force of the heart and small arteries caused by excitement of the sympathetic nervous system, while the increase in DBP is mainly associated with the increased peripheral vascular resistance caused by the overactivation of the renin-angiotensin-aldosterone system.[25,26] It has been found that the sedative and analgesic effects of moxibustion can significantly inhibit excitement in the sympathetic nervous system, but the regulatory effect of moxibustion on the renin-angiotensin-aldosterone system remains uncertain.[27] Therefore, we speculate that the differential therapeutic effects of moxibustion on SBP and DBP may be due to the differential regulatory capabilities of moxibustion on these two systems. On the other hand, the sensitivity analysis based on the randomized per-protocol set excluding patients with poor moxibustion compliance showed a significantly greater reduction in DBP in the moxibustion group than in the control group. Since a dose-effect relationship between moxibustion frequency and antihypertensive effects has been reported,[28] it is possible that the negative effect on DBP may be due to the lower moxibustion frequency in the randomized moxibustion group. The analysis of the nonrandomized population with overall better moxibustion compliance, which showed a significantly greater DBP reduction in the moxibustion group at month 6, validates this interpretation. Considering this uncertainty, the effects of moxibustion on DBP need to be further verified.

We conducted subgroup analysis on different background antihypertensive regimens for SBP and DBP. Since our study did not have a stratified randomization by background antihypertensive drugs, there may have been imbalances in baseline characteristics between the moxibustion and control groups within the antihypertensive regimen subgroups in the randomized population.[29] In addition, in some subgroups (e.g., the no-drug and multiple-drug subgroups) of the randomized population, small sample sizes may result in insufficient statistical power. Therefore, we used a merged sample of both randomized and nonrandomized populations for the subgroup analysis. Our results indicated that moxibustion led to a significant reduction in SBP at month 6 in all subgroups of background antihypertensive regimens, including the no-drug subgroup. However, a significant reduction in DBP with moxibustion was observed only in the CCB subgroup, suggesting that moxibustion may have a direct effect on reducing SBP independent of antihypertensive drugs, while its effect on reducing DBP may be achieved by enhancing the effect of CCBs. It is important to note that since this was a post hoc subgroup analysis, the findings should be considered exploratory and require validation through future evidence.

The safety of self-administered moxibustion is of concern since it involves combustion and smoke. A total of 20 adverse events that were definitely associated with moxibustion occurred in our study, including 12 cases of burn blisters and 8 cases of skin itching. During the 6-month period, the patients performed more than 4000 sessions of moxibustion, with an adverse event incidence of approximately 0.5 cases per 100 sessions. Given that all moxibustion-related or potentially related adverse events were remitted with simple or no specific treatment and did not result in withdrawals, we conclude that self-administered moxibustion is generally safe. The cause of all burn blisters and most skin itching was that patients removed the flannel bag wrapped around the moxibustion jar when they felt insufficient heat. Therefore, patient training should strongly emphasize proper moxibustion manipulation and appropriate temperature control.

Compliance and costs are also pivotal factors in popularizing moxibustion. Encouragingly, our findings indicate that three-quarters of the patients in the randomized moxibustion group underwent at least two sessions of moxibustion each month, and this figure exceeded 95% in the nonrandomized population. Overall, a desirable every-other-day frequency of moxibustion was achieved. However, a clear trend was that patient compliance decreased over time, so how to encourage long-term adherence to moxibustion is worth considering. In addition, patients who were mandatorily randomized had poorer compliance with moxibustion than those who were voluntarily randomized, suggesting the need for additional measures to improve patient compliance in explanatory RCTs of self-administered moxibustion. With regard to economic evaluation, the mean cost increase for moxibustion during the 6-month period was only $80.9 in the randomized population, and the ICER based on health-related QoL was much lower than the per capita gross domestic product in China, indicating that self-administered moxibustion can improve the overall health of

hypertension patients at a low cost and is worthy of community-level generalization.

This study has several limitations. First, it was not possible to blind patients or utilize a placebo (i.e., sham moxibustion) in the control group, which may have led to an overestimation of the efficacy of moxibustion due to the placebo effect. However, the placebo effect can also be considered part of the effectiveness in a pragmatic RCT.[30] Second, the acupoints we selected were relatively fixed, so the results only represent the treatment effects of moxibustion on these acupoints and cannot be extrapolated to other acupoints. Third, limited by funding, we were unable to measure blood pressure more accurately using 24-hour ambulatory blood pressure monitoring, and errors in instantaneous blood pressure measurements may reduce the accuracy of the efficacy evaluation. Fourth, due to limited funding and manpower, we were unable to monitor patients' lifestyle changes, such as adherence to a low-salt diet and increased physical activity, throughout the trial process. However, it is worth mentioning that the assessed baseline characteristics were well balanced between the moxibustion group and the control group among the randomized population, indicating that the randomization process was thorough and effective. Therefore, we speculate that the lifestyle factors between the two groups should also be balanced in the randomized population, minimizing any significant impact on the results.

## 5 | CONCLUSIONS

Evidence from a pragmatic RCT with randomized and nonrandomized arms suggests that self-administered moxibustion is generally safe and can reduce SBP and improve hypertensive symptoms and QoL in community hypertension patients, although its effect on DBP remains uncertain. Considering the good compliance and low cost of long-term dosing, heat-sensitive moxibustion may be considered an adjunctive treatment technique for the management of hypertension in community primary care.

### AUTHOR CONTRIBUTIONS

Xu Zhou designed the study and drafted the manuscript. Qiuyun Xue, Jianyu You, and Shuqing Li were involved in the investigation and revised the manuscript; Ling Li and Weifeng Zhu provided critical methodological advice, performed data analysis, and revised the manuscript; Yong Fu and Xin Sun conceived and designed the study, reviewed the manuscript, and acts as the guarantors. All authors have read and approved the final version of the manuscript.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### PATIENT CONSENT STATEMENT

Individual person's data contained in the article were consent for publication from those people.

### CLINICAL TRIAL REGISTRATION

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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