



Original Article

Acupuncture or cupping plus standard care versus standard care in moderate to severe COVID-19 patients: An assessor-blinded, randomized, controlled trial



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ABSTRACT

Background: Non-pharmacological strategies that have been proposed by complementary medical systems, can be effective in management of COVID-19.

Methods: This study was designed as a three-arm, assessor-blinded, randomized controlled trial. A total of 139 hospitalized COVID-19 patients were randomly assigned into three groups: (1) acupuncture (ACUG), (2) cupping (CUPG), and (3) control (CTRG). All participants received conventional treatment. The primary study endpoint included changes in respiratory signs including oxygen saturation (SpO₂) and respiratory rate (RR). The secondary endpoints were COVID-19-related hospitalization duration and serious adverse events such as intensive care unit (ICU) admission, intubation or death, all up to day 30. Also, improvements in cough, dyspnea, chest tightness, oxygen demand, anorexia, headache, weakness, sore throat, and myalgia were evaluated.

Results: Forty-two patients in ACUG, 44 patients in CUPG, and 42 patients in CTRG completed the trial. After 3 days, SpO₂ and RR improved significantly in CUPG and ACUG compared with CTRG (effect size: 8.49 (6.4 to 10.57) and 8.51 (6.67 to 10.34), respectively: $p < 0.001$). Compared with CTRG, patients in CUPG and ACUG recovered faster (mean difference: 6.58 (4.8 to 8.35) and 9.16 (7.16 to 11.15), respectively) and except for two patients in ACUG who were admitted to ICU, none of patients in ACUG or CUPG needed ICU or intubation ($p < 0.001$ in comparison to CTRG). Amelioration of clinical COVID-19 related symptoms reached a high level of statistical significance in CUPG and ACUG in comparison with CTRG ($p < 0.01$).

Conclusion: Cupping and acupuncture are promising safe and effective therapies in management of COVID-19. Trial registration: This study was registered at Iranian Registry of Clinical Trials: IRCT20201127049504N1 (<https://en.irct.ir/trial/52621>).

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus disease 2019 (COVID-19), has spread

rapidly throughout the world since December 2019. The associated burden on health-care systems, especially intensive care units (ICU), has been overwhelming in several affected countries¹. At present, no treatment options with strong evidence of clinical benefit exist. Thus, national and international guidelines recommend using experimental drugs as part of investigational trials². There is a high demand and urgent global need for effective, safe and inexpensive treatment options for patients with moderate to severe

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COVID-19, especially in low- and middle-income countries (LMICs) with high disease burden and scarce resources³.

Patients with moderate-to-severe COVID-19 often suffer from breathlessness, dry cough and chest tightness that may progress to acute respiratory distress syndrome (ARDS) and septic shock. This is the result of a virus-induced cytokine storm, an overly aggressive immune response in the body⁴. Thus, any drug or medical manipulation that improves the body's ability to cope with the cytokine storm and modulate the immune system, can be beneficial. Many published reports have shown that Complementary and Alternative Medicine (CAM) can efficaciously help in the management of acute and critical illnesses, including infectious disease outbreaks⁵.

Once conventional medicine failed to deliver highly effective and approved treatment in past epidemic diseases including the Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and H1N1 influenza, CAM was used in combination with routine treatment to attain synergistic effects⁶⁻⁸. As a CAM modality against COVID-19, "China's model" has been fully confirmed as successful according to the World Health Organization (WHO) reports. The report of WHO-China Joint Mission published on February 2020, specifically points out the highly effective role of non-pharmaceutical measures such as acupuncture, moxibustion and cupping in management of COVID-19⁹.

According to research reports, cupping contributes to activation of the complement system, as well as modulation of the cellular component of immunity. It reduces peripheral and local P-substance and inflammation significantly, and regulates the immune system. As an immunomodulator, cupping can significantly increase levels of immune products such as interferon and tumor necrotizing factor¹⁰. According to Persian Medicine (PM) resources such as "Exir-e Azam" and "Al-Havi", warm cupping of the posterior thorax, can play an important role in treatment of acute respiratory diseases¹¹⁻¹³.

Likewise, acupuncture is an effective adjunctive non-pharmacological treatment, with a wealth of experience in the prevention and control of epidemic diseases since ancient times. Having been used for various acute infectious diseases in the modern times, the efficacy of this CAM modality has been clearly and reliably reported¹⁴. Acupuncture decreases expression of the pro-inflammatory proteins such as tumor necrosis factor alpha (TNF- α) and interleukin (IL)-6 and increases cytotoxicity of leukocytes and serum IL-10 level. It can also reduce pulmonary inflammation and alleviate airway inflammation^{15,16}. It seems that cupping and acupuncture improve the body's ability to cope with a cytokine storm, a process that has been found to lead to lung inflammation, pneumonia and death in COVID-19.

Global randomized controlled trials of CAM manual therapies in hospitalized COVID-19 patients have shown conflicting results but reported potential 1) decrease in the number of severe cases and the intensive care burden; 2) increase in cure rate, and improvement in hospital discharge rate⁹. The COVID Iran Acupuncture and Cupping (COIRACCU) trial is, to our knowledge, the first randomized controlled trial of non-pharmacological treatment in COVID-19 performed entirely in an LMIC. For the first time, we evaluated the effectiveness of acupuncture -as a pure Traditional Chinese Medicine (TCM) method- versus warm cupping -as a PM method- to prevent progression of COVID-19, decrease symptom duration and improve respiratory signs including oxygen saturation (SpO₂) and respiratory rate (RR) among hospitalized patients with moderate-to-severe SARS-CoV-2 infection.

2. Methods

The protocol of this study was registered at the Iranian Registry of Clinical Trials (IRCT) (identifier: IRCT20201127049504N1, <https://en.irct.ir/trial/52621>). This study is reported according to

the CONSORT checklist of information when reporting a randomized trial assessing non-pharmacological treatments.

2.1. Trial design

COIRACCU was a randomized, three-arm trial, with blinded outcome assessment and 1:1:1 randomization to acupuncture, warm cupping and control groups. This study investigated the clinical outcomes of acupuncture or warm cupping plus standard care versus standard care alone in hospitalized COVID-19 patients with moderate-to-severe symptoms.

2.2. Participants

After approval by the Tehran University of Medical Science ethics committee (IR.TUMS.MEDICINE.REC.1399.1124) and receiving a trial registration code from IRCT, the study was conducted in the Department of infection diseases, Shohadaye Pakdasht Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran and Shahid Ziaiean Hospital, Tehran University of Medical Sciences, Tehran, Iran. Eligible patients included 18-75 year old men and non-pregnant women admitted to hospital with moderate-to-severe SARS-CoV-2 infection - defined according to the Iranian clinical management protocol for COVID-19 ninth version, December 2020¹⁷. This guideline defines moderate disease as RR 15-24 per minute and SpO₂ 90-93%; and severe disease as RR \geq 24 per minute or SpO₂ <90% in ambient air. Other inclusion criteria comprised chest CT-scan with COVID-19 pattern. Patients with respiratory failure who required mechanical ventilation, pregnant or lactating women, and also patients with a positive history of allergies or any skin lesions in the area of manipulation were excluded. Patients with a diagnosis of pulmonary embolism and serious underlying diseases, such as coronary heart disease, chronic obstructive pulmonary disease, obstructive pulmonary disease, meningitis, encephalitis, or cirrhosis were not included. Laboratory exclusion criteria comprised platelet counts of less than 50000 cells per μ L, and alanine aminotransferase or aspartate aminotransferase concentrations more than ten times upper normal limits within 24 h of screening or baseline.

