

Steroid, thiamine, and ascorbic acid for comatose out-of-hospital cardiac arrest survivors (STAR): a randomised, placebo-controlled, phase 2 trial



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Summary

Background Pharmacologic neuroprotection for out-of-hospital cardiac arrest (OHCA) remains elusive. We evaluated whether early hydrocortisone, ascorbic acid, and thiamine reduced neuronal injury in comatose OHCA survivors.

Methods In this multicentre, placebo-controlled trial across four South Korean hospitals, comatose adult OHCA survivors undergoing targeted temperature management were randomly assigned (1:1) to intravenous hydrocortisone (100 mg), ascorbic acid (50 mg/kg), and thiamine (200 mg) every 12 h for 3 days, or placebo. Randomisation was computer-generated. Bedside clinicians were aware of treatment allocation, whereas laboratory personnel and independent outcome assessors were masked. The primary outcome was peak neuron-specific enolase (NSE) concentration, defined as the highest available value measured at 48 h or 72 h after return of spontaneous circulation. Efficacy was analysed using a modified intention-to-treat (mITT) principle, with multiple imputation for the full intention-to-treat (ITT) population. The completed trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) on June 4, 2021 (NCT04921189).

Findings Between Dec 31, 2021, and Dec 7, 2024, 160 participants (123 male, 37 female) were assigned (80 per group); 147 were included in the mITT analysis (74 treatment, 73 placebo). Peak NSE levels were 47.4 ng/mL (interquartile range [IQR] 22.4–262.6) in the treatment group and 53.3 ng/mL (IQR 26.6–244.2) in the placebo group (median difference –5.9 ng/mL; 95% confidence interval [CI] –34.5–40.8; $p = 0.54$). ITT sensitivity findings were consistent (geometric mean ratio 0.94; 95% CI 0.61–1.46; $p = 0.80$). At 180 days, survival (63.5% vs 69.9%) and good neurological outcome (54.1% vs 56.2%) were similar. Serious adverse events were comparable in the ITT population (52.5% vs 50.0%), with none deemed related to the study medication.

Interpretation Early administration of hydrocortisone, ascorbic acid, and thiamine did not reduce neuronal injury or improve 6-month clinical outcomes. The findings do not support empiric neuroprotective use in comatose OHCA survivors.

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Keywords: Out-of-hospital cardiac arrest; Neuroprotection; Neuron-specific enolase; Hydrocortisone; Ascorbic acid; Thiamine

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Research in context

Evidence before this study

We searched PubMed, Embase, and the Cochrane Library from database inception to Nov 30, 2021, without language restrictions, using terms including “cardiac arrest”, “ascorbic acid”, “thiamine”, “hydrocortisone”, and “metabolic resuscitation”. We considered randomised and non-randomised clinical studies evaluating hydrocortisone, ascorbic acid, or thiamine, alone or in combination, after cardiac arrest. Preclinical studies, case reports, and studies without post-cardiac-arrest outcomes were excluded. The available clinical evidence was limited by small sample sizes, observational or single-centre designs, and heterogeneous interventions. Although this combination had been evaluated in sepsis, we identified no multicentre randomised trial evaluating its early administration in comatose survivors of out-of-hospital cardiac arrest.

Added value of this study

To our knowledge, this trial is the first multicentre, placebo-controlled randomised trial to evaluate hydrocortisone, ascorbic acid, and thiamine administered during the early

post-resuscitation period, at a median of 3.9 h after cardiac arrest. Despite substantially increasing serum vitamin C and thiamine concentrations, the intervention did not reduce neuronal injury, measured by peak neuron-specific enolase concentration (median difference -5.9 ng/mL [95% confidence interval -34.5 to 40.8]), or improve 180-day survival or neurological outcomes.

Implications of all the available evidence

Together with evidence from other critically ill populations, these findings do not support routine empiric administration of hydrocortisone, ascorbic acid, and thiamine for neuroprotection in unselected comatose survivors of out-of-hospital cardiac arrest. The absence of clinical benefit despite confirmed systemic exposure suggests that universal metabolic supplementation is unlikely to modify post-cardiac-arrest neuronal injury. Future studies should focus on phenotype-directed treatment, objectively confirmed micronutrient deficiency, biological target engagement, and rigorous safety assessment.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major global health burden, with more than 3.7 million cases occurring annually, yet barely 10% of patients survive with favourable neurological status.¹ Among patients who achieve return of spontaneous circulation (ROSC) and receive intensive care, hypoxic-ischaemic brain injury, resulting from initial global ischaemia during cardiac arrest and subsequent ischaemia-reperfusion injury after ROSC, is the leading cause of death and long-term disability.^{2–6} Post-cardiac arrest syndrome (PCAS) is characterised by systemic ischaemia-reperfusion injury, neuroinflammation, oxidative stress, endothelial dysfunction, and mitochondrial impairment. Together, these processes constitute a dysregulated systemic response that contributes to ongoing neuronal injury during the post-cardiac arrest period.^{4,7–9}

Targeted temperature management (TTM) is a standard component of post-cardiac arrest care and may modulate cerebral metabolic demand and inflammatory and oxidative responses. Nevertheless, substantial secondary neuronal injury persists, and pharmacological neuroprotective therapies have not demonstrated consistent clinical benefit.^{8,10} Previous clinical trials have largely focused on single agents targeting isolated mechanisms, including inhaled gases, antioxidants, and vitamins.^{11–14} The available evidence is further limited by small sample sizes, single-centre designs, and substantial heterogeneity in interventions and trial methods. One plausible explanation is that interventions targeting a single pathway may be

insufficient to halt the multifaceted cascade of reperfusion injury. In this context, a combination strategy designed to modulate multiple pathogenic pathways simultaneously may be more effective. The combination was selected to target complementary components of PCAS: hydrocortisone to attenuate glucocorticoid-responsive inflammatory signalling and cytokine production, ascorbic acid to mitigate oxidative stress and preserve endothelial function, and thiamine to support pyruvate dehydrogenase-dependent mitochondrial energy metabolism.^{8,15–20} This combination has shown mixed results in sepsis,^{18–20} and its efficacy in attenuating ischaemia-reperfusion injury among comatose OHCA survivors has not been established.

