



Original Article

Development, Implementation, and Clinical Outcomes of A Therapeutic Hypothermia Management Protocol for Patients with Neurocritical Illness: A Before-and-after Study



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Abstract

Background and objectives: Therapeutic hypothermia (TH) is widely used as a neuroprotective strategy, but variability in bedside implementation may limit its optimal application. This study aimed to develop a standardized TH management protocol for patients with neurocritical illness and evaluate the clinical outcomes associated with its implementation.

Methods: An evidence-based TH protocol was developed through a two-round Delphi consensus process. A subsequent observational before-and-after study included 244 patients with neurocritical illness receiving TH. The historical control group ($n = 120$) received routine care, whereas the TH protocol group ($n = 124$) was managed according to the standardized protocol. No single primary endpoint was prespecified for the final comparative analysis. Outcomes were interpreted as exploratory and included temperature-management process indicators, individual TH-related complications requiring intervention, and neurological outcomes assessed using the Glasgow Outcome Scale.

Results: Protocol implementation was associated with more favorable temperature-management process indicators, including earlier TH initiation, a shorter recorded time to target temperature, fewer unplanned treatment interruptions, a longer controlled rewarming phase, and greater adherence to rewarming criteria. In exploratory analyses, the TH protocol group had lower incidences of selected TH-related complications and more favorable Glasgow Outcome Scale outcomes at discharge than the historical control group.

Conclusions: Implementation of a consensus-derived TH management protocol was associated with more consistent temperature-management processes, fewer selected TH-related complications, and more favorable short-term neurological outcomes. These findings support prospective evaluation of protocolized TH management in larger multicenter cohorts.

Keywords: Therapeutic hypothermia; Targeted temperature management; Neurocritical care; Delphi technique; Quality improvement; Neurological outcome.

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Introduction

Patients with severe neurological conditions may experience central thermoregulatory impairment and fever, making fever management a common component of neurocritical care.¹⁻³ Fever is associated with secondary brain injury mechanisms, including increased cerebral metabolic demand, inflammatory activation, oxidative stress, blood-brain barrier disruption, and cerebral edema.⁴⁻⁶ These processes may worsen localized cerebral hypoxia and accelerate neuronal apoptosis, highlighting the need for timely

and effective temperature control in neurocritical care.

Targeted temperature interventions are clinically important for mitigating these secondary injury pathways. Hypothermia may exert neuroprotective effects by reducing cerebral metabolic demand, attenuating inflammatory responses, and limiting secondary neuronal injury.⁶ Therapeutic hypothermia (TH) is a controlled clinical process that combines physical cooling methods with pharmacologic interventions to lower core body temperature to a predetermined target range. After the maintenance period, patients are gradually rewarmed at a controlled rate to reduce the risk of secondary temperature instability. TH may be used to suppress refractory fever, maintain normothermia, or actively induce hypothermia. International guidelines and consensus recommendations,^{1-3,7} together with Chinese expert consensus documents and evidence summaries,⁸⁻¹¹ recognize temperature management as an important supportive strategy in selected neurocritical populations.

Although TH has shown neuroprotective potential in selected clinical contexts, its standardized implementation remains challenging because targeted temperature management (TTM) is a complex intervention requiring standardized cooling methods, temperature monitoring, shivering control, sedation, maintenance, and rewarming procedures.^{1,12} In routine clinical practice, barriers such as low protocol adherence, variable target-temperature control, and a lack of standardized operating procedures persist. Nurses play a central role in all stages of TH delivery; however, adherence to TTM protocols and consistency of bedside implementation remain important challenges in intensive care unit (ICU) nursing practice.^{13,14} To address these clinical gaps, this study used an evidence-based nursing approach to develop a standardized and practical TH management protocol for patients with severe neurological conditions. Using an observational before-and-after design, we then evaluated clinical outcomes associated with protocol implementation.

Materials and methods

This study was conducted in two sequential phases. Phase 1 involved the development of a TH management protocol using an evidence-based nursing framework and the Delphi method. Phase 2 used a nonrandomized before-and-after design to evaluate clinical outcomes associated with protocol implementation in a neurosurgical ICU.