All patients or their legally acceptable representatives provided written informed consent to participate in the study. The study was conducted in accordance with Iran regulatory requirements. The protocol and any amendments were approved by the Tehran University of Medical Sciences research and ethics committee at each study site in accordance with Iran regulations.

2.3. Randomization

A researcher explained the details of the trial and provided participants with informed consent forms to sign and complete. After applying the inclusion and exclusion criteria, eligible participants were randomly assigned in a 1:1:1 ratio to three groups using block randomization. The randomization sequence was generated using Random Allocation Software (RAS), version 9.4 by a researcher who was not in direct contact with patients and not involved in statistical analysis. Patients were divided into three intervention groups as A: acupuncture group (ACUG); B: cupping group (CUPG); and C: control group (CTRG). To perform random allocation, 23 blocks of 6 (AABBCC, AACBCB, etc.) were prepared and placed in envelopes. In order of entry and hospitalization (the time recorded in patient files), one envelope was randomly selected and based on the obtained block, six patients were assigned to three groups. If the number of patients to be randomized was more than 6, it was necessary to open more than one envelope.

This study was assessor-blinded. Participants and researchers performing the procedures were not blind, but the researcher who

completed the questionnaire and evaluated outcomes and the analyst were unaware of the grouping. Intervention groups were available to the outcome assessor as A, B, and C and the analyst had access to data as groups A, B and C.

2.4. Interventions

All patients in both intervention and control groups received conventional treatment based on the Iranian clinical management protocol for COVID-19, ninth version¹⁷. Participants in intervention group were allocated to either cupping therapy or acupuncture.

In the cupping group, we combined TCM and PM techniques of cupping in respiratory and infective diseases. The primary method included retained warm cupping on Urinary Bladder-13 (BL13) acupoint (on the back, 1.5 cun lateral to the lower border of the spinous process of the third thoracic vertebra) for one minute. This was supplemented with sliding (moving) cupping of paraspinal (1.5 cun lateral to the spinous process of thoracic vertebrae) and lung regions at least 1.5 cun lateral to the spinous process of thoracic vertebrae for five minutes. Patients were in sitting or lateral decubitus position. The procedure was performed three times a day for 3-7 consecutive days (based on patient hospitalization, from the first day of hospitalization to the maximum of the seventh day of hospitalization), with a medium glass (5 cm mouth diameter and 8 cm height), and a suction amount of 10 to 15 mm.

Cups had the texture of a transparent glass. Moving cupping involves standardized manipulations in PM¹⁰. First of all, vaseline is applied to the posterior thorax as a lubricant with no therapeutic effect. Using the flashing method, a 95% ethanol-soaked cotton ball is held with tweezers and the cup is held upside-down. After the cotton ball is ignited, it is immediately moved into the cup and removed; the cup is then quickly placed on the skin of apex of lungs, and the created vacuum causes the skin to be drawn into the cup. Then, the cup is held in one hand and pulled and pushed from the apex toward the base of the lungs and back while applying light force, such that the skin of the treatment area turns purple. Even force is applied when moving the cup to prevent falling off due to air leakage. This is repeated on the posterior thorax for five minutes.

In the acupuncture group, standard needling method (without electrical stimulation and by using disposable tube needles) was performed with 0.25 mm × 40 mm, single-use, sterile, stainless-steel needles. Selected acupoints included: Governor Vessel-20 (GV20; Baihui), Lung-5 (LU5; Chize), Lung-7 (LU7; Lieque), Large Intestine-4 (LI4; Hegu), Liver-3 (LR3; Taichong), Liver-14 (LR14; Qimen), Conception Vessel-12 (CV12; Zhongwan), Conception Vessel-17 (CV17; Tanzhong) and Stomach-36 (ST36; Zusanli). Patients were in recumbent position. Hand sanitizer was used for hand hygiene. Each acupoint was sterilized strictly according to the requirements of disinfection and protection in the negative-pressure ward. After disinfection, the cotton balls were disposed of into the infectious contaminant bucket in the inpatient ward buffer area.

The needles were inserted perpendicularly, at a 90 degree angle with the skin, 20-25 mm in depth at LR3, LI4, ST36 and LU5. At GV20, LU7, CV12, CV17 and LR14 the needle was inserted obliquely, at a 15-30 degree angle, with the needle tip toward the elbow at LU7 and toward the distal point at other points, 5 to 10 mm in depth. The acupoints, except GV20, were stimulated and manipulated after 10 minutes with even manipulating technique for 10 seconds. Needle manipulation was accomplished by means of a twirling, and up and down movement. Needles were retained for 20 minutes each session, and were then disposed of in the sharp instrument box in the inpatient ward buffer area. The acupuncture therapy was given once daily, for 3-7 days consecutively (based on patient hospitalization, from the first day of hospitalization to a maximum of the seventh day of hospitalization).

Interventions of this study were performed by one acupuncturist and two physicians performing cupping. The acupuncturist had more than two years of treatment experience, and the cupping physicians had more than eight years of cupping experience.

2.5. Outcomes

The primary endpoint was changes in respiratory signs (SpO₂ percentage and RR). Secondary endpoints were COVID-19-related hospitalization duration and serious adverse events (SAEs) such as ICU admission, intubation or death, all up to day 30. Further secondary clinical outcomes included severity scores of respiratory symptoms, defined by cough, shortness of breath or dyspnea, unusual chest pain or chest tightness, and type of oxygen therapy, based on the National Institute of Health (NIH) endorsed Protocol to research Patient Experience of COVID-19, modified Medical Research Council (mMRC) Dyspnea Scale and Respiratory Symptoms Scale^{18,19}. Moreover, severity of anorexia, headache, weakness, sore throat, and myalgia were recorded. Study evaluations were through intervention days (3-7 days) based on hospitalization duration. Symptom scores were self-reported by participants every day after cupping therapy or acupuncture on an ordinal scale: 0 = not affected, 1 = minimally affected, 2 = affected and 3 = severely affected, and the type of oxygen therapy was determined: 0 = not needed, 1 = nasal cannula, 2 = simple face mask, 3 = mask with reservoir and 4 = continuous positive airway pressure and non-invasive ventilation (CPAP/NIV) mask. We also checked SpO₂ just before and five minutes after interventions. Additionally, SpO₂ was recorded four hours after acupuncture and also the last cupping session each day. We collected longitudinal outcomes in the control group at the same time as intervention groups. Outcomes were evaluated at three time points: beginning of the study, day 3 and day 7 of intervention.