Given the narrow therapeutic window of post-cardiac arrest ischaemia-reperfusion injury, we hypothesised that early simultaneous modulation of these inflammatory, endothelial, oxidative, and metabolic pathways would attenuate secondary neuronal injury. The STAR (corticoidSteroid, Thiamine, and Ascorbic acid during post-Resuscitation period for comatose out-of-hospital cardiac arrest survivors) trial aimed to investigate whether the combined administration of hydrocortisone, thiamine, and ascorbic acid during this critical phase attenuates secondary neuronal injury in comatose OHCA survivors treated with TTM. The primary outcome was the peak serum neuron-specific enolase (NSE) level, a well-validated biomarker of hypoxic-ischaemic neuronal injury,¹⁰ with 6-month clinical outcomes, including survival and functional recovery, assessed as secondary endpoints.

Methods

Study design

The STAR trial was a multicentre, randomised, placebo-controlled, parallel-group superiority trial with a 1:1 allocation ratio. As an exploratory phase 2 trial, it was conducted at four tertiary academic hospitals in South Korea; participating sites were required to have established protocols for TTM. Although nine sites were initially planned, enrolment was limited to four sites due to operational constraints related to coronavirus disease 2019. The study protocol (NCT04921189) was previously published,²¹ and the final statistical analysis plan is provided in [Appendix](#) (p 17). The trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov/study/NCT04921189) on June 4, 2021 (NCT04921189; <https://clinicaltrials.gov/study/NCT04921189>). The protocol was approved by the Ministry of Food and Drug Safety of Korea. Patients were enrolled from December, 2021 through December, 2024, with final follow-up in June 2025.

Ethics statement

The protocol was approved by the Institutional Review Boards (IRBs) of all participating hospitals (lead centre: Asan Medical Center, approval number 2021-0613), and subsequent protocol amendments were approved by the relevant IRB before implementation. Because all participants lacked decision-making capacity at enrolment, written informed consent was obtained from a legally authorised representative before enrolment and randomisation. Consent was obtained as soon as practicable after return of spontaneous circulation and before administration of the first study medication. Under an Institutional Review Board-approved amended consent procedure, participants who subsequently regained decision-making capacity were informed of their study participation and given the opportunity to withdraw; separate written reconsent was not required. The study was conducted in accordance with the Declaration of Helsinki.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting of this trial.

Participants

Eligible patients were Korean nationals aged 19–79 years who had been successfully resuscitated from OHCA of presumed cardiac origin, remained comatose after ROSC, and were treated with TTM (protocol-permitted target 32–36 °C). Data on sex assigned at birth and ethnicity were extracted from electronic medical records at each participating site. Ethnicity was classified according to the category recorded in routine clinical documentation, and all enrolled participants were recorded as Asian. Key exclusion criteria included administration of the study drug >12 h from arrest; treatment limitations (e.g., Do-Not-Resuscitate orders)

or terminal illness; prior high-dose vitamin C (≥ 1 g/day) or thiamine use; or other contraindications to the study medications. Full inclusion/exclusion criteria are provided in [Appendix](#) (p 2).

Randomisation and masking

A designated statistician generated the randomisation sequence using R software (version 3.3.3) with site-stratified permuted blocks of four. Participants were randomised in a 1:1 ratio to the treatment or placebo group. Allocation was concealed using tamper-evident, sequentially numbered, opaque, sealed envelopes opened only at the time of assignment. Attending physicians, serving as co-investigators, screened patients for eligibility and enrolled participants by opening the envelopes in strict numerical order at the time of assignment. The assigned study medication or matching placebo was prepared in light-shielded infusion bags by a separate unblinded study staff member responsible for medication preparation and not involved in outcome assessment. All active study drugs were colourless after preparation. The prepared study product was then administered by bedside nurses in the emergency department or intensive care unit (ICU) according to the assigned regimen.

Placebo infusions consisted of matching 50-mL 0.9% saline infusions; however, bedside clinicians and nurses administering the assigned infusions were aware of treatment allocation. Legal representatives, laboratory personnel, and independent outcome assessors were blinded to treatment allocation throughout the study period. Primary and secondary outcomes were assessed by independent researchers who were not involved in the clinical care of the participants. Formal assessment of masking success was not performed.

Procedures

As soon as possible after ROSC, participants received the assigned regimen within 12 h of cardiac arrest. The treatment group received intravenous hydrocortisone (100 mg per dose; Cotisolu, Hanall Biopharma Co., Ltd., Seoul, South Korea), thiamine (200 mg per dose; Jeil Thiamine Hydrochloride Injection, Jeil Pharmaceutical Co., Ltd., Seoul, South Korea), and ascorbic acid (50 mg/kg; maximum single dose 3 g; Jeil Ascorbic Acid Injection, Jeil Pharmaceutical Co., Ltd., Seoul, South Korea). Study medications were administered intravenously every 12 h for 3 days (six total doses). If hydrocortisone was unavailable, a hydrocortisone-equivalent 100-mg dose of an alternative corticosteroid was permitted. The placebo group received identical-appearing 50-mL saline infusions on the same schedule.

Concomitant care

All patients received conventional post-resuscitation care in accordance with current international

guidelines.^{22,23} TTM was applied for at least 24 h according to each participating hospital's institutional protocol, within the protocol-permitted target range of 32–36 °C, and vasopressors or inotropes were administered to maintain a mean arterial pressure ≥ 65 mmHg. When clinically indicated, patients underwent coronary angiography and percutaneous coronary intervention, as well as other organ-supportive therapies according to the treating physician's judgement. Supplementation with ascorbic acid, thiamine, or corticosteroids was permitted only when deficiency or adrenal insufficiency was clinically suspected; additional corticosteroid use was allowed for patients requiring high-dose vasopressors, based on the physician's judgement. Neurological prognostication was performed according to contemporary international guidelines using a multimodal assessment and each participating hospital's institutional post-cardiac arrest care protocol. Decisions regarding withholding or withdrawal of life-sustaining treatment (WLST) were made by the treating clinical team in consultation with the legally authorised representative according to institutional practice; no trial-specific centralised WLST algorithm or independent adjudication was used.

