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Review Article

Efficacy of acupuncture for cardiopulmonary cerebral resuscitation: A systematic review and meta-analysis

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ABSTRACT

Background: Cerebral resuscitation is one of the main therapeutic aims in the treatment of cardiac arrest (CA) patients who experience a return of spontaneous circulation (ROSC). However, the therapeutic effects of current treatments are not ideal. The purpose of this study was to evaluate the efficacy of neurological function of acupuncture combined with conventional cardiopulmonary cerebral resuscitationthe (CPCR) for patients after ROSC.

Methods: Seven electronic databases and other related websites were searched to identify studies on acupuncture combined with conventional CPCR for patients after ROSC. R software was used to conduct a meta-analysis, and the outcomes that could not be pooled were analyzed using a descriptive analysis.

Results: Seven RCTs involving 411 participants who had experienced ROSC were eligible for inclusion. The main acupoints were *Neiguan* (PC6), *Shuigou* (DU26), *Baihui* (DU20), *Yongquan* (KI1), and *Sanyinjiao* (SP6). Compared to conventional CPCR, acupuncture combined with conventional CPCR led to significantly higher Glasgow Coma Scale (GCS) scores on day 3 (mean difference (MD)=0.89, 95% CI: 0.43, 1.35, $I^2 = 0\%$), day 5 (MD = 1.21, 95% CI: 0.27, 2.15; $I^2 = 0\%$), and day 7 (MD = 1.92, 95% CI: 1.35, 2.50; $I^2 = 0\%$).

Conclusion: Acupuncture-assisted conventional CPCR may have a potential role in improving neurological function in CA patients after ROSC, but the certainty of evidence is very low and more high-quality studies are required.

Protocol registration: This review was registered at the International Prospective Registry of Systematic Reviews (PROSPERO): CRD42021262262.

1. Introduction

Cardiac arrest (CA) is one of the most common critical acute illnesses, with an annual out-of-hospital incidence ranging from 52.5 to 112.9 per 100,000 individuals worldwide.[1] With the substantial advancement of cardiopulmonary resuscitation (CPR) technology and the increased use of ventilators, a number of patients who have experienced return of spontaneous circulation (ROSC) has increased.[2] However, prolonged ischemia after CA and reperfusion damage after ROSC often result in post-CA brain injury.[3] The studies showed that 65% patients after ROSC died from neurological injury and only 8% patients who discharged from hospital had good neurological functions.[4] Therefore, reducing brain damage and restoring neurological function is essential for improving the prognosis of CA patients with ROSC.[5] Current therapies for brain injury after ROSC mainly including targeted temper-

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ature management (TTM), treatment of seizures, and maintenance of normal physiology, have unsatisfactory efficacy.[6]

Acupuncture, a type of traditional Chinese medicine (TCM) therapy, has long been used for medical emergencies and post-emergency rehabilitation,[7,8] and its role in promoting neurological recovery has been well recognized, such as neurological recovery from stroke and traumatic brain injury,[9–11] but it is less often used for neurological recovery for cardiopulmonary cerebral resuscitation (CPCR). Animal experiments have also indicated its potential for alleviating cerebral ischemia/reperfusion injury during CPCR by activating antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx),[12,13] reducing the generation of reactive oxygen species (ROS),[14] repairing mitochondrial respiratory function[15] and promoting DNA repair by upregulating Ref-1 in the hippocampus.[16,17] In recent years, clinical studies on acupuncture for CPCR have emerged,[18] and a systematic review of the latest clinical evidence can not only explore the possible efficacy of acupuncture for CPCR and provide a possible therapy for the neurological recovery of patients after ROSC, but also help to expand additional indications of acupuncture.

2. Methods

This systematic review and meta-analysis was registered with the International Prospective Registry of Systematic Reviews (PROSPERO) under the registration number CRD42021262262. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Acupuncture (PRISMA-A) checklist to report this review.[19]

2.1. Literature search and study selection

We searched the MEDLINE (via PubMed), Web of Science (WOS), Embase, Cochrane library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese Biomedical (CBM) databases from database inception to September 1, 2022. The main search terms for studies on CPCR were "Cardiopulmonary Resuscitation", "CPR", "Heart arrest", "Cardiac arrest", "Circulatory arrest", "Cardiopulmonary arrest", "Chest compression", "Cardiac massage", "Heart massage", "Heart standstill", "Heart stoppage", and "Sudden death*". The main search terms for studies on acupuncture were "Acupuncture", "Meridians", "Electroacupuncture", "Moxibustion", "Acupressure", "Acupoint*", "Needl*", "Trigger Point*", and "Auriculotherapy". In addition, we searched the official websites of the World Federation of Acupuncture-Moxibustion Societies (http://www.wfas.org.cn/), China Association of Acupuncture-Moxibustion (http://www.caam.cn/), Google Scholar, and the reference lists of all included studies for relevant studies. The search strategy is shown in **Supplementary Material 1.** Two reviewers (HS Li and YK Zhang) independently screened the literature by reading the titles/abstracts and then reviewing the full texts and a third reviewer (YL Liu) confirmed the eligibility of the studies.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