2.6. Statistical analysis

At the time of design and registration of the proposal, no study had been conducted to investigate the effect of cupping and acupuncture on COVID-19. Therefore, using Power Analysis and Sample Size 11 (PASS-11) software, a sample size of 30 patients in each arm and a total of 90 participants was calculated in order to achieve 90% power ($\alpha=0.05$). As decided by the epidemiologist consultant, an Interim Analysis was performed during the study, to adjust sample size based on calculated power.

After data collection, all patients who completed the interventions were included in statistical analysis, which was performed using IBM SPSS version 22 and MedCalc software. Data is presented as mean with standard deviation (SD) and confidence interval (CI) for quantitative variables and frequency with percentage for qualitative ones. In case of normal distribution, one-way ANOVA with Bonferroni as post-hoc. For non-normally distributed data, Friedman test and Kruskal-Wallis test were utilized. To compare the frequency distribution between groups, χ^2 or Fisher's exact test were used.

3. Results

3.1. Patients

Initially, 90 COVID-19 patients were planned to be included. However, the power analysis performed during the study revealed low power, and thus, sample size was increased according to the consult of the epidemiologist. Finally, out of the 307 patients assessed for eligibility, 139 underwent randomization and were assigned to the groups between February 15 and May 15, 2021.

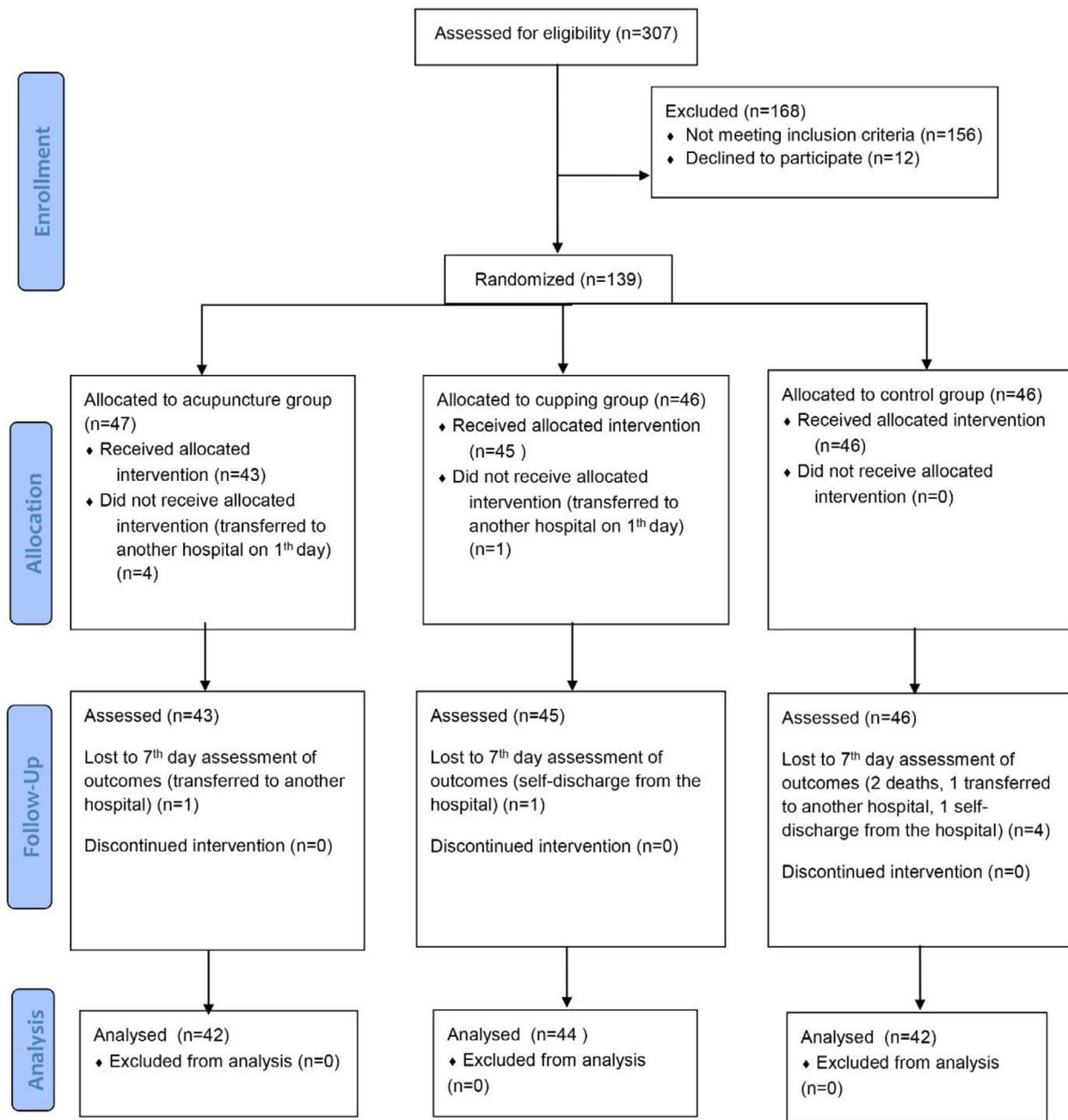


Fig. 1. Consort flow diagram of the patient selection process.

Forty-three patients received acupuncture plus standard care, 45 patients received cupping plus standard care, and 46 patients received only standard care (as CTRG). Patients who were transferred to another hospital and lost to follow-up were excluded. Overall, 42 patients (89.36%) in the ACUG, 44 patients (95.65%) in the CUPG, and 42 patients (91.30%) in the CTRG completed the trial. Fig. 1 represents the patient selection process according to Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

The mean age of ACUG, CUPG, and CTRG were 52.74 ± 12.72 , 54.68 ± 13.79 , and 57.90 ± 12.15 years, respectively ($p=0.187$). Seventeen patients in ACUG (40.47%), 16 patients in CUPG (36.36%), and 14 patients in CTRG (33.33%) were male ($p=0.793$). There was no significant difference between ACUG, CUPG, and CTRG in terms of underlying disease, radiologic lung involvement, or laboratory data ($p>0.05$) (Table 1 and Table S1).

3.2. Primary outcome (ACUG and CUPG vs. CTRG)

The improvement in primary outcome is shown in Table 2 and Fig. 2. Between-group analysis of RR showed no significant difference at the beginning of the study between CTRG and ACUG or CUPG, as well as SpO₂ between CTRG and ACUG; however, the level of SpO₂ in CTRG was significantly higher in comparison with CUPG ($p=0.013$). The SpO₂ progression in ACUG and CUPG substantially increased after 3 days of intervention and lasted up to day 7 (mean change, 10% and 11%, respectively) ($p<0.001$); however, there was no significant difference even after day 7 in CTRG. No significant difference was reported between ACUG and CUPG ($p>0.05$). While RR did not change remarkably in CTRG within 3 days, it decreased significantly in CUPG and ACUG after 3 days ($p<0.001$). Although within group analysis showed significant

Table 1
Baseline characteristics of randomized participants.