Phase 1: Protocol development

Research team assembly

A multidisciplinary protocol-development team was established, comprising one chief nurse, one associate chief nurse, one chief physician, one attending physician, six senior clinical nurses, and two graduate students. The team was responsible for literature retrieval, evidence appraisal, questionnaire design, Delphi consultation management, and protocol finalization.

Literature search and quality appraisal

Based on the “5S” evidence-pyramid model, we searched major biomedical databases, guideline repositories, and evidence-based resources from inception to May 16, 2024, to identify relevant clinical guidelines, expert consensus statements, systematic reviews, and evidence summaries on targeted temperature man-

agement. We searched the following English-language databases: PubMed, MEDLINE (Ovid), EMBASE (Elsevier), Web of Science (Clarivate), the Cochrane Library, and the JBI EBP Database. We also searched guideline repositories, including UpToDate, BMJ Best Practice, NICE, RAO, SIGN, and GIN, as well as professional-society websites. Chinese databases included CNKI, Wanfang Data, SinoMed, and Medlive. The search strategy combined free-text terms across four domains according to the PIOS framework: population, intervention, outcome, and study design. Detailed Boolean search strategies for all databases are provided in [Supplementary File 1](#). We screened the retrieved records using predefined criteria. Documents were eligible if they focused on patients aged 18 years or older with neurocritical illness, addressed temperature-management practices, and were clinical guidelines, evidence summaries, systematic reviews, or expert consensus statements. As shown in [Figure 1](#), eight core publications were included: four guidelines,^{1-3,7} three expert consensus documents,⁸⁻¹⁰ and one evidence summary.¹¹ Two researchers independently appraised the methodological quality of the included literature. The guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and received high methodological-quality ratings.¹⁵ The consensus statements and evidence summaries were assessed using JBI appraisal tools and evidence-synthesis guidance.^{16,17} All eight documents were judged sufficiently rigorous to inform the protocol.

Delphi expert consultation

To ensure clinical applicability, we used purposive sampling to recruit 20 multidisciplinary experts from several tertiary hospitals in accordance with established Delphi methods.¹⁸⁻²² Medical experts were required to hold a doctoral degree, have the professional title of associate chief physician or higher, and have at least 10 years of clinical experience. Nursing experts were required to have at least a bachelor's degree, a senior nursing title, and equivalent specialized experience. According to institutional requirements, the Delphi expert consultation did not require separate ethics approval. All experts provided written informed consent before participation. The Delphi questionnaire comprised four sections: an introduction, a quantitative evaluation in which experts rated protocol items on a 5-point Likert scale, a demographic survey, and a self-assessment matrix. To minimize peer influence, the consultation was conducted anonymously by email. After the first round, items with an importance score above 3.5 and a coefficient of variation below 0.25 were retained. The core research team reviewed items that did not meet these thresholds and modified them according to their clinical relevance. This iterative process continued until consensus was reached.

Phase 2: Clinical implementation and evaluation

Study setting and population

This observational, non-randomized before-and-after study was conducted in the neurosurgery ICU of a tertiary hospital in Hubei Province, China. The standardized TH protocol was implemented at the unit level as the routine clinical pathway from July 2024. The decision to initiate TH was made by the treating physicians according to clinical indications and independently of study enrollment; the investigators did not assign individual patients to TH