Studies were eligible for this systematic review if they met all the following criteria:

- **Population:** CA patients who experienced ROSC.
- **Intervention:** acupuncture combined with conventional CPCR. Acupuncture refers to the use of various different needles or ignited moxa flos to stimulate acupuncture points and meridians, including all types of acupuncture, such as electro-acupuncture, fire acupuncture, water acupuncture, ear acupuncture, moxibustion, etc.
- **Comparison:** conventional CPCR (with or without placebo/sham acupuncture), including hypothermia (TTM), dehydration, hyperbaric oxygen, prevention and treatment of cerebral convulsions, anticoagulation, and other advanced or long-term life support treatments.[20]
- **Primary outcomes:** Glasgow Coma Scale (GCS) score on day 1, 3, 5, and 7 after ROSC. GCS score indicates level of consciousness; the scores for eyes opening (maximum 4 points), verbal response (maximum 5 points), and motor response (maximum 6 points) are added together to provide a total score between 3 and 15. Higher scores indicate better neurological function (3–8, 9–12, and 13–15 indicate severe, moderate, and mild consciousness disorder, respectively).[21] A one-point increase in mean GCS score is considered clinically meaningful; as GCS score is ordinal and not continuous, non-integer values are not meaningful.[22]
- **Secondary outcomes:** (1) recovery time of consciousness and neurological deficit score (NFI); (2) neuro-electrophysiological monitoring results, including electroencephalogram (EEG), bispectral index (BIS), somatosensory evoked potential (SSEP) results; (3) biomarkers, including neuron-specific enolase (NSE) and S-100β protein; and (4) neuroimaging results, including brain computed tomography (CT) and magnetic resonance imaging (MRI) results.[23]
- **Study type:** randomized controlled trials (RCTs) and cohort studies.

2.2.2. Exclusion criteria

Studies meeting at least one of the following criteria were excluded:

- Multiple TCM therapies were used in the intervention group.
- Duplicates.

2.3. Data extraction

Two reviewers (YL Liu and ZR Kuang) independently extracted data according to a pre-designed data extraction form, with any disagreements being resolved through discussion with a third reviewer (XF Luo). Data were recorded using Microsoft Excel 2019, including basic information (first author, publication year, and sample sizes), participant characteristics (age, sex, cause of CA, and time from CA to CPR), intervention information (acupuncture types, duration, and frequency, and selection of acupoints), and outcome information.

2.4. Quality appraisal

Two reviewers (YL Liu and MJ Ren) independently assessed the risk of bias of the included RCTs using the Cochrane Collaboration's tool for assessing risk of bias (RoB),[24] and any disagreements were resolved by discussion with a third reviewer (XF Luo). The RoB tool contains seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other bias. A judgement of high, low, or unclear risk of bias was assigned for each item.

2.5. Data synthesis

The assessment of RoB was carried out using Review Manager (RevMan, version 5.3) software and the meta-analysis was performed using R Studio 2021 software. We planned to estimate the effect size using the mean difference (MD) for continuous data and relative risk (RR) for dichotomous data, along with 95% confidence intervals (CIs). The chi-square test (Cochrane's Q statistic) and I^2

statistic were used to assess potential heterogeneity across studies. If $I^2 < 50\%$, the heterogeneity was considered low, and results were pooled using a fixed effects model, otherwise, a random effects model was used to pooled the results and subgroup analysis was used to explore the possible causes of heterogeneity.[25] The meta-analysis results are presented using a forest plot. In addition, descriptive analyses were performed for outcomes that could not be pooled in a meta-analysis. We also conducted a sensitivity analysis with the leave-one-out method to assess whether the results were robust. Furthermore, we planned to use funnel plots to assess the publication bias if there were greater than or equal to 10 included studies.

2.6. Rating the certainty of evidence

Two authors (YL Liu and MJ Ren) rated the certainty of evidence for each outcome in the meta-analysis using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE),[26] assigning one of the following four grades: A (high-certainty evidence), B (moderate-certainty evidence), C (low-certainty evidence) and D (very-low-certainty evidence). The level of evidence from the RCTs was initially automatically rated as "High (A)" and then downgraded due to risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Study selection

We retrieved 4359 records through a systematic search of various databases and relevant websites. After removing duplicates, conference abstracts, letters or editorials using EndNote software, and then reading the titles and abstracts to exclude irrelevant studies, the remaining 19 were screened by reading the full text. Two non-RCTs or non-cohort studies,[27,28] three combined with other Chinese medicine therapies,[29–31] three with outcomes that did not meet the inclusion criteria,[32–34] one with duplicate data,[35] and one was performed simultaneously with CPR were excluded,[36] resulting in a total of seven RCTs that were ultimately included in the systematic review.[37–43] Outcomes from six of the RCTs were pooled in the quantitative synthesis.[37–41,43] The flowchart of study identification is shown in Fig. 1.