Characteristic		Group			P value
		Acupuncture	Control	Cupping	
Age (years) (Mean ± SD)		52.74±12.72	57.90±12.15	54.68±13.79	0.187 [†]
Sex	Male	17 (40.47)	14 (33.33)	16 (36.36)	0.793*
	Female	25 (59.53)	28 (66.67)	28 (63.64)	
Patients with coexisting disorders	Diabetes mellitus	13 (30.95)	15 (35.71)	10 (22.72)	0.410*
	Hypertension	15 (35.71)	17 (40.47)	12 (27.27)	0.425*
	Hypothyroid	5 (11.90)	1 (2.38)	2 (4.54)	0.167*
N (%)	Anemia	2 (4.76)	0 (0.0)	3 (6.81)	0.249*
	Asthma	0 (0.0)	0 (0.0)	0 (0.0)	-
	Cancer	0 (0.0)	0 (0.0)	0 (0.0)	-
	Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	-
	Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	-
	Duration of symptoms before admission ¹ (days) (Mean ± SD)	5.29±3.71	7.02±3.50	7.26±3.64	0.026 [†]
Computed tomography (CT) scan findings	Mild	18 (31.0)	22 (37.9)	18 (31.0)	0.524*
	Moderate	16 (32.7)	17 (34.7)	16 (32.7)	0.926*
	Severe	4 (28.6)	4 (28.6)	6 (42.9)	0.778*
	Non typical COVID-19	3 (34.9)	1 (14.3)	3 (42.9)	0.561*

*Chi-Square Tests; [†]ANOVA test; 1: data is represented by mean ± standard deviation or frequency (percentage).

Table 2
Statistical analysis of primary outcomes¹.

Symptom	Time	Group			Mean difference		
		Acupuncture	Control	Cupping	Δ1	Δ2	Δ3
Oxygen saturation (%)	Before intervention	86.2±2.90 ^{a,b}	87.83±2.72 ^a	85.19±4.75 ^b	1.63 (0.40 to 2.85)	2.64 (0.96 to 4.31)**	-1.01 (-2.7 to 0.68)
	Day 3	93.12±5.36 ^a	87.5±4.42 ^b	94.02±3.88 ^a	-5.62 (-7.75 to -3.48)***	-6.52 (-8.30 to -4.73)***	0.9 (-1.09 to 2.89)
	Day 7	96.2±2.84 ^a	87.61±6.47 ^b	96.72±1.40 ^a	-8.59 (-10.75 to -6.42)***	-9.11 (-11.09 to -7.12)***	0.52 (-0.43 to 1.47)
	P value (within groups)	<0.001	0.194	<0.001			
Respiratory rate (per minute)	Before intervention	22.44±4.88 ^a	24.64±6.06 ^{a,b}	26.79±6.99 ^b	2.2 (-0.18 to 4.58)	-2.15 (-4.96 to 0.66)	4.35 (1.75 to 6.94)**
	Day 3	16.32±4.53 ^a	24.81±5.83 ^b	21.35±4.87 ^c	8.49 (6.22 to 10.75)***	3.46 (1.16 to 5.75)**	5.03 (3.01 to 7.04)***
	Day 7	13.32±3.15 ^a	21.81±6.01 ^b	13.3±1.22 ^a	8.49 (6.4 to 10.57)	8.51 (6.67 to 10.34)***	-0.02 (-1.03 to 0.99)
	P value (within groups)	<0.001	0.007	<0.001			

¹ Data is represented by mean ± standard deviation for groups and mean (95% confidence interval) for mean difference; different letters (a-c) show significant statistical difference between groups and significance levels are represented as Δ1: acupuncture compared to control; Δ2: cupping compared to control; Δ3: acupuncture compared to cupping; * P<0.05, ** P<0.01, or *** P<0.001.

reduction in RR in all groups after 7 days, (mean change: CTRG: 11.4%, ACUG: 40.64%, and CUPG: 50.41%), mean difference of RR in ACUG and CUPG were significantly higher than CTRG (p<0.001).

3.3. Secondary outcomes (ACUG and CUPG vs. CTRG)

Patients who received acupuncture plus standard care recovered a mean of 6 days faster than CTRG (mean difference: 6.16, CI: 4.16 to 8.15) (p<0.001). The fastest recovery time belonged to patients who received cupping plus standard care (mean: 3.82±1.45 days). Throughout the intervention period, COVID-19-related SAEs were significantly lower in ACUG and CUPG in comparison with CTRG: intubations and deaths were reported in 19% of CTRG (8 patients), but neither in ACUG (relative risk: 0.05), nor in CUPG (relative risk: 0.05). None of the patients in the CUPG (relative risk: 0.03), two patients in ACUG (4.8%; relative risk: 0.15), and 13 patients in CTRG (31%) received ICU care (p<0.001).

Among key secondary outcomes, dyspnea, type of oxygen therapy, and cough did not differ between groups at the beginning of the study, but mean score of chest tightness was higher in ACUG.

Within-group analysis showed that severity score of dyspnea, type of oxygen therapy, chest tightness, dry cough, and wet cough declined significantly among all three intervention groups (p<0.01), except wet cough in CTRG patients (p=0.472) after 7 days; however, between-group analysis demonstrated that after 3 days of intervention, reduction of the severity score of all symptoms was statistically greater in both ACUG and CUPG in comparison with CTRG (dyspnea: p<0.001, type of oxygen therapy: p<0.001, chest tightness: p<0.001, dry cough: p<0.001, and sputum: p=0.002), and this significant difference remained up to day 7. The mean score of other secondary outcomes - including sore throat, myalgia and headache - did not vary between groups at the beginning of the study, except weakness (compared to ACUG, p=0.01, and CUPG, p=0.014) and anorexia (compared to ACUG, p=0.009) that were higher in CTRG. After 3 days of intervention, within-group analysis showed significant reduction in severity score of weakness, sore throat, myalgia, anorexia, and headache in all three intervention groups (p<0.01) - except sore throat in CTRG (p=0.135) - and this significant difference remained up to day 7 of intervention. Between-group analysis showed greater symptom severity change