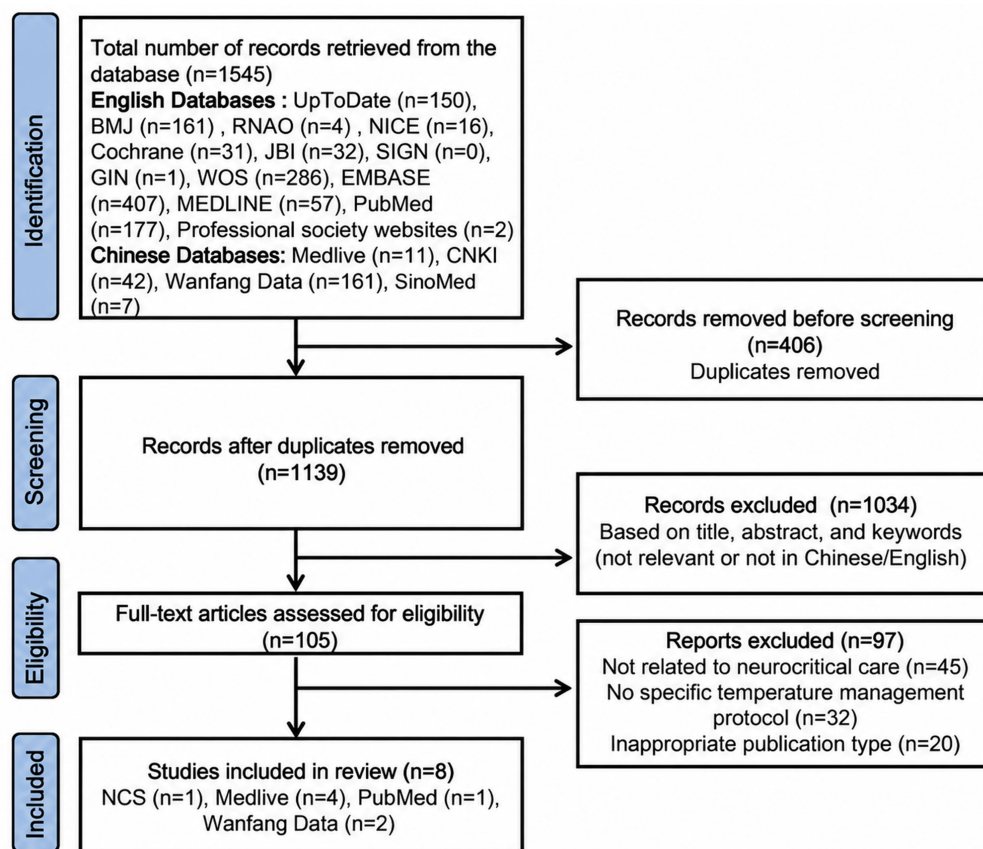


Fig. 1. Literature retrieval and screening flow diagram. BMJ, British Medical Journal; CNKI, China National Knowledge Infrastructure; EMBASE, Excerpta Medica Database; GIN, Guidelines International Network; JBI, Joanna Briggs Institute; MEDLINE, Medical Literature Analysis and Retrieval System Online; NCS, Neurocritical Care Society; NICE, National Institute for Health and Care Excellence; RNAO, Registered Nurses' Association of Ontario; SIGN, Scottish Intercollegiate Guidelines Network; WOS, Web of Science.

for research purposes or allocate patients between study groups. Accordingly, the clinical evaluation comprised a retrospective pre-implementation historical cohort and a prospectively observed post-implementation cohort. Patients admitted between January and June 2024 were included in the historical control group, whereas those admitted between July and December 2024, after implementation of the standardized TH protocol, were included in the TH protocol group.

The clinical evaluation phase was approved by the Medical Ethics Committee of Union Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology (approval No. 20240979-01; approved June 3, 2024). The requirement for individual informed consent was waived for the retrospective historical control group under institutional ethics requirements. For patients enrolled during the prospective implementation phase, written informed consent was obtained from patients or their legally authorized representatives.

Inclusion criteria were adult patients (≥ 18 years) requiring TH for severe neurological conditions (e.g., severe traumatic brain injury, central hyperthermia, post-cardiac arrest coma, or extensive cerebral infarction). We excluded patients with severe sepsis or septic shock, uncorrected hemorrhagic shock or active

bleeding, spontaneous hypothermia ($<35.5^{\circ}\text{C}$ at admission), terminal or moribund conditions, pregnancy, or other prespecified contraindications to TH. Patients with missing key screening data were also excluded. The participant screening, exclusion, grouping according to admission period, and final analysis process is summarized in [Figure 2](#).

Sample size calculation

The sample size calculation was based on preliminary quality-improvement data collected in our ICU before implementation of the standardized TH management protocol. Because this study aimed to evaluate clinical outcomes associated with protocol standardization, the calculation used the incidence of clinically significant TH-related complications requiring intervention. In the preliminary audit, the incidence of clinically significant TH-related complications during routine TH management was estimated at 26.31% ($p1$). Based on the anticipated improvement after implementation of the standardized TH management protocol, we assumed that this incidence would decrease to 3.51% ($p2$). These estimates were derived from preliminary clinical observations and were used solely for sample size calculation rather than as a prespecified composite endpoint for the final comparative analysis. Therefore, no single primary endpoint was