3.2. Characteristics of the included RCTs

The characteristics of the included RCTs are shown in Table 1. All seven included RCTs were conducted in China and published in Chinese. They involved a total of 411 participants with sample sizes ranging from 33 to 90. Five RCTs[38–40,42,43] reported the causes of CA, which can be divided into cardiogenic and non-cardiogenic diseases. The cardiogenic diseases mainly included coronary heart disease (CHD), and the non-cardiogenic diseases mainly included cerebrovascular diseases (CVD), respiratory failure (RF), and shock. Three RCTs[38,39,42] reported the times from CA to CPR of <6 min. Additionally, all RCTs reported that there were no significant differences in gender, age, cause of CA, time from CA to CPR, or initial GCS score after ROSC (before) between the acupuncture and control groups.

Conventional CPCR was performed in the control groups of all included RCTs, which was an integrated therapy, involving head cooling or sub-hypothermia therapy, sedation, dehydration, symptomatic treatment, respiratory and circulatory maintenance, and water-electrolyte balance maintenance. Manual acupuncture was investigated in five RCTs,[37,39–41,43] electroacupuncture in one,[42] and CPR therapeutic acupuncture equipment in one.[38] The most widely used acupoints were *Neiguan* (PC6) ($n = 7$), *Shuigou* (DU26) ($n = 6$), *Baihui* (DU20) ($n = 4$), *Yongquan* (KI1) ($n = 3$), and *Sanyinjiao* (SP6) ($n = 3$). acupuncture was administered twice per day in four RCTs,[37–39,43] and the duration was 7 days in five RCTs.[37–41]

3.3. Risk of bias of included RCTs

The assessment results of risk of bias for the included RCTs are presented in Fig. 2. Five RCTs[38,40–43] used a random number table, leading to low risk of bias regarding random sequence generation, and the other two RCTs[37,39] did not describe the method of randomization, leading to unclear risk of bias. The risk of bias of allocation concealment and blinding of outcome assessment was unclear for all RCTs due to lack of relevant reported details. All RCTs were open-label RCTs, so the risk of bias for blinding of participants and personnel was high. The risk of bias regarding incomplete outcome data was unclear for one RCT[38] with missing data, and the rest had low risk. One RCT[38] had high risk regarding selective reporting due to partial outcome reporting, and the rest had unclear risk.

3.4. GCS score effect size estimate

The pooled GCS score results on day 1, 3, 5, and 7 of acupuncture combined with conventional CPCR after ROSC are shown in Fig. 3. The GRADE results and reasons for the downgrades are shown in Table 2. GCS score data on day 1 were available from three RCTs ($n = 176$).[37,39,40] Pooled results showed no significant difference between acupuncture and control groups (MD = 0.75, 95% CI: −0.39, 1.88, $I^2 = 74\%$, random effects model; very-low-certainty evidence). Due to the small number of included studies, subgroup analysis was not performed. GCS score data on day 3 were available from four RCTs ($n = 266$).[37,39,40,43] Acupuncture combined with conventional CPCR showed a significant but not a clinically meaningful improvement (MD = 0.89, 95% CI: 0.43, 1.35; $I^2 = 0\%$, fixed effects model; very-low-certainty evidence). GCS score data on day 5 were available from two RCTs ($n = 116$).[37,39] Acupuncture combined with conventional CPCR showed a significant and clinically meaningful improvement (MD = 1.21, 95% CI: 0.27, 2.15; $I^2 = 0\%$, fixed effects model; very low-certainty evidence), but sensitivity analyses showed that the results were not robust and were highly influenced by individual studies. The initial GCS scores of participants included in the two RCTs were significantly different, and acupuncture may have different effects on the improvement of different degrees of initial brain injury. GCS score data on day 7 were available from five RCTs ($n = 249$).[37–41] Acupuncture combined with conventional CPCR showed a significant and clinically meaningful improvement (MD = 1.92, 95% CI: 1.35, 2.50; $I^2 = 0\%$, fixed effects model; low-certainty evidence). It is remarkable that the efficacy of acupuncture appeared to increase over time.

3.5. Other outcomes

A descriptive analysis was performed as fewer RCTs[38,40,42] reported on the following outcomes (**Supplement 2**). The RCTs showed that acupuncture combined with conventional CPCR shortened the recovery time of consciousness (56.52 ± 17.25 h vs. 67.22 ± 14.37 h, $P < 0.05$) and reduced the Neurobehavioral Functioning Inventory (NFI) score on day 7 after ROSC (30.62 ± 7.21 *vs.* 98.4 ± ± 34.9, $P < 0.05$).[40] Additionally, the acupuncture group had decreased values of NSE, a biomarker for prognostic assessment of brain injury, and increased BIS and electrophysiology monitoring values on day 7 and 14 after ROSC, compared to the control group.[42]

Table 1
Characteristics of included RCTs.