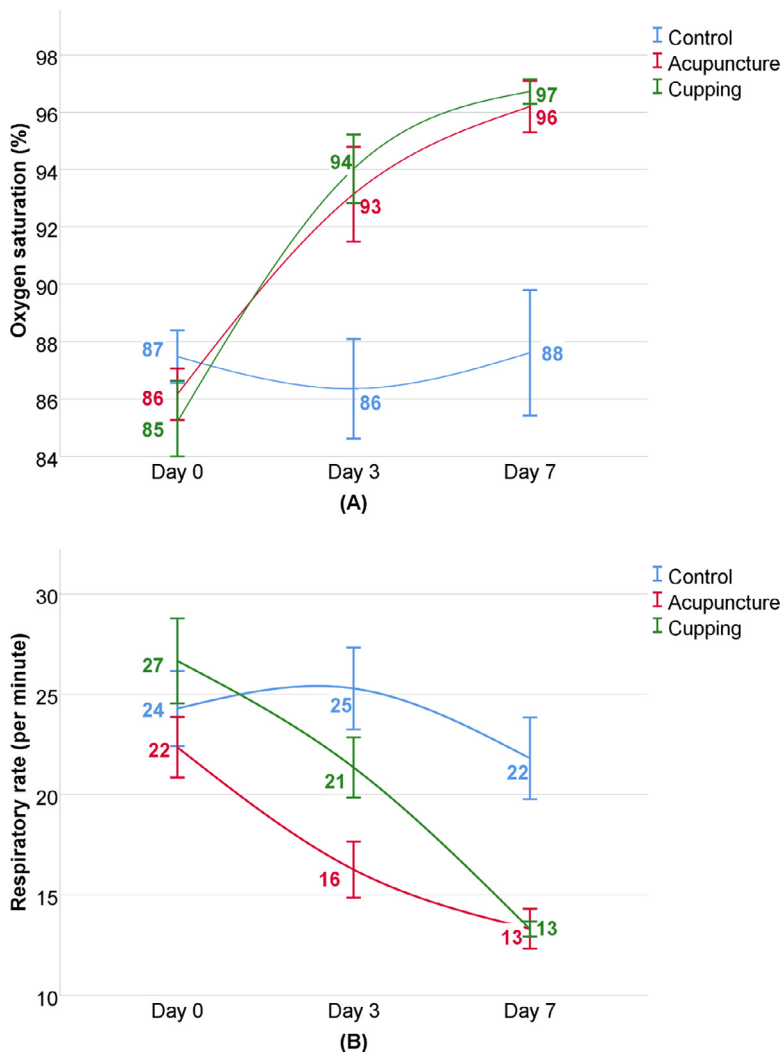


Fig. 2. Progression of primary outcomes: (A) Oxygen saturation (%), (B) Respiratory rate (per minute).

in ACUG and CUPG compared with CTRG in all symptoms (weakness: $p < 0.001$, sore throat: $p < 0.001$, myalgia: $p < 0.001$, anorexia: $p < 0.001$, and headache: $p = 0.004$) (Table 3, Fig. 3).

3.4. Primary and secondary outcomes (ACUG vs. CUPG)

The mean difference of SpO₂ (mean: 0.52, CI: -0.43 to 1.47, $p = 0.416$) and RR (mean: -0.02, CI: -1.03 to 0.99, $P = 0.976$) were not significant between ACUG and CUPG after 7 days. Moreover, statistical analysis showed no significant difference between ACUG and CUPG in means of secondary outcomes including dyspnea (mean: -0.1, CI: 0.28 to 0.08, $p = 0.835$), type of oxygen therapy (mean: -0.13, CI: -0.37 to 0.11, $p = 0.481$), chest tightness (mean: 0.02, CI: -0.02 to 0.06, $p = 0.853$), dry cough (mean: -0.08, CI: -0.23 to 0.07, $p = 0.539$), sputum (mean: 0.03, CI: -0.05 to 0.11, $p = 0.788$), weakness (mean: 0, CI: 0, $p > 0.05$), sore throat (mean: 0, CI: 0, $p > 0.05$), myalgia (mean: 0, CI: 0, $p > 0.05$), anorexia (mean: 0.05, CI: -0.01 to 0.11, $p = 0.661$), and headache (mean: 0.02, CI: -0.02 to 0.06, $p = 0.695$). Although no patient in ACUG or CTRG underwent intubation or died, two patients in ACUG but no patient in CUPG were admitted to ICU (relative risk: 5.23, CI: 0.25 to 105.89, $p = 0.241$).

In CUPG, 91% of the participants experienced the side effect of ecchymosis. Although some patients expressed concern, this ecchymosis was completely resolved after 3-5 days. In ACUG, 47% of the patients reported mild focal numbness or tingling. No important harms or unintended effects were reported.

4. Discussion

This clinical research confirmed that the two non-pharmaceutical therapies including warm cupping and acupuncture provide opportunities to improve respiratory signs (SpO₂ and RR), reduce hospitalization duration and SAEs, and also alleviate symptoms in COVID-19 patients.

As a major component of TCM, acupuncture has a wealth of experience in prevention and treatment of acute respiratory infectious diseases. Its efficacy in control of epidemic disease and relieving respiratory symptoms has been clearly reported^{14,20}. Since the outbreak of COVID-19 in China, acupuncture has played a significant role in management of COVID-19-related respiratory symptoms as an adjuvant treatment and many researchers have published guidelines on its potential benefits²⁰.

From the TCM point of view, pathogenesis of COVID-19 involves blood stasis, heat, dampness, toxicity, and Qi stagnation – Qi is commonly explained as life energy, one of the functions of which is very close to the function of immune system²¹. COVID-19 is divided into different stages consisting of cold-damp with accumulation of heat, damp-toxin, and Qi stagnation²². Acupoints used in this study were proposed according to a specific differential diagnosis based on our previous study: GV20 decreases liver-Yang (heat symptoms); LU5 reduces lung heat and phlegm (inflammation in lungs); LU7 expels wind and raises Qi up to the head; LI4 expels wind, removes coldness, helps in first stages of upper respi-