Outcome measures

The primary outcome was the peak serum NSE concentration, defined as the higher of the NSE values measured at 48 h or 72 h after ROSC. Patients who died before 48 h were excluded from the primary analysis per protocol; if death occurred between 48 and 72 h, the 48-h NSE value was used. Serum NSE was measured at 24 h, 48 h, and 72 h after ROSC at all participating sites using the same commercial electrochemiluminescence immunoassay (Elecsys NSE®; Roche Diagnostics, Mannheim, Germany) according to site-standardised procedures. To ensure the validity of the primary endpoint, samples with significant haemolysis were censored based on automated indices reviewed by a blinded laboratory medicine specialist.²⁴

Prespecified secondary outcomes were Δ NSE, defined as the peak NSE level at 48 h or 72 h minus the level at 24 h after ROSC; and Δ Sequential Organ Failure Assessment (SOFA) score, defined as the SOFA score at enrolment minus the maximum score between 24 h and 72 h after ROSC, where negative values indicate worsening organ failure and a maximum score of 24 was imputed if death occurred within 72 h. Clinical outcomes comprised overall survival (assessed at 7, 30, 90, and 180 days and at hospital discharge), duration of survival (time to death), intensive care unit and hospital length of stay (censored at 180 days), and time to awakening, defined as days to first Glasgow Coma Scale >13 . Vasopressor-related outcomes were analysed as exploratory secondary outcomes. Maximum vasopressor dose was defined as the maximum norepinephrine-equivalent dose during the first 72 h

after ROSC. Vasopressor-free days through day 7 were defined as days alive and free from vasopressor support within the first 7 days after ROSC; patients who died within 7 days were assigned 0 vasopressor-free days. Neurological outcomes were evaluated using both the Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) at 30, 90, and 180 days by study investigators blinded to treatment allocation, following the standardised procedures of the Korean Hypothermia Network Prospective Registry (KORHN-PRO).²⁴ Both CPC and mRS were assessed using prespecified favourable-outcome thresholds of CPC 1–2 and mRS 0–2. When the classifications were discordant, the CPC classification determined the prespecified binary neurological outcome. After discharge, follow-up assessments were conducted by telephone with the participant when reliable communication was possible or, otherwise, with a family member primarily involved in the participant's care. Pharmacodynamic markers included serum vitamin C and thiamine concentrations measured by high-performance liquid chromatography at baseline and 72 h after ROSC.

Safety outcomes of interest included urticaria or rash, angioedema or anaphylaxis, vomiting or diarrhoea, gastrointestinal bleeding, ventilator-associated pneumonia, catheter-related infection, and uncontrolled hyperglycaemia. Serious adverse events were reported to institutional review boards of participating hospitals and regulatory authorities according to mandatory timelines. To avoid vitamin C-related pseudo-hyperglycaemia, capillary glucose metres were not used; instead, blood glucose was monitored via arterial or venous samples every 4 h during TTM through 72 h, following the KORHN-PRO protocol.²⁴

Statistical analysis

Sample size calculation was based on data from a national prospective multicentre registry among comatose OHCA survivors treated with TTM, where the mean peak NSE was 114 ng/mL (standard deviation [SD] 119 ng/mL). A conventional mean-difference framework was used for sample-size planning because the available registry data were summarised as mean and SD, whereas a rank-based calculation would have required additional assumptions about the distribution of peak NSE concentrations and the expected treatment effect. Given the exploratory nature of this phase 2 trial, the sample size was calculated to detect a clinically transformative effect size to justify a subsequent confirmatory phase 3 trial. Assuming a 50.0% reduction in the treatment group compared with the placebo group, a two-sided α of 0.05, and 80% power, we calculated that 68 patients per group were required. Accounting for a dropout rate of 15% due to early mortality (<48 h) or missing data, the target enrolment was set at 80 patients per group (total 160). No interim analyses for efficacy or futility were planned or performed.

Statistical analyses were performed on the modified intention-to-treat (mITT) and intention-to-treat (ITT) sets. The primary analysis was performed in the mITT set, which comprised patients who survived 48 h or longer after ROSC and had observed NSE levels at 48 h or 72 h ($n = 147$). The ITT set included all randomised patients ($n = 160$). The per-protocol (PP) population comprised participants who met the protocol-defined criteria for study completion without major protocol deviations; because all participants in the mITT population met these criteria, the PP and mITT populations were identical. Baseline characteristics were compared using standardised mean differences (SMDs), with values greater than 0.20 indicating potential imbalance.

The original full trial protocol (version 1.1, March 2021) provided a broad statistical framework. The subsequently published protocol, submitted before completion of enrolment, further specified the analysis populations, multiple-imputation sensitivity analysis, site-adjusted mixed-effects modelling, and subgroup framework. Before database lock and treatment unmasking, the final statistical analysis plan prespecified the outcome-specific methods used for the principal analyses: Wilcoxon rank-sum tests for the primary and continuous secondary outcomes, a linear mixed-effects model for serial NSE, χ^2 or Fisher's exact tests for binary outcomes, and log-rank analysis for overall survival.

Peak NSE concentrations were compared using the prespecified Wilcoxon rank-sum test because they were expected to be right-skewed and susceptible to extreme values, based on distributions observed in previous studies of patients after cardiac arrest.^{17,24} No formal normality testing of the trial data was used to select or modify this prespecified statistical method. The treatment effect was quantified using the Hodges–Lehmann estimator of the between-group location shift, with 95% confidence intervals (CIs). Serial NSE levels at 24 h, 48 h, and 72 h were analysed using linear mixed-effects models with recruitment site as a random effect and adjustments for prespecified fixed covariates (sex, initial rhythm, prior ischaemic stroke, chronic kidney disease, and the grade of the revised post-Cardiac Arrest Syndrome for Therapeutic hypothermia [rCAST] score)²⁵ and any additional baseline variables with an SMD >0.20 .

For binary secondary and safety outcomes, between-group differences were analysed using the chi-square test or Fisher's exact test and reported as risk differences with 95% CIs. Continuous secondary outcomes were compared using Wilcoxon rank-sum test and reported using Hodges–Lehmann estimates of between-group location shifts with 95% CIs. Overall survival was estimated using the Kaplan–Meier method and compared by the log-rank test. Although the original protocol included Bonferroni correction for multiple comparisons and subgroup analyses, the final statistical analysis plan, completed before database lock and

before treatment unmasking, prospectively specified that, if the primary outcome was not statistically significant, secondary and subgroup analyses would be treated as exploratory without formal multiplicity adjustment. Because the primary outcome was not statistically significant, these results are reported as point estimates with 95% CIs and nominal p values and should be interpreted as exploratory.