Study	Sample sizes (A/C), Gender (female, A/C), Age (years, A/C)	Cause of CA (n, A/C)	Time from CA to CPR (min, A/C)	Initial GCS score after ROSC (min, A/C)	Acupuncture	Control	Acupoints	Duration (day)/ frequency (daily)	Outcome measures
Zhao 2007[37]	22/21, NR, NR	NR	NR	6.2/ 6.3	MA+ CPCR	CPCR	DU26, DU20, PC6, KI1	7d, 2 times	GCS
Qin 2008[38]	17/16, NR 42.0	AMI (3), ARF (4), GIB (1), CVA (8), Uremia (6), Trauma (5), Unknown (11)	NR	4.11/3.81	Acupuncture CPR* + CPCR	CPCR	DU26, PC6, EX-UE11, LU5, PC3, BL40	7d, 2 times	GCS, RTC
Liu 2011[39]	37/36, 18/20 67.2/68.6	CHD (27), CVD (15), RF (12), Electrolyte disturbance (8), Shock (3), Others (8)	3.23/ 3.06	3.7/3.8	MA + CPCR	CPCR	DU26, DU20, PC6	7d, 2 times	GCS
Yu 2017[40]	30/30, 12/13 61.2/62.4	Cardiogenic (12/13), Noncardiogenic (18/17)	4.80/4.70	3.7/ 3.8	MA + CPCR	CPCR	DU26, PC6, SP6	7d, NR	GCS, NFI, QOL
Jiang 2020[41]	20/20, 4/9 68.6/72.4	NR	NR	3.3/ 3.34	MA + CPCR	CPCR	DU20, *DU26, PC6, SP6	7d, 1 time	GCS
Xiao 2020[42]	36/36 17/15 62.0	Cardiogenic (15/18), RF (8/7), Electrolyte disturbance (5/3), Poisoning (3/2), Others (5/6)	5.19*	NR	EA + TTM	TTM	DU26, PC6, LI4, PC8, KI1, HT7, ST36, SP6	14d, NR	BIS, NSE
Wang 2022[43]	45/45 25/23 58.4/59.1	CHD (26/24), Stroke (9/10), PHD (8/8), Others (2/3)	NR	6.4/6.4	MA + CPCR	CPCR	DU20, EX-HN1, PC6, SI3, KI1	NR, 2 times	GCS

A: Acupuncture group; AMI: Acute myocardial infarction; ARF: Acute respiratory failure; BIS: Bispectral Index; C: Control group; CA: Cardiac arrest; CHD: Coronary heart disease; CPCR: Cardiopulmonary cerebral resuscitation; CVA: Cerebral vascular accident; CVD: Cerebrovascular disease; EA: Electroacupuncture GCS: Glasgow Coma Scale; GIB: Gastrointestinal bleeding; MA: Manual acupuncture; NFI: Neurobehavioral Functioning Inventory; NR: Not reported; NSE: Neuron-specific enolase; PHD: Pulmonary heart disease; QOL: Quality of life; RF: Respiratory failure; ROSC: Return of spontaneous circulation; RTC: Recovery time of consciousness; TTM: Targeted temperature management.

* Acupuncture CPR (therapeutic equipment) mainly refers to the stimulation is maintained by applying cardiac pacing electrodes to specific acupuncture points.

Table 2
Results of the GRADE evidence quality rating.

Question: Compared to conventional CPCR, what is the effect of acupuncture combined with conventional CPCR on GCS score in cardiac arrest patients who experienced ROSC?												
No of RCTs	Study design	Certainty assessment								Effect (95% CI)	I^2	Overall certainty of evidence
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large magnitude of effect	Dose–response gradient	Plausible confounding			
Day 1 GCS												
3 (176)	RCT	serious[a]	serious[b]	not serious	serious[c]	serious[d]	none	none	none	MD 0.75 (−0.39, 1.88)	74%	⨁◯◯◯ Very Low
Day 3 GCS												
4 (266)	RCT	serious[a]	not serious	not serious	serious[c]	serious[d]	none	none	none	MD 0.89 (0.43, 1.35)	0%	⨁◯◯◯ Very Low
Day 5 GCS												
2 (116)	RCT	serious[a]	not serious	not serious	serious[c]	serious[d]	none	none	none	MD 1.21 (0.27, 2.15)	0%	⨁◯◯◯ Very Low
Day 7 GCS												
4 (189)	RCT	serious[a]	not serious	not serious	not serious	serious[d]	none	none	none	MD 1.92 (1.35, 2.50)	0%	⨁◯◯◯ Low

Note: CI: confidence interval; CPCR: cardiopulmonary cerebral resuscitation; GCS: Glasgow Coma Scale; MD: mean difference; RCT: randomized controlled trial.
Explanations.
a: downgrade one level: Risk of bias is high due to limitations of study design.
b: downgrade one level: Heterogeneity regarding data synthesis results, I^2>50%.
c: downgrade one level: Sample size is less than optimal information sample (OIS) or confidence interval is too wide.
d: downgrade one level: Potential publication bias because of the language limited and the small sample size.
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