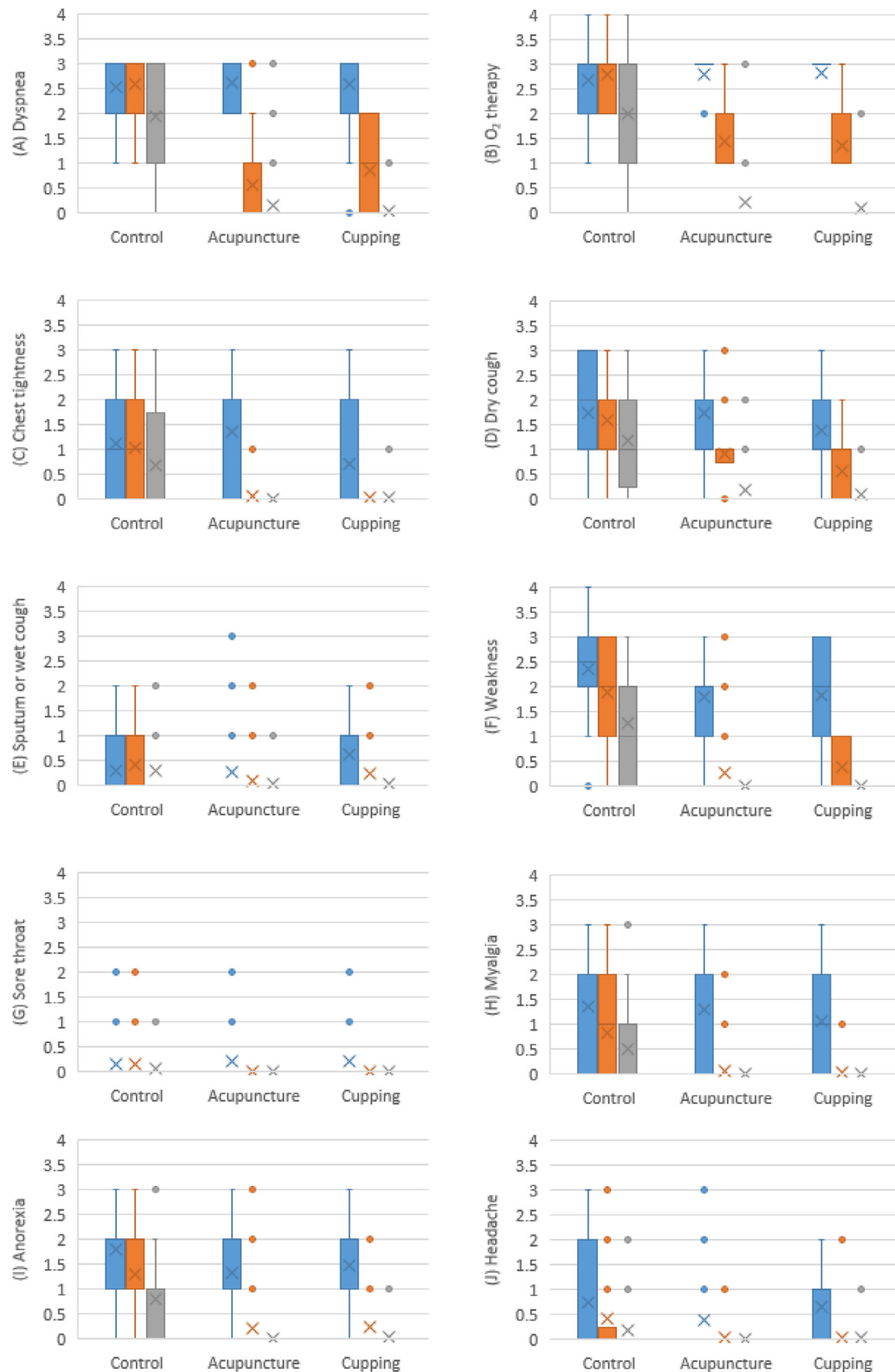


Fig. 3. Progression of secondary outcomes: (A) Dyspnea, (B) Type of oxygen therapy, (C) Chest tightness, (D) Dry cough, (E) Sputum or wet cough, (F) Weakness, (G) Sore throat, (H) Myalgia, (I) Anorexia, and (J) Headache. For each group, the first column (blue) is day 0, the second column (orange) is day 3, and the third column (gray) is day 7. The cross sign and circle sign are representative for mean score and outlier points, respectively. Numbers are mean score in each time: severity score of symptoms is described as: 0=not affected; 1= minimally-affected; 2=affected; and 3=severely-affected. Severity score of oxygen therapy is described as: 0 = not needed; 1= nasal cannula; 2= simple face mask; 3= mask with reservoir; and 4= continuous positive airway pressure and non-invasive ventilation (CPAP/NIV) Mask.

Table 3
Statistical analysis of secondary outcomes¹.

Secondary outcomes	Time	Group			Mean difference		
		Acupuncture	Control	Cupping	Δ1	Δ2	Δ3
Hospitalization duration	-	4.24±3.02 ^a	10.4±5.75 ^b	3.82±1.45 ^a	6.16 (4.16 to 8.15)***	6.58 (4.8 to 8.35)***	-0.42 (-1.42 to 0.58)
ICU admission	up to day 30	2 (4.8) ^a	13 (31) ^b	0 (0) ^a	RR: 0.15 (0.03 to 0.64) ** ARR: 3.81 (2.4 B to 9.26 B)	RR:0.03 (0 to 0.57) * ARR: 3.3 (2.26 B to 6.11 B)	RR: 5.23 (0.25 to 105.89) ARR: 21.26 (8.18 H to 35.48 B)
Intubation	up to day 30	0 (0) ^a	8 (19) ^b	0 (0) ^a	RR: 0.05 (0 to .098)* ARR: 5.37 (3.23 B to 15.93 B)	RR: 0.05 (0 to 0.94) * ARR: 5.36 (3.25 B to 15.13 B)	RR: 1.04 (0.02 to 51.57) ARR: 1935 (22.31 H to 22.83 B)
Death	up to day 30	0 (0) ^a	8 (19) ^b	0 (0) ^a	RR: 0.05 (0 to 0.98)* ARR: 5.37 (3.23 B to 15.93 B)	RR: 0.05 (0 to 0.94) * ARR: 5.36 (3.25 B to 15.13 B)	RR: 1.04 (0.02 to 51.57) ARR: 1935 (22.31 H to 22.83 B)
Dyspnea or ² breathlessness	Before intervention	2.62±0.49 ^a	2.52±0.71 ^a	2.59±0.66 ^a	-0.1 (-0.36 to 0.16)	-0.07 (-0.36 to 0.22)	-0.03 (-0.28 to 0.22)
	Day 3	0.57±0.86 ^a	2.6±0.66 ^b	0.86±0.86 ^a	2.03 (1.69 to 2.36)***	1.74 (1.41 to 2.06)***	0.29 (-0.07 to 0.65)
	Day 7	0.15±0.57 ^a	1.94±1.09 ^b	0.05±0.21 ^a	1.79 (1.41 to 2.16)***	-0.1 (-0.28 to 0.08)***	-0.1 (0.28 to 0.08)
Oxygen therapy ³	P value (within groups)	<0.001	0.001	<0.001			
	Before intervention	2.79±0.42 ^a	2.69±0.6 ^a	2.82±0.39 ^a	-0.1 (-0.32 to 0.12)	-0.13 (-0.34 to 0.08)	0.03 (-0.14 to 0.2)
	Day 3	1.45±0.71 ^a	2.8±0.6 ^b	1.35±0.53 ^a	1.35 (1.06 to 1.63)***	1.45 (1.2 to 1.69)***	-0.1 (-0.36 to 0.16)
Chest tightness	Day 7	0.22±0.69 ^a	2±1.22 ^b	0.09±0.43 ^a	1.78 (1.34 to 2.21)***	1.91 (1.52 to 2.29)***	-0.13 (-0.37 to 0.11)
	P value (within groups)	<0.001	<0.001	<0.001			
	Before intervention	1.36±1.08 ^a	1.12±1.13 ^{a,b}	0.73±1.02 ^b	-0.24 (-0.71 to 0.23)	0.39 (-0.07 to 0.85)	-0.63 (-1.08 to -0.17)**
Dry cough	Day 3	0.07±0.26 ^a	1.02±1.12 ^b	0.05±0.21 ^a	0.95 (0.59 to 1.3)***	0.97 (0.62 to 1.31)***	-0.02 (-0.12 to 0.08)
	Day 7	0 ^a	0.69±1.04 ^b	0.02±0.15 ^a	0.69 (0.37 to 1)***	0.67 (0.35 to 0.98)***	0.02 (-0.02 to 0.06)
	P value (within groups)	<0.001	0.002	<0.001			
Sputum or Wet cough	Before intervention	1.74±0.89 ^a	1.74±1.06 ^a	1.39±0.95 ^a	0 (-0.42 to 0.42)	0.35 (-0.08 to 0.78)	-0.35 (-0.74 to 0.04)
	Day 3	0.93±0.68 ^a	1.6±1.06 ^b	0.56±0.59 ^c	0.67 (0.28 to 1.05)***	0.17 (-0.1 to 0.44)***	1.04 (0.67 to 1.4)*
	Day 7	0.17±0.44 ^a	1.19±0.89 ^b	0.09±0.29 ^a	1.02 (to 1.32)***	1.1 (0.81 to 1.38)***	-0.08 (-0.23 to 0.07)
Weakness	P value (within groups)	<0.001	<0.001	<0.001			
	Before intervention	0.29±0.74 ^a	0.31±0.56 ^a	0.61±1.02 ^a	0.02 (-0.26 to 0.3)	-0.3 (0.65 to 0.05)	0.32 (-0.06 to 0.7)
	Day 3	0.1±0.37 ^a	0.4±0.7 ^b	0.26±0.54 ^{a,b}	0.3 (0.05 to 0.54)*	0.14 (-0.12 to 0.4)	0.16 (-0.03 to 0.35)
Sore throat	Day 7	0.02±0.16 ^a	0.31±0.62 ^b	0.05±0.21 ^a	0.29 (0.09 to 0.48)**	0.26 (0.06 to 0.45)**	0.03 (-0.05 to 0.11)
	P value (within groups)	0.004	0.472	<0.001			
	Before intervention	1.81±0.83 ^a	2.36±0.82 ^b	1.84±1.16 ^a	0.55 (0.19 to 0.9)*	0.52 (0.08 to 0.95)*	0.03 (-0.4 to 0.46)
Myalgia	Day 3	0.26±0.66 ^a	1.88±0.94 ^b	0.4±0.49 ^a	1.62 (1.26 to 1.97)***	0.88 (0.53 to 1.22)***	0.14 (-0.1 to 0.38)
	Day 7	0 ^a	1.28±1.03 ^b	0 ^a	1.28 (0.96 to 1.59)***	1.28 (0.97 to 1.58)***	0 (0)
	P value (within groups)	<0.001	<0.001	<0.001			
Sore throat	Before intervention	0.21±0.52 ^a	0.17±0.49 ^a	0.23±0.57 ^a	-0.04 (-0.25 to 0.17)	-0.06 (-0.28 to 0.16)	0.02 (-0.21 to 0.25)
	Day 3	0 ^a	0.14±0.42 ^b	0 ^a	0.14 (0.01 to 0.26)**	0.14 (0.01 to 0.26)**	0 (0)
	Day 7	0 ^a	0.06±0.23 ^a	0 ^a	0.06 (-0.01 to 0.13)	0.06 (0 to 0.12)	0 (0)
Myalgia	P value (within groups)	0.001	0.135	0.001			
	Before intervention	1.29±1.13 ^a	1.36±1.03 ^a	1.07±1.15 ^a	0.07 (-0.39 to 0.53)	0.29 (-0.17 to 0.75)	-0.22 (-0.7 to 0.26)
	Day 3	0.07±0.34 ^a	0.83±0.93 ^b	0.05±0.21 ^a	0.76 (0.45 to 1.06)***	0.78 (0.49 to 1.06)***	-0.02 (-0.14 to 0.1)
P value (within groups)	Day 7	0 ^a	0.5±0.85 ^b	0 ^a	0.5 (0.23 to 0.76)***	0.5 (0.24 to 0.75)***	0 (0)
	P value (within groups)	<0.001	<0.001	<0.001			