Subgroup analyses for the primary outcome, Δ NSE, and good neurological outcome at 180 days were prespecified in the final statistical analysis plan completed before database lock and treatment unmasking. The subgroup set was updated from the original full trial protocol in the subsequently published protocol and retained in the final plan; therefore, the reported subgroup analyses were not post hoc. Baseline NSE, 24-h NSE, and low-flow-time subgroups were not retained, with low-flow time replaced by total collapse time. The prespecified 48-h NSE subgroup was not reported because it was a post-randomisation biomarker closely related to the primary outcome, and the thiamine-deficiency subgroup was not analysed because no participant met the predefined criterion. Treatment-by-subgroup interaction tests were performed for the primary outcome and 180-day good neurological outcome. For Δ NSE, between-group comparisons were performed within each subgroup, but interaction testing was not performed because negative values precluded the planned log-transformed model. Subgroup analyses for thiamine deficiency were not performed because no participants met the predefined criterion for thiamine deficiency at baseline. Sensitivity analyses for the primary outcome were performed in the ITT population using multiple imputation for missing NSE values. Ten imputed datasets were generated using a Markov chain Monte Carlo method under the missing-at-random assumption, with the imputation model including the demographic, medical history, cardiac arrest, and post-resuscitation variables presented in Table 1. In each imputed dataset, peak NSE was natural-log transformed and analysed using linear regression; estimates were combined using Rubin's rules and exponentiated to obtain ratios of geometric means with 95% CIs. In post hoc sensitivity analyses, primary and secondary efficacy outcomes in the mITT population that did not already account for recruitment site were reanalysed with site as the stratification factor. All statistical tests were two-sided. For the primary outcome, a p value less than 0.05 was considered statistically significant. Analyses were performed using SAS (version 9.4), IBM SPSS Statistics (version 21.0), and R (version 3.6.1). An independent data and safety monitoring board reviewed safety data annually.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or

	Treatment (n = 80)	Placebo (n = 80)	Standardised mean difference
Demographic characteristics			
Age, years	59.0 (13.0)	57.8 (14.4)	0.09
Male	57 (71.3%)	66 (82.5%)	0.27
Medical history			
Hypertension	39 (48.8%)	33 (41.3%)	0.15
Diabetes mellitus	22 (27.5%)	27 (33.8%)	0.14
Previous myocardial infarction	6 (7.5%)	9 (11.3%)	0.13
Ischaemic heart disease	11 (13.8%)	14 (17.5%)	0.10
Arrhythmia	5 (6.3%)	9 (11.3%)	0.18
Heart failure	6 (7.5%)	3 (3.8%)	0.16
Previous ischaemic stroke	5 (6.3%)	2 (2.5%)	0.18
Chronic lung disease	3 (3.8%)	2 (2.5%)	0.06
Chronic kidney disease	4 (5.0%)	9 (11.3%)	0.23
Liver cirrhosis	1 (1.3%)	2 (2.5%)	0.09
Cancer	2 (2.5%)	1 (1.3%)	0.09
Previous PCI or CABG	6 (7.5%)	8 (10.0%)	0.09
Characteristics of the cardiac arrest			
Witnessed	61 (76.3%)	53 (66.3%)	0.22
Bystander CPR	65 (81.3%)	54 (67.5%)	0.32
Prehospital shockable rhythm	43 (53.8%)	47 (58.8%)	0.10
Prehospital defibrillation	45 (56.3%)	48 (60.0%)	0.08
No flow time, min	0 (0-4.0), n = 77	0.5 (0-3.0), n = 76	0.03
Resuscitation duration, min	27.5 (15.8-45.5), n = 78	30.0 (15.0-44.3), n = 78	0.11
Total collapse time, min	27.0 (15.0-45.0), n = 79	30.0 (15.0-45.0), n = 78	0.09
ROSC before ED admission	36 (46.2%), n = 78	34 (43.0%), n = 79	0.06
Extracorporeal cardiopulmonary resuscitation	3 (3.8%)	11 (13.8%)	0.36
Cardiac aetiology arrest	74 (92.5%)	76 (95.0%)	0.10
Post-resuscitation characteristics			
GCS after ROSC	3.0 (3.0-3.8)	3.0 (3.0-5.0)	0.08
ST-segment elevation on post-resuscitation ECG	11 (13.8%)	19 (23.8%)	0.26
Shock after ROSC	50 (62.5%)	51 (63.7%)	0.03
rCAST severity			0.20
Low	10 (12.5%)	12 (15.0%)	
Moderate	43 (53.8%)	35 (43.8%)	
High	27 (33.8%)	33 (41.3%)	
SOFA score	11.0 (10.0-12.0)	12.0 (11.0-14.0)	0.34
Time from cardiac arrest to the first study drug administration, hours	4.2 (2.1-6.3), n = 79	3.6 (2.5-5.8), n = 77	0.19
Time from randomisation to the first study drug administration, hours	1.0 (0.5-2.1)	1.1 (0.5-2.2), n = 79	0.03
Target temperature during post-resuscitation care, °C	35.0 (33.0-36.0)	35.0 (33.0-36.0)	0.13
Data are shown as median (interquartile range), mean (standard deviation), or number (%) as appropriate. Standardised mean differences are presented to describe baseline balance between the randomised groups. No hypothesis tests or p values were calculated for baseline characteristics. Abbreviations: CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; ECG, electrocardiography; ED, emergency department; GCS, Glasgow Coma Scale; rCAST, revised post-Cardiac Arrest Syndrome for Therapeutic hypothermia; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment.			

Table 1: Baseline characteristics and post-resuscitation care of the patients.

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 31, 2021, and Dec 7, 2024, 160 patients were randomised to treatment (n = 80) or placebo (n = 80) (Fig. 1). Thirteen patients were excluded from the primary analysis set due to unavailable NSE data.