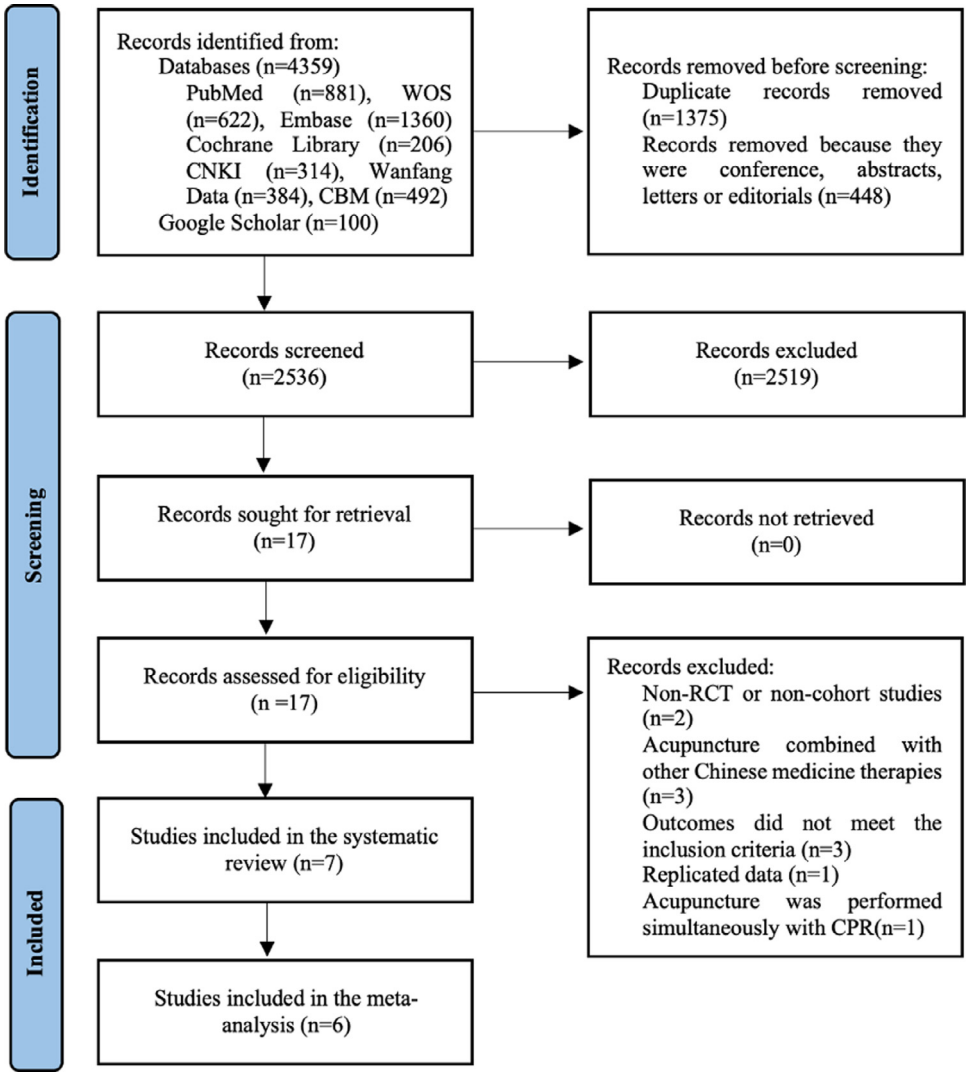

Fig. 1. Flowchart of study identification. CBM: Chinese Biomedical databases; CNKI: China National Knowledge Infrastructure; CPR: cardiopulmonary resuscitation; RCT: randomized controlled trial; WOS: Web of Science.

3.6. Publication bias

Funnel plots were not conducted to detect publication bias, as the power of the test for publication bias is very low when there are less than 10 RCTs.[44]

3.7. Sensitivity analyses

The significance of the meta-analysis results did not change regarding the GCS scores on day 1 day 3 and 7 but did regarding the GCS scores on day 5, which were more influenced by individual RCTs (Supplement 3).

4. Discussion

4.1. Main finding

Seven RCTs (involving 411 participants) revealed that acupuncture combined with conventional CPCR could improve the GCS score on day 7 after ROSC, and also improved neurobiological marker (NSE) and neuro-electrophysiological monitoring (BIS) values on day 7 and 14. Delayed reperfusion injury can be observed between 4 h and 7 days after ROSC, indicating that neurological damage is established after 7 days,[45] which was closely related to the long-term neurological prognosis of CA patients.[46] Therefore, acupuncture combined with conventional CPCR may improve the long-term neurological prognosis by reducing neurological damage on day 7 after ROSC.

Brain death generally occurs 3–4 days after ROSC,[47] and patients who fail to revive on day 3 (with poor neurological prognosis) are at high risk of developing severe cognitive impairment or even being in a vegetative state.[48] The 2021 European Resuscitation Council and European Society of Intensive Care Medicine guidelines also recommend that neurological prognosis should be assessed at 72 h after ROSC to help clinicians determine treatment goals and inform families of the likely prognosis.[20] Our results showed a significant improvement in GCS score on day 3, but the improvement was not clinically significant (MD = 0.89, 95% CI: 0.43, 1.35; four RCTs, 266 participants; I^2 = 0%, fixed effects model), and there were also no significant improvements in the neurological biomarker (NSE) or neuro-electrophysiological monitoring (BIS) values on day 3. Therefore, we are not sure whether acupuncture combined with conventional CPCR could improve neurological function during the first 3 days or reduce patient mortality.