(continued on next page)

Table 3 (continued)

Secondary outcomes	Time	Group			Mean difference		
		Acupuncture	Control	Cupping	Δ1	Δ2	Δ3
Anorexia	Before intervention	1.33±0.79 ^a	1.81±0.8 ^b	1.48±0.88 ^{a,b}	0.48 (0.13 to 0.82)**	0.33 (-0.03 to 0.69)	0.15 (-0.2 to 0.5)
	Day 3	0.21±0.61 ^a	1.31±0.9 ^b	0.23±0.53 ^a	1.1 (0.76 to 1.43)***	1.08 (0.76 to 1.39)***	0.02 (-0.22 to 0.26)
	Day 7	0 ^a	0.81±0.86 ^b	0.05±0.21 ^a	0.81 (0.54 to 1.07)***	0.76 (0.49 to 1.02)***	0.05 (-0.01 to 0.11)
	P value (within groups)	<0.001	<0.001	<0.001			
Headache	Before intervention	0.38±0.85 ^a	0.74±1.04 ^a	0.66±0.99 ^a	0.36 (-0.05 to 0.77)	0.08 (-0.35 to 0.51)	0.28 (-0.11 to 0.67)
	Day 3	0.05±0.22 ^a	0.43±0.83 ^b	0.05±0.3 ^a	0.38 (0.11 to 0.64)**	0.38 (0.11 to 0.64)**	0 (-0.11 to 0.11)
	Day 7	0 ^a	0.19±0.47 ^b	0.02±0.15 ^a	0.19 (0.04 to 0.33)**	0.17 (0.02 to 0.31)**	0.02 (-0.02 to 0.06)
	P value (within groups)	0.001	0.002	<0.001			

¹ Data is represented by mean± standard deviation or frequency (percentage) for groups and mean (95% confidence interval) for mean difference.

² Severity score of symptoms is described as: 0=not affected; 1= minimally-affected; 2=affected; and 3=severely-affected. ³ Severity score of oxygen therapy is described as: 0 = not needed; 1= nasal cannula; 2= simple face mask; 3= mask with reservoir; and 4= continuous positive airway pressure and non-invasive ventilation (CPAP/NIV) Mask; different letters (a-c) show significant statistical difference between groups and significance levels are represented as Δ1: acupuncture compared to control; Δ2: cupping compared to control; Δ3: acupuncture compared to cupping; * P<0.05, ** P<0.01, or *** P<0.001; RR: Relative Risk; ARR: Absolute Relative Reduction; H: Harm; B: Benefit.

ratory infections, and regulates Qi movements; LR3 controls Liver-Yang, manages Qi flow, resolves dampness, and reduces anxiety; LR14 promotes Qi flow; CV12 expels dampness and phlegm, and reduces anxiety; CV17 tonifies Qi, and opens the chest (reducing breathlessness); ST36 tonifies Qi, increases the vigor against exterior pathogens, and expels cold and dampness²³. A systematic review by Chen et al. (2020) showed that LI4 and ST36 acupoints are among the most frequent acupoints used in trials performed on COVID-19 patients²⁰.

On the other hand, modern medicine literature describes the mechanism of action of acupuncture. In a systematic review and meta-analysis, Wu et al. (2020) showed that a combination of acupuncture and standard care in respiratory diseases reduces cytotoxic T lymphocyte CD8⁺ associated with airway inflammation and obstruction, improves the ratio of T-cell CD4⁺/CD8⁺, and enhances respiratory functions²⁴. Results of another study indicated that parameters of spirometry (FEV1, FVC, and PEF), anti-inflammatory biomarkers (IL-4, IL-8, and interferon gamma), and T-cells (CD3⁺ and CD4⁺/CD8⁺ ratio) improve significantly with acupuncture²⁵. Also, an animal study by Wei et al. (2015) demonstrated that via regulating serum cytokine levels, acupuncture reduces hypersensitive and inflammatory conditions and excessive mucus excretion in airways²⁶.