Specifically, there were 12 deaths before 48 h (5 in the treatment group and 7 in the placebo group) and one unmeasurable value in the treatment group, yielding an mITT cohort of 147 patients (treatment, n = 74; placebo, n = 73). Final follow-up was completed for all survivors on June 6, 2025.

Baseline demographic and clinical characteristics were generally comparable between the groups in both the ITT (Table 1) and mITT populations (Appendix p 3). The mean age of the total population was 58.4 years

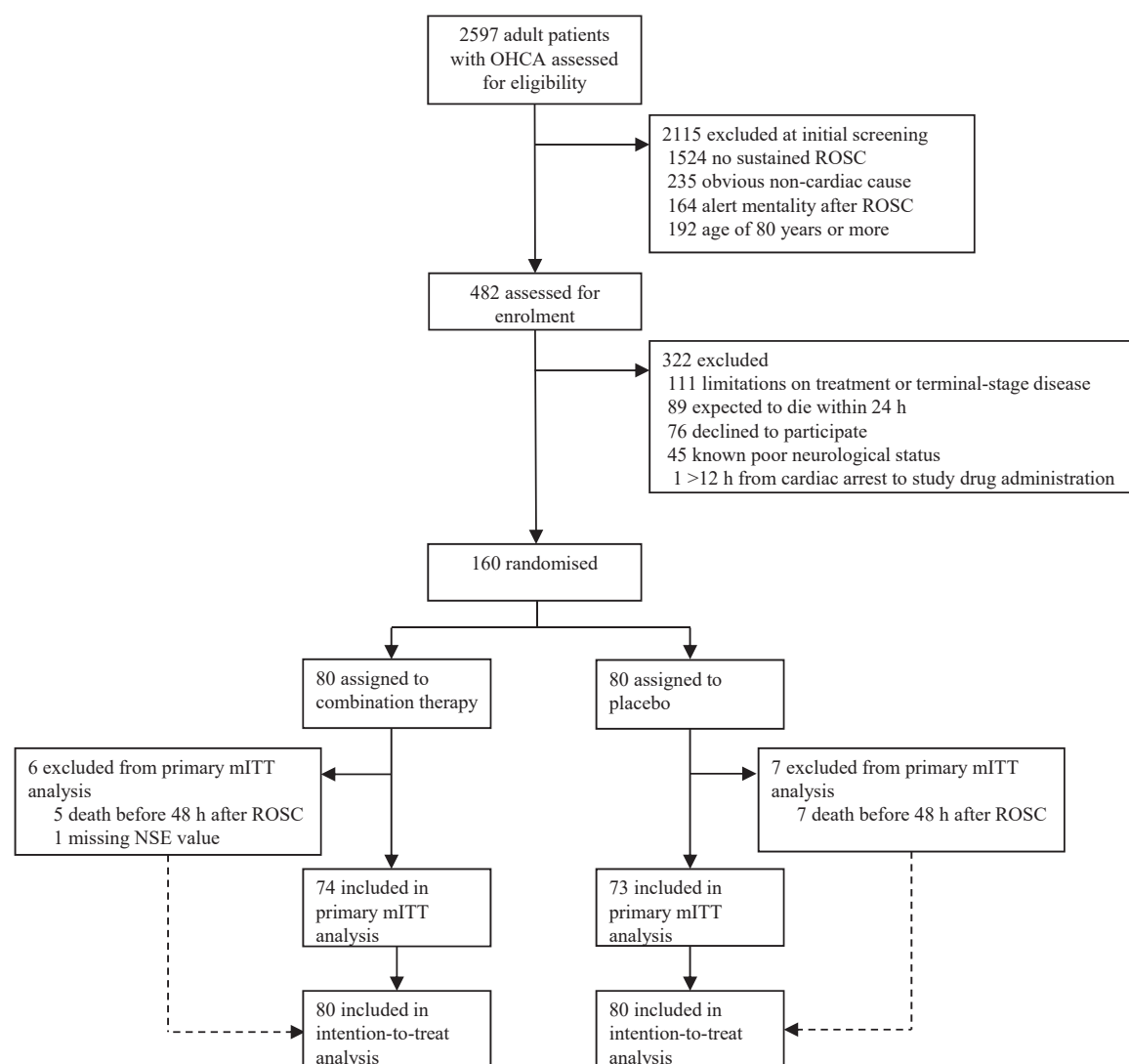


Fig. 1: Trial profile. Abbreviations: mITT, modified intention-to-treat; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

(SD 13.7), and 123 (76.9%) of 160 patients were men. Within the mITT cohort, the median time from cardiac arrest to the first study-drug administration was 3.9 h (interquartile range [IQR] 2.3–6.1), and the median target temperature during post-resuscitation care was 35.0 °C (IQR 33.0–36.0) in both groups (SMD 0.14). Among patients included in the mITT population, all completed six scheduled infusions. In the ITT population, six patients in the placebo group received open-label corticosteroids due to persistent shock, whereas no patients in the treatment group received additional open-label corticosteroids beyond the study protocol. Open-label thiamine outside the assigned study regimen was administered to three patients in the placebo group and none in the treatment group. All

patients who received open-label corticosteroids or thiamine were included in the mITT population. No patients in either group received open-label ascorbic acid. Serum vitamin C and thiamine concentrations were comparable at baseline and significantly higher in the treatment group at 72 h after ROSC (both $p < 0.0001$; [Appendix p 14](#)). No participants met the prespecified criterion for thiamine deficiency at baseline or at 72 h.