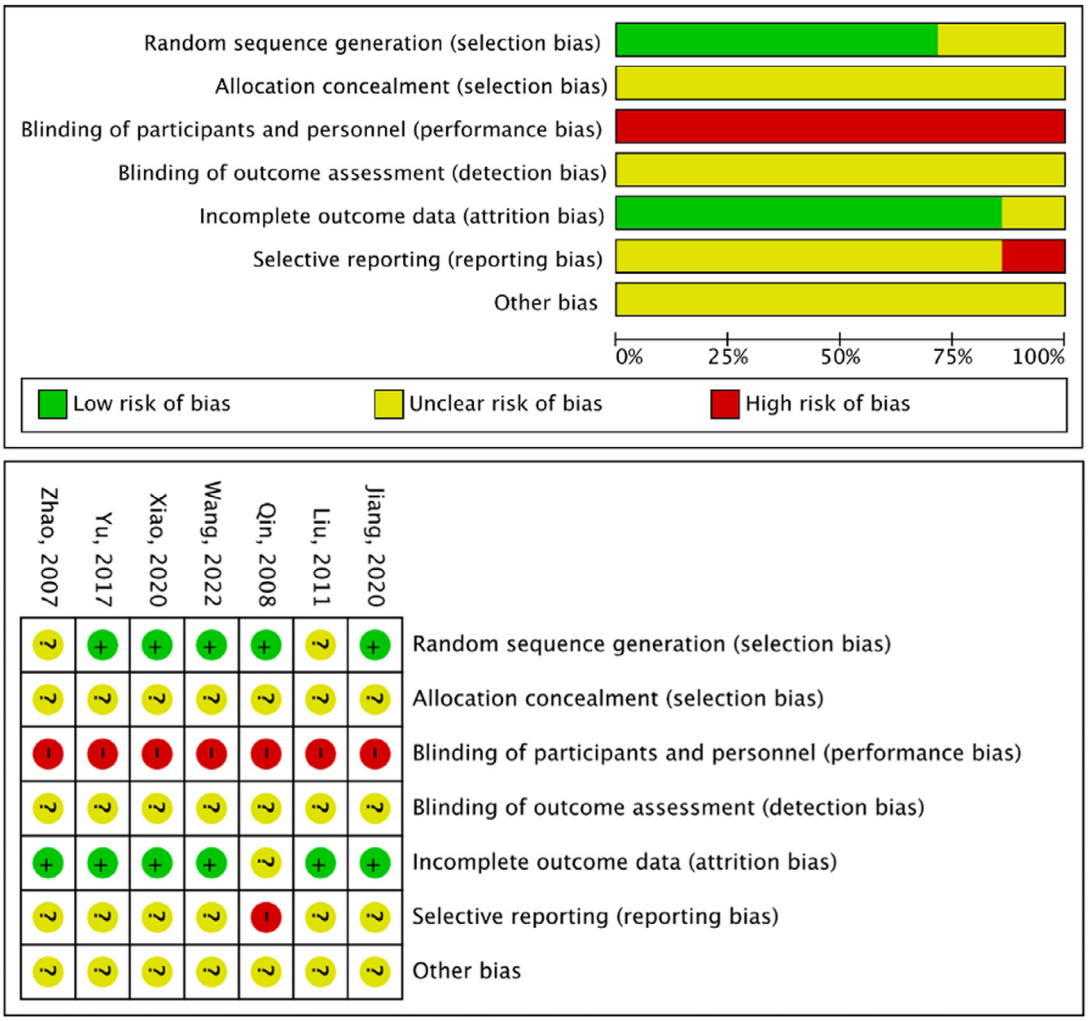

Fig. 2. Risk of bias (RoB) of included RCTs.

4.2. Theoretical basis

Neiguan (PC6) *Shuigou* (DU26), *Baihui* (DU20), and *Yongquan* (KI1) are commonly used emergency acupoints in clinical practice for waking the brain and unblocking the meridians.[18] Their possible mechanisms for neurological recovery during CPCR have been explored in several animal experiments. For example, acupuncture at *Shuigou* (DU26) and *Neiguan* (PC6) acupoints in rabbits after ROSC helped to: (1) increase blood flow and oxygenation in the brain by increasing the blood flow velocity in the cerebral arteries, improving mitochondrial respiratory function in brain tissue, and increasing the rate of adenosine triphosphate (ATP) production[49]; (2) reduce early cerebral edema and energy failure in the ischemia-reperfusion area by improving Na+-K+-ATPase activity in brain tissue and maintaining ion homeostasis and osmotic pressure balance in and out of the cells[50]; (3) reduce oxidative stress and lipid peroxidation after cerebral ischemia/reperfusion injury by improving SOD activity after CPR, promoting the scavenging of superoxide anion free radicals, and reducing malondialdehyde (MDA) and lipid peroxidation damage.[51] In addition, acupuncture at the *Baihui* (DU20) and *Neiguan* (PC6) acupoints attenuated the inflammatory response,[52] and acupuncture at the *Yongquan* (KI1) acupoint improved the number and function of synapses and induced stronger neuronal activity.[53,54] The efficacy of acupuncture in improving ischemia/reperfusion injury and neurological function has also been demonstrated in other conditions, such as stroke and traumatic brain injury.[9–11]