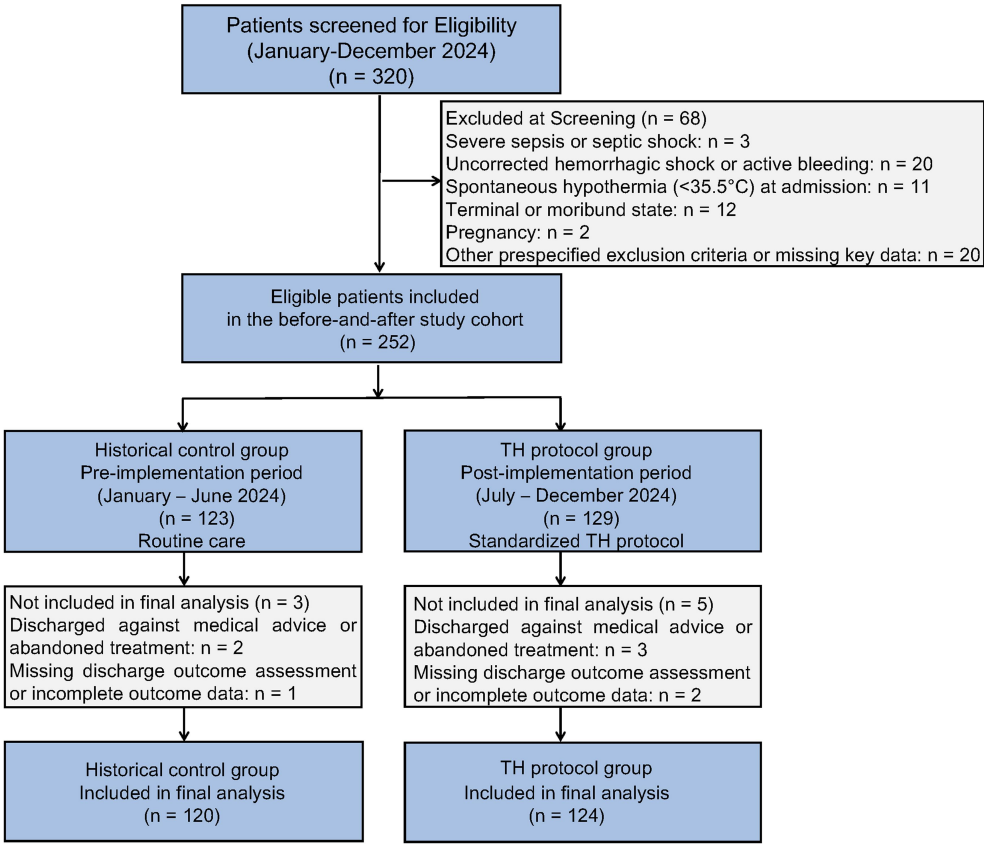


Fig. 2. Participant flow diagram for the before-and-after clinical evaluation phase. Patients admitted from January to June 2024 were included in the historical control group; those admitted from July to December 2024 were included in the TH protocol group. TH, therapeutic hypothermia.

prespecified for the final comparative analysis, and all comparative outcomes were interpreted as exploratory and hypothesis-generating. The sample size was calculated using PASS software with a two-sided α level of 0.05 and 80% statistical power. The minimum required sample size was 45 patients per group. Allowing for 15% attrition or incomplete data, the target sample size was increased to at least 53 patients per group.

Intervention strategies

The historical control group received routine temperature management based on standard physician orders. This typically involved conventional cooling blankets and intermittent axillary temperature monitoring using mercury thermometers, with treatment discontinuation based on clinical judgment. In the historical control group, target temperature was determined by the treating physician and documented in physician orders when available; selection and documentation were not standardized. In the TH protocol group, target temperature was selected according to the patient’s clinical condition and the standardized protocol, which permitted a range of 32.0–36.0°C. The protocol group underwent continuous core-temperature monitoring, whereas the historical control group was monitored intermittently using axillary thermometers. A dedicated TH nursing team was

established and trained before implementation. The protocol required continuous core-temperature monitoring, a target temperature range of 32.0–36.0°C to be achieved within 2–4 h, a maintenance period of at least 24 h, and controlled rewarming at 0.10–0.25°C/h. In addition, evidence-based prevention bundles were implemented for complications such as shivering and deep vein thrombosis.