A study by Jin et al. (2020) revealed that high levels of TNF-α and IL-6 are associated with higher mortality rate in COVID-19 patients. Hence, via inhibiting macrophage activation and regulating the level of proinflammatory cytokines such as TNF-α, IL-6, IL-1b, etc., acupuncture significantly reduces duration of hospitalization, ICU admission and mortality rate in COVID-19 patients²⁷. Furthermore, Wang et al. (2020) conducted an acupuncture-based clinical trial on 93 hospitalized COVID-19 patients. This study revealed that acupuncture significantly shortens duration of hospitalization compared with standard treatment²⁸. Our study found similar results in comparing duration of hospitalization, ICU admission and mortality rate between ACUG and CTRG.

Additionally, we found that adding acupuncture to standard care, resulted in improvement of SpO₂ and RR. Previous studies have reported regulation of IL-12 and TNF-α, and subsequent improvement in oxygen levels of pneumonia patients undergoing acupuncture²⁹. Similar results have been demonstrated in the studies evaluating acupuncture as a therapeutic intervention to treat dyspnea and hypoxia in COVID-19 patients^{30,31}. For example, Gong et al. (2020) reported the case of an 81-year-old COVID-

19 patient suffering from respiratory symptoms and hypoxia (SpO₂ 69%). After one week of acupuncture, chest tightness relieved and SpO₂ raised to 99% with 5 liter/minute oxygen therapy, and after two weeks of treatment, SpO₂ remained 98% without oxygen therapy³².

As reported in the results section, recovery rate of dyspnea, cough, chest tightness, weakness, sore throat, myalgia, anorexia and headache were higher in ACUG in comparison with CTRG on days 3 and 7. Research by Guan et al. (2020), Gong et al. (2021), Zha et al. (2020) and Tao et al. (2020) have also reported promising efficacy for adding acupuncture to standard care in COVID-19 patients. Their results were indicative of respiratory and gastrointestinal symptom improvement after 7-10 days³³. Moreover, no adverse events³⁴ or recurrence were observed in at least a 4-week follow-up³⁰.

As a non-pharmacological treatment in TCM, acupuncture has been clinically used to improve respiratory symptoms in COVID-19. However, this intervention is not common and easily-available in Iran. So, there was a high demand to develop a specific and suitable non-pharmacological PM-based treatment. We retrieved previously published studies and found that cupping therapy has been used for many purposes including common symptoms (cough and dyspnea) of a number of respiratory diseases such as asthma, bronchitis, and pneumonia in PM^{13,31,35}.

Recent studies have reported that cupping significantly improves the severity scores of respiratory symptoms (cough, sputum disposal, rhinitis, and sore throat) and spirometry parameters (FEV1, FVC, and PEF) in comparison with control groups^{34,36}. Similar results were shown in our case series that evaluated the effectiveness cupping in COVID-19 patients. The case series suggests that warm cupping of the posterior thorax is effective in improving respiratory symptoms and reducing mortality and intubation in COVID-19 patients with ARDS³⁷. Furthermore, a case report by Cheng demonstrated amelioration of dyspnea and chest tightness in a COVID-19 patient with cupping³⁸. These promising outcomes led to this randomized clinical trial, the results of which suggest that adding cupping to standard care shortens hospitalization duration and has significant preventive effects on severe COVID-19 outcomes (ICU admission and death)- according to the relative risk presented in Table 3, acupuncture and cupping decrease risk of ICU admission by 85% and 97%, respectively, and adding acupuncture or cupping to standard care declines the risk of intubation and death by 95%.

The cupping protocol used in this study was proposed according to our previous study. In this study, respiratory signs including RR and SpO₂ significantly improved in CUPG in comparison with the control group. These effects might be attributed to the anti-inflammatory effects of warm cupping. Cupping increases anti-inflammatory lipids (such as prostaglandin E₁) and decreases production of pro-inflammatory lipids (such as 12-HETE and Thromboxane B₂), inflammatory cytokines (e.g., IL-4, IL-5, IL-6 and TNF- α), immunoglobulin (Ig)-E, and the number, activity and cytotoxicity of natural killer lymphocytes^{31,39,40}.

In addition to RR and SpO₂, we found that respiratory symptoms improved in CUPG in comparison with CTRG after 3 days of intervention. Some patients expressed that after receiving cupping they felt more comfortable breathing. A 53-year-old female questioned whether she could continue cupping at home after discharge, as she had a really good feeling with cupping due to ease of breathing. Many patients stated that: "Cupping opens my lungs, I can breathe easier, and I cough less than before". Cupping helps alleviate respiratory symptoms by decreasing deoxyhemoglobin and enhancing blood microcirculation, endothelial repair, angiogenesis, and oxygenation^{10,41-43}. Additionally, cupping regulates parasympathetic activity, vasodilation, interstitial fluid exertion, and lung ventilation⁴⁴.

In the present clinical trial, cupping relieved chest tightness, headache, weakness and myalgia. Recent studies have demonstrated that cupping ameliorates muscle weakness, fatigue^{45,46}, reduces frequency and intensity of headache, and improves quality of life⁴⁷. According to an article that has described effects and mechanisms of action, cupping controls pain by increasing levels of brain opioid production, improving blood circulation, and eliminating toxins from the bloodstream¹⁰.

Limitations of this study include restricting outcomes to clinical symptoms. Inflammatory markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH) or procalcitonin, and follow-up chest CT scan were not considered herein because of the regulations imposed by isolation policies and lack of sufficient funding. All symptom reports were based on subjective assessment.

To our knowledge, this is the first randomized controlled trial that compared the effects of acupuncture and cupping in COVID-19 patients and represented the equal effectiveness of these two methods on COVID-19 symptoms. This study suggests the feasibility and reliability of cupping and acupuncture for management of COVID-19 respiratory symptoms. In addition to being safe and effective, cupping and acupuncture are low-cost and noninvasive modalities. Although COVID-19 is a worldwide outbreak with increasing number of infected patients, there are still controversies regarding treatments such as antiviral and antibiotic medications, corticosteroids, and healing plasma⁴⁸. Hence, CAM methods with strong literature support seem promising adjunctive treatments.

In conclusion, the COIRACCU trial provides evidence that cupping or acupuncture in combination with standard care improve respiratory signs, reduce progression to mechanical ventilation or death, hospital stay, hypoxemia, tachypnea, dyspnea, cough, sore throat, weakness, myalgia, anorexia, headache, and need for oxygen therapy in hospitalized COVID-19 patients.

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CRedit authorship contribution statement

Reihane Alipour: Data curation, Writing – original draft, Writing – review & editing. **Saeidreza Jamalimoghaddamsiahkali:** Supervision. **Mehrdad Karimi:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Asma Asadi:** Supervision. **Haleh Ghaem:** Formal analysis, Methodology, Validation, Writing – review & editing. **Mohammad Sadegh Adel-Mehraban:** Formal analysis, Writing – review & editing. **Amir Hooman Kazemi:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Conflict of interest

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

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Ethical statement

This study was approved by the Tehran University of Medical Science ethics committee (IR.TUMS.MEDICINE.REC.1399.1124).

Data availability

The data associated with this study can be made available by authors upon reasonable request.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.imr.2022.100898](https://doi.org/10.1016/j.imr.2022.100898).
Supplementary Table S1. Baseline characteristics.

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