4.3. Clinical implications and directions for future research

Many studies have explored the potential effect of acupuncture for neurological function after ROSC,[18] our findings also provide some limited support for acupuncture as a suitable assistive therapy along with conventional CPCR for improving neurological function in CA patients who experienced ROSC. Patients with CA due to cardiogenic or non-cardiogenic disease were included in our study and all had severe neurological impairment (all participants had an initial GCS score after ROSC of 3–7), which suggest that acupuncture combined with conventional CPCR has some efficacy in severe neurological impairment, but its efficacy in patients with different causes of CA is unknown. A retrospective non-randomized controlled trial published in 2018 found that conventional CPCR combined with electroacupuncture at the *Zusanli* (ST36) acupoint was most effective in CA patients with severe neurological impairment due to non-cardiogenic disease, but a larger sample size and more rigorously designed studies are still needed.[55] As for the duration of acupuncture, our meta-analysis showed the best improvement in GCS scores on day 7 after ROSC in the acupuncture group, but one RCT found that the GCS score was slightly better on day 17 than day 7,[38] though this effect

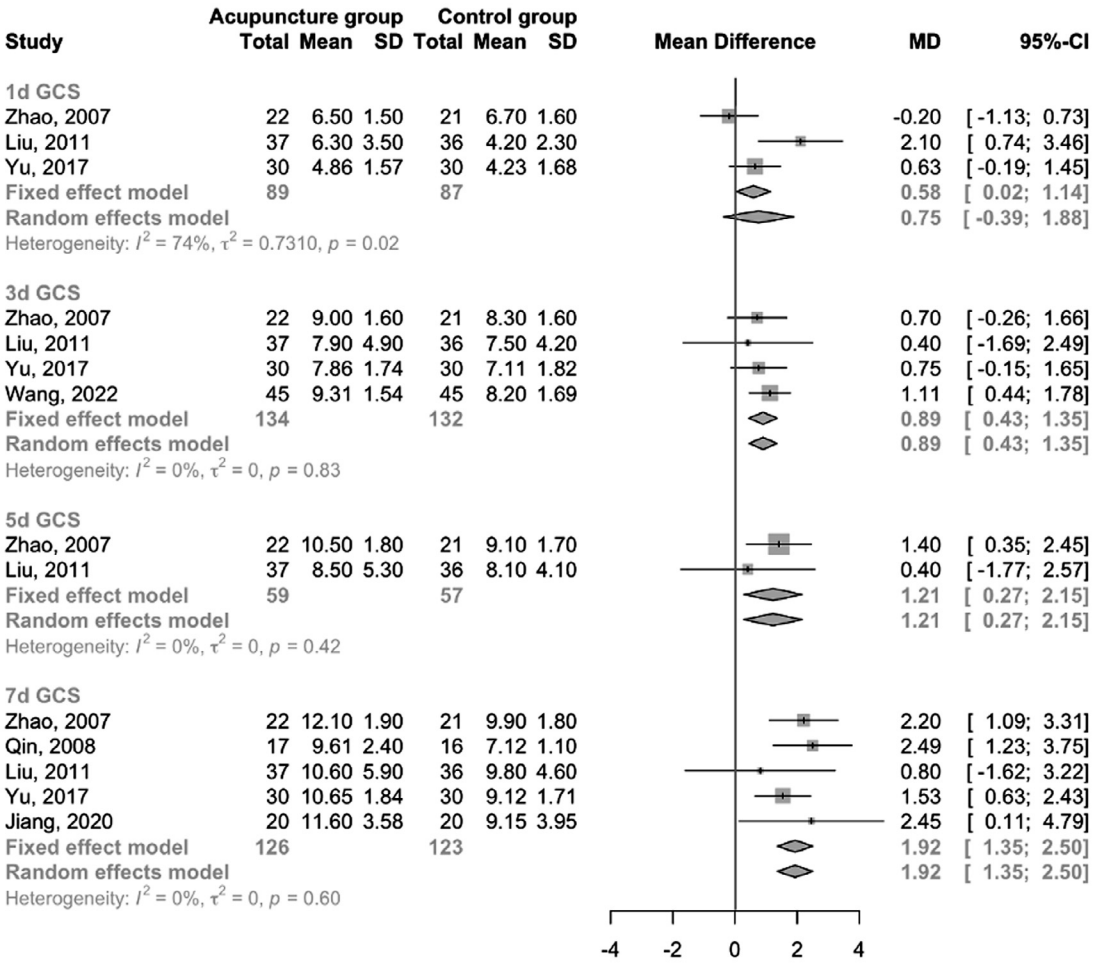

Fig. 3. Forest plot of GCS scores in acupuncture versus control group. d: day; GCS: Glasgow Coma Scale.

needs to be validated. The combinations of acupoints, acupuncture modality (needling acupuncture, electroacupuncture, acupuncture CPR therapeutic equipment, or balance acupuncture), acupuncture duration (seven days or more), and acupuncture frequency (once or twice a day) were inconsistent in the included RCTs. Therefore, we are not sure which combination will achieve optimal efficacy for CPCR. This should be explored further in future practice and research.