Outcome measures and data collection

To describe the baseline characteristics of the historical control and TH protocol cohorts, demographic and clinical data were collected from medical records and prospective implementation records, including age, sex, educational level, health insurance type, primary diagnosis, admission temperature, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, admission Glasgow Coma Scale (GCS) score, surgery, and mechanical ventilation status. No single primary endpoint was prespecified for the final comparative analysis. For reporting purposes, comparative outcomes were interpreted as exploratory and organized into three domains: (1) temperature-management process indicators, (2) individual TH-related complications requiring intervention, and (3) neurological outcomes.

First, temperature-management process indicators included time from admission to TH initiation, time to target temperature,

achievement of the target temperature within 4 h, duration of TH maintenance, unplanned treatment interruptions, duration of controlled rewarming, and adherence to rewarming criteria. Time from admission to TH initiation was defined as the interval between hospital admission and the documented start of TH. Time to target temperature was defined as the interval between TH initiation and the first documented temperature within the prespecified target range. Achievement of the target temperature within 4 h was defined as reaching the prespecified range within 4 h after TH initiation. An unplanned treatment interruption was defined as unintended discontinuation or suspension of TH before completion of the planned treatment period because of clinical instability, device-related problems, or other reasons outside the protocol. Adherence to rewarming criteria was defined as initiation and completion of rewarming according to prespecified protocol criteria, including appropriate clinical readiness and adherence to the controlled rewarming rate of 0.10–0.25°C/h. In the historical control group, temperature-related parameters were extracted from routine nursing records based on intermittent axillary temperature measurements. In the TH protocol group, these parameters were obtained from continuous core-temperature monitoring records and standardized TH nursing flow sheets. Because the groups underwent different temperature-monitoring strategies, these process indicators may have been influenced by differences in measurement site and recording frequency.

Second, individual TH-related complications requiring intervention were assessed separately, including shivering, electrolyte disturbance, deep vein thrombosis, and gastrointestinal dysfunction. The same prespecified clinical definitions were applied during both study periods. In the historical control group, complication data were retrospectively extracted from electronic medical records and related clinical documentation. In the TH protocol group, routine lower-extremity Doppler ultrasonography was performed as part of the prevention and surveillance bundle, whereas Doppler ultrasonography in the historical control group was performed when clinically indicated. Shivering was documented only when escalation of pharmacologic sedation was required (e.g., Bedside Shivering Assessment Scale ≥ 2). Electrolyte disturbance was defined as a clinically significant electrolyte abnormality requiring medical correction during TH. Deep vein thrombosis was defined as newly diagnosed venous thrombosis confirmed by Doppler ultrasonography during hospitalization. Gastrointestinal dysfunction was defined as severe feeding intolerance requiring cessation of enteral nutrition for more than 24 h. Patients could experience more than one TH-related complication and could therefore be included in multiple categories; however, each complication was analyzed separately according to its prespecified clinical definition. Third, neurological outcomes at hospital discharge were assessed using the Glasgow Outcome Scale (GOS).²³ GOS grade distribution, favorable neurological outcome (GOS grades IV–V), and overall GOS score were evaluated. Two senior clinicians who were not involved in TH protocol implementation independently assessed GOS scores from discharge records to minimize observer bias. Disagreements were resolved through discussion; if consensus could not be reached, a third senior clinician adjudicated the final GOS score. The assessors were blinded to the study hypothesis and group-level outcomes. Because this was a before-and-after study, complete

blinding to the admission period was not feasible.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0. Continuous variables are presented as the mean $\pm$ standard deviation and were compared using independent-samples *t* tests or Mann–Whitney *U* tests, as appropriate. Categorical variables are presented as frequencies and percentages and were compared using the Pearson chi-square test or Fisher exact test. Expert agreement in the Delphi process was evaluated using Kendall's *W*. For all exploratory comparative outcomes, unadjusted effect estimates, including odds ratios (ORs), mean differences (MDs), and 95% confidence intervals (CIs), were calculated as appropriate. For individual TH-related complications, unadjusted ORs were reported. Because shivering, deep vein thrombosis, and gastrointestinal dysfunction had few events relative to the number of model parameters, multivariable adjustment was not performed for these