In the primary mITT analysis, peak NSE concentration did not differ significantly between the treatment and placebo groups ($p = 0.54$; [Table 2](#)). The ITT sensitivity analysis using multiple imputation yielded consistent results ($p = 0.80$). Key secondary clinical outcomes, including 180-day survival (mITT $p = 0.41$;

Outcome	Analysis Population	Treatment	Placebo	Effect Estimate (95% CI)	p-value
Primary outcome					
Peak NSE at 48 or 72 h, ng/mL	mITT (n = 74/73)	47.4 (22.4–262.6)	53.3 (26.6–244.2)	–5.9 (–34.5 to 40.8) ^a	0.54
	ITT sensitivity (n = 80/80) ^b	59.3 (23.1–300.0)	62.2 (31.1–319.2)	0.94 (0.61–1.46) ^c	0.80
Secondary outcomes					
180-day survival	mITT (n = 74/73)	47 (63.5%)	51 (69.9%)	–6.4% (–21.6 to 8.9) ^d	0.41
	ITT (n = 80/80)	49 (61.3%)	51 (63.8%)	–2.5% (–17.5 to 12.5) ^d	0.74
180-day good neurological outcome	mITT (n = 74/73)	40 (54.1%)	41 (56.2%)	–2.1% (–18.2 to 14.0) ^d	0.80
	ITT (n = 80/80)	41 (51.3%)	41 (51.3%)	0% (–15.5 to 15.5) ^d	>0.99
Safety outcome					
Patients with ≥1 SAE	mITT (n = 74/73)	39 (52.7%)	38 (52.1%)	0.7% (–15.5 to 16.8) ^d	0.94
	ITT (n = 80/80)	42 (52.5%)	40 (50.0%)	2.5% (–13.0 to 18.0) ^d	0.75

Values are expressed as median (interquartile ranges) or number (%) as appropriate. The mITT population was the primary analysis population for the primary outcome. Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) were assessed using prespecified favourable-outcome thresholds of CPC 1–2 and mRS 0–2, respectively. When the classifications were discordant, CPC determined the prespecified binary neurological outcome. Serious adverse events were defined as events leading to prolonged hospitalisation, life-threatening conditions requiring re-hospitalisation, or death. All-cause mortality was analysed as a secondary outcome and not counted as serious adverse events to avoid redundant reporting. All serious adverse events were assessed as unrelated or unlikely to be related to the study medication. Other specific serious adverse events are presented in [Tables S9 and S10](#). Abbreviations: CI, confidence interval; ITT, intention-to-treat; mITT, modified intention-to-treat; NSE, neuron-specific enolase; SAE, serious adverse event. ^aHodges-Lehmann estimate of the between-group location shift. ^bFor peak NSE analysis in ITT population, P values and 95% CIs were calculated using linear regression after natural logarithmic transformation (multiple imputation approach). Regression coefficients for the difference were exponentiated and interpreted as ratios of geometric means. Ten imputed datasets were generated using a Markov chain Monte Carlo (MCMC) method under the missing at random (MAR) assumption. The imputation model incorporated all variables listed in [Table 1](#), including demographics, medical history, cardiac arrest characteristics, and post-resuscitation data. Parameter estimates were combined using Rubin's rules implemented in PROC MIANALYZE (SAS Institute Inc.). ^cGeometric mean ratio. ^dRisk difference. Risk differences are shown as percentage-point differences.

Table 2: Key efficacy and safety outcomes in mITT and ITT populations.

ITT $p = 0.74$) and 180-day good neurological outcome (mITT $p = 0.80$; ITT $p > 0.99$), were also similar between groups. The complete ordinal distributions of 180-day CPC and mRS scores are presented in [Figure S2](#) for both the mITT and ITT populations ([Appendix p 15](#)). Δ NSE did not differ between groups in the mITT population ($p = 0.84$). Other secondary outcomes were also similar between groups, including Δ SOFA score (mITT $p = 0.99$; ITT $p = 0.86$), time to awakening (mITT $p = 0.15$; ITT $p = 0.11$), and ICU length of stay (mITT $p = 0.56$; ITT $p = 0.73$) and hospital length of stay (mITT $p = 0.51$; ITT $p = 0.42$; [Appendix p 5](#), [Appendix p 6](#)). Exploratory vasopressor-related outcomes, including vasopressor-free days through day 7 (mITT $p = 0.78$; ITT $p = 0.65$) and maximum norepinephrine-equivalent dose within the first 72 h after ROSC (mITT $p = 0.45$; ITT $p = 0.23$), also showed no clear between-group differences in either population ([Appendix p 5](#), [Appendix p 6](#)). The site-adjusted sensitivity analysis of peak NSE yielded a consistent result ($p = 0.47$), and site adjustment did not materially alter the findings for the secondary efficacy outcomes ([Appendix p 7](#)).

Subgroup analyses showed no clear evidence of heterogeneity in treatment effect across the reported subgroups for the primary outcome ([Fig. 2](#), [Appendix p 8](#)). A borderline interaction by sex was observed (p for interaction = 0.06). Subgroup analyses for Δ NSE and good neurological outcome showed no clear evidence of between-group differences across the reported subgroups ([Appendix p 9](#), [Appendix p 10](#)). Subgroup

analysis by baseline thiamine deficiency was not performed because no participants were thiamine-deficient at baseline. Baseline variables with standardised mean differences >0.20 were additionally included in the prespecified mixed-effects model for serial NSE trajectories. In this adjusted model, there was no significant treatment-by-time interaction during the first 72 h after ROSC (p for interaction = 0.85; [Fig. 3](#)). Overall survival through 180 days did not differ between the groups (log-rank $p = 0.39$; [Appendix p 16](#)).

The proportion of patients experiencing at least one serious adverse event was similar between groups in both the mITT and ITT populations ([Table 2](#)). Detailed safety outcomes are summarised in [Tables S9 and S10](#). No adverse events were adjudicated as probably or definitely related to study medication. WLST occurred in 8 (10.8%) patients in the treatment group and 5 (6.8%) in the placebo group, with no clear between-group difference in its frequency or timing ([Appendix p 13](#)).