Regarding the time point of acupuncture for CPCR, since neurological impairment is initiated during circulatory interruption and accentuated during the reperfusion phase,[56] while the recovery time of ROSC was independently related to brain injury and the neurological function prognosis at discharge.[57] Previous studies have shown that acupuncture performed simultaneously with CPR may improve the success rate of CPR,[58] shorten the recovery time of ROSC[59,60]and the consciousness of patients.[60] Meanwhile, some international researches proposed the possibility of integrating acupuncture into the International Liaison Committee on Resuscitation (ILCOR) protocol for life support.[61] Acupuncture performed simultaneously with CPR or after ROSC may have potential efficacy on the neurological function for CA patients, and which acupuncture time point has better efficacy or whether combined those two time points have better efficacy can be further explored in the future.

4.4. Strengths and limitations

This study is the first systematic review and meta-analysis of the efficacy of acupuncture combined with conventional CPCR for improving neurological function in CA patients who experienced ROSC. A systematic search of the relevant literature was conducted, providing a reference for the use of acupuncture in CA cases.

However, our study also has some limitations, including: (1) Only seven RCTs was included and the sample size was small, ranging from 33 to 90 patients, which may affect the stability and precision of the results. (2) The included RCTs may have a high risk of bias. Two RCTs did not describe the randomization method, and all the RCTs had high risk of bias regarding blinding of participants and personnel, all of which may affect the scientific validity and reliability of the RCTs. (3) The outcomes for assessing neurological recovery were not sufficiently comprehensive. Firstly, there were limitations in the reporting of GCS scores, with only the total GCS score being reported in the included RCTs; there were no separate scores for the three GCS elements. However, research has shown that eyes opening (E) and motor response (M) correlated better with the prediction of long-term neurological recovery,[62] and the same total GCS score can represent different component scores, for example, a total GCS score of 12 could represent a patient with grading E4, V3, and M5 or E2, V5, and M5. Secondly, there was a lack of outcomes such as electroencephalography (SSEP and EEG), neuroimaging (CT and MRI), and biomarker (NSE and S-100β protein) results. (4) Only one RCT evaluated the safety of acupuncture, so there was insufficient evidence on the safety of acupuncture for CPCR. (5) We searched only English and Chinese databases/websites, and all included RCTs were published in Chinese. RCTs published in other languages, such as Korean and Japanese, might be disregarded, which may lead to publication bias.

4.5. Differences between registration and the systematic review

In conducting the systematic review, there were some inconsistencies with the registration information, including: 1) We added a search of the Embase database to include more studies; 2) Because of the small number of included studies, we included additional secondary outcomes based on a consensus for assessing neurological function after ROSC and performed a descriptive analysis of them. 3) In addition, because of the inclusion of fewer studies, subgroup analyses of the included studies were also not performed based on the particular features of the included studies mentioned in the registration information (e.g., the intervention methods [type, time, and cycle] and the measurement methods used in the clinical trials) and other factors, but instead of a sensitivity analysis with the leave-one-out method to assess whether the results were robust.

4.6. Conclusion

This study showed that acupuncture-assisted conventional CPCR may have a potential role for improving neurological function of CA patients after ROSC, but the very low-certainty evidence indicates that these results must be interpreted cautiously. Therefore, rigorously designed, multicenter, and large-sample RCTs may be needed to evaluate the efficacy and safety of acupuncture interventions for CPCR.

Ethical statement

This review did not require an ethical approval.

Data availability

All data is included in the publication. There is no additional data available.

Declaration of Competing 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.

CRediT authorship contribution statement

Yunlan Liu: Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Mengjuan Ren:** Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Zhuoran Kuang:** Investigation, Validation, Writing – review & editing. **Xufei Luo:** Investigation, Validation, Writing – review & editing. **Huishan Li:** Investigation, Writing – review & editing. **Yikai Zhang:** Investigation, Writing – review & editing. **Wanxin Wen:** Writing – review & editing. **Yefeng Cai:** Writing – review & editing. **Xiaojia Ni:** Conceptualization, Writing – review & editing, Supervision. **Yaolong Chen:** Conceptualization, Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.100925.

Supplement 1. search strategy.

Supplement 2. Comparison of secondary outcomes between acupuncture and control groups.

Supplement 3. Sensitivity analysis of GCS scores on day (a) 1, (b) 3, (c) 5, and (d) 7.

Supplement 4. PRISMA 2020 checklist

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