Discussion

In this multicentre randomised trial involving comatose OHCA survivors, early administration of a combination of hydrocortisone, ascorbic acid, and thiamine during the post-resuscitation period did not significantly reduce peak NSE concentrations at 48 or 72 h compared with placebo. Consistent with this neutral biomarker effect, secondary outcomes, including survival, neurological recovery, and ICU and hospital length of stay, were similar between groups. Although the

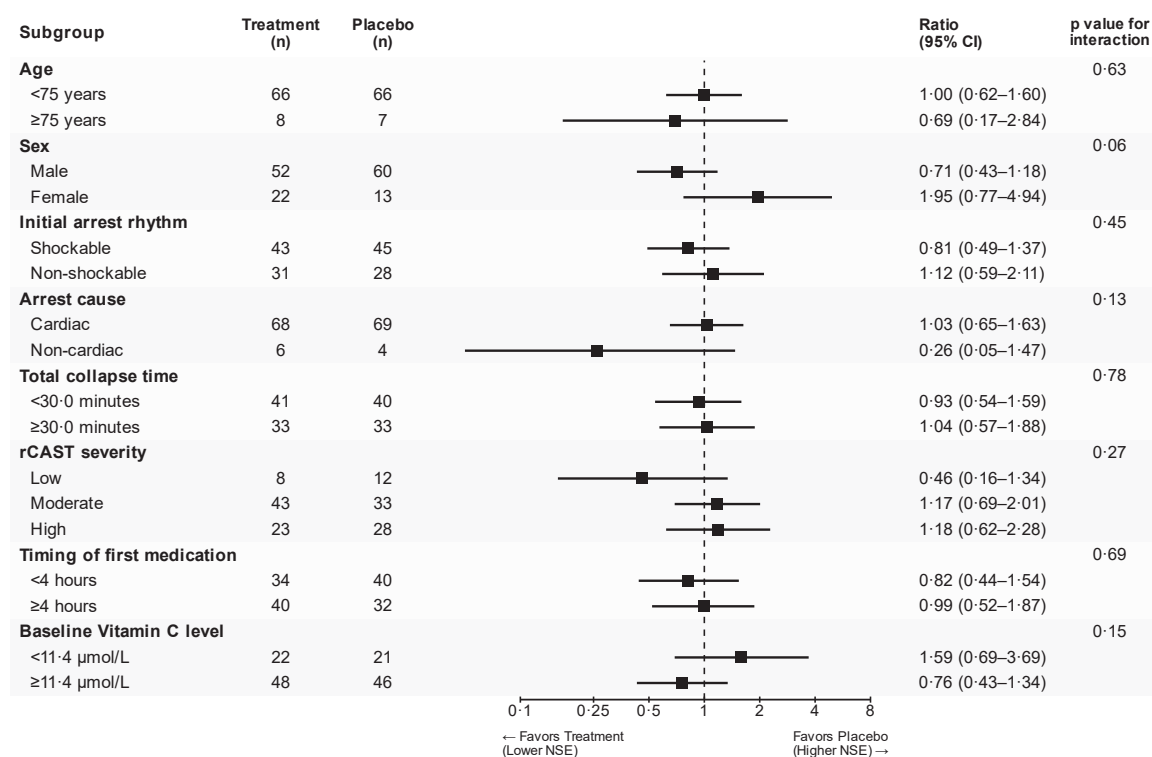


Fig. 2: Subgroup analysis of peak neuron-specific enolase levels. Points indicate geometric mean ratios (treatment vs placebo) for peak neuron-specific enolase (NSE) concentration at 48 h or 72 h, and horizontal lines indicate 95% confidence intervals. p values for interaction represent the heterogeneity of treatment effect across subgroups. The subgroup defined by NSE level at 48 h after ROSC was included in the original statistical analysis plan but was not reported because it was a post-randomisation biomarker closely related to the primary outcome. Abbreviations: CI, confidence interval; rCAST, revised post-Cardiac Arrest Syndrome for Therapeutic hypothermia; ROSC, return of spontaneous circulation.

intervention achieved significantly higher serum vitamin C and thiamine concentrations, this biochemical improvement did not translate into measurable neuroprotection in the overall study population. These findings were consistent across the ITT sensitivity analysis and serial biomarker models.

Our neutral findings should be considered alongside accumulating evidence that pharmacological administration of vitamin C or thiamine might not be benign in critically ill or post-cardiac arrest populations. The VITAMINS trial showed no benefit of treatment with intravenous vitamin C, hydrocortisone, and thiamine in patients with septic shock.¹⁸ In the LOVIT trial, intravenous vitamin C increased the risk of death or persistent organ dysfunction at 28 days in adults with sepsis receiving vasopressor therapy in the ICU.²⁶ The VITaCCA trial found no reduction in organ dysfunction after OHCA and reported worse organ-function, myocardial, renal, and neurological outcomes with the supraphysiological 10 g/day regimen.²⁷ A randomised trial of high-dose vitamin C in adults with severe burns was also terminated early after crossing a prespecified futility or harm threshold.²⁸ With respect to thiamine,

two phase 2 trials in in-hospital cardiac arrest and OHCA survivors showed no improvement in lactate levels and were terminated after mortality signals differing by baseline lactate raised safety concerns.^{29,30} Although these studies differed in patient population, treatment regimen, and dose, and some safety signals were observed with higher vitamin C doses than those used in the STAR trial, their findings caution against assuming that pharmacological vitamin administration is necessarily beneficial or inherently safe.

The regimen was intended to target inflammatory, oxidative, endothelial, and metabolic components of PCAS. Because all participants received TTM, which may itself modulate cerebral metabolism and inflammatory and oxidative responses, the trial evaluated the incremental effect of the study regimen beyond these background effects. This biological overlap might have reduced any additional treatment effect. However, increased serum vitamin concentrations confirmed systemic exposure but not biological target engagement, and pathway-specific biomarkers were not measured. The trial therefore cannot determine whether the intended pathways were not engaged or

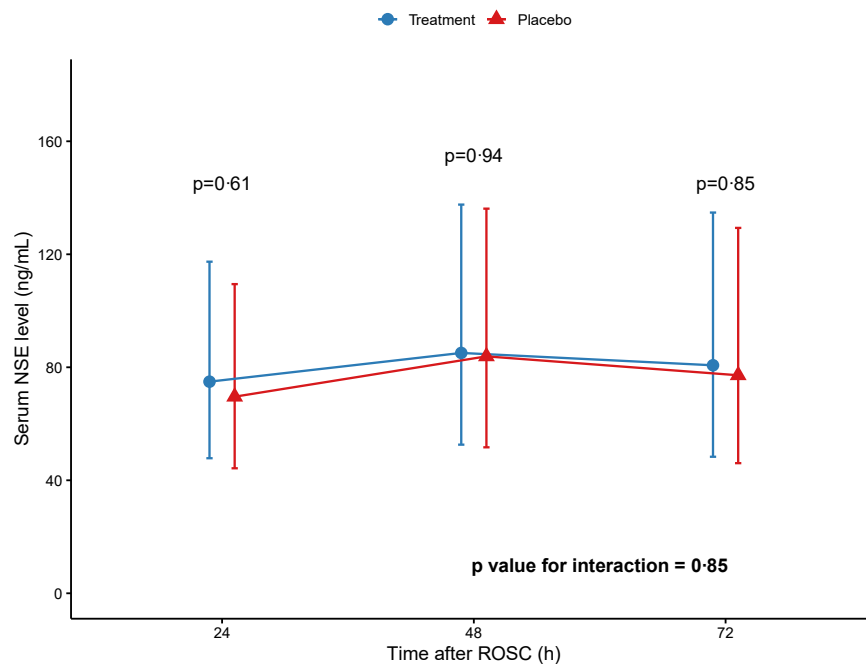


Fig. 3: Serial changes in serum neuron-specific enolase levels during the first 72 h after return of spontaneous circulation. Data are estimated marginal means with 95% confidence intervals from a linear mixed-effects model in the modified intention-to-treat population ($n = 147$), adjusted for recruitment site and baseline imbalances. Abbreviations: NSE, neuron-specific enolase; ROSC, return of spontaneous circulation.

whether their modulation was insufficient to prevent neuronal injury. Biological heterogeneity might also have contributed: no participant had baseline thiamine deficiency, and vitamin C deficiency was present in only 31.4%. Subgroup analyses provided no clear evidence of treatment-effect heterogeneity by vitamin C status (Appendix p 8); however, the trial was not powered for interaction testing, and the inclusion of only 43 participants with vitamin C deficiency limited the precision of this analysis. Clinically meaningful differences in treatment effect according to vitamin C status therefore cannot be excluded.

A strength of our trial was the measurement of baseline vitamin C and thiamine concentrations before study-drug administration, enabling characterisation of pretreatment micronutrient status and prespecified subgroup analyses. Treatment was also initiated relatively early, at a median of 3.9 h after ROSC, compared with previous in-hospital intervention studies.^{11,18,19} Nevertheless, neuronal injury pathways might already have been established by this time. Given the neutral findings, earlier administration of the same empiric regimen cannot be assumed to improve outcomes. Future research should distinguish physiological replacement of objectively confirmed deficiency from pharmacological dosing and prioritise biologically validated targets, prospective confirmation of target engagement, and rigorous safety assessment.

Several limitations must be acknowledged. First, death before 48 h after ROSC precluded NSE assessment in five patients in the treatment group and seven in the placebo group. Excluding these early deaths from the mITT analysis may have introduced survivor-selection bias, although their frequency was similar between groups and the ITT sensitivity analysis yielded concordant results. Because NSE concentrations after death are unobservable, residual bias cannot be excluded. Second, although all participating sites used the same commercial NSE assay and site-standardised procedures, residual inter-laboratory variability may have increased measurement error and reduced the precision of the treatment-effect estimate. However, site-stratified randomisation reduced the likelihood of differential measurement bias between groups. Third, bedside clinicians and nurses administering the assigned infusions were aware of treatment allocation; however, legal representatives, laboratory personnel, and independent outcome assessors were blinded. Although WLST frequency and timing were similar between groups, neuroprognostication and WLST decisions were not centrally standardised or independently adjudicated, and residual influence on survival and long-term neurological outcomes cannot be excluded. Fourth, open-label co-interventions occurred in the placebo group, including corticosteroids in 8.2% (6/73) and thiamine in 4.1% (3/73) of patients in the

mITT population, potentially diluting between-group differences and biasing treatment-effect estimates toward the null. Fifth, the trial was powered to detect a 50% reduction in peak NSE and not to assess treatment-by-subgroup interactions. This optimistic effect-size assumption was selected to represent a substantial reduction from the registry mean of 114 ng/mL towards the approximately 60 ng/mL threshold incorporated into contemporary neuroprognostication guidelines. The use of a conventional mean-difference framework for sample-size planning and a non-parametric primary analysis may have affected statistical power. The observed between-group difference was small and did not support an effect of the magnitude assumed in the sample-size calculation, although smaller overall and subgroup-specific treatment effects cannot be excluded. Finally, enrolment was limited to four South Korean centres and to Korean adults aged 19–79 years with presumed cardiac-cause OHCA who underwent TTM. The findings might therefore not be generalisable to broader OHCA populations, including older patients, those with non-cardiac causes of arrest, those not receiving TTM, or populations in other countries and health-care settings, where sociocultural, dietary, socioeconomic, structural, and health-system factors may differ.

In conclusion, early intravenous administration of hydrocortisone, thiamine, and ascorbic acid did not significantly reduce peak NSE concentrations or improve clinical outcomes in comatose OHCA survivors, despite achieving clear pharmacodynamic effects. These findings do not support routine use of this combination therapy as a neuroprotective adjunct in an unselected post-cardiac arrest population.

Contributors

Y-J Kim and WY Kim were responsible for conceptualisation and methodology. HJ Kwon, BS Ko, Y-I Roh, K-C Cha, and YH Kim were responsible for investigation, resources, and data curation. S Kim was responsible for formal analysis and validation. Y-J Kim was responsible for writing—original draft. WY Kim was responsible for supervision, and project administration. Y-J Kim and WY Kim were responsible for funding acquisition. All authors were responsible for writing—review & editing. YH Kim and WY Kim have directly accessed and verified the underlying data reported in the manuscript. All authors had access to the study data, and the corresponding author had final responsibility for the decision to submit for publication.

Data sharing statement

Deidentified individual participant data, along with a data dictionary defining each field and the statistical code used for the analysis, will be made available upon reasonable request. Additional related documents, including the study protocol and statistical analysis plan, will also be available. These data will be shared with researchers who provide a methodologically sound proposal for the purpose of individual participant data meta-analysis. Data will be available beginning with publication and ending 5 years following publication. To gain access, data requestors will need to sign a data access agreement. Requests should be directed to the corresponding author at wonpia73@naver.com.

Declaration of interests

We declare no competing interests.

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During the preparation of this manuscript, the authors used Gemini (Google) to refine the language and tone. Following the use of this tool, the authors reviewed and edited the content to ensure accuracy and take full responsibility for the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2026.104191>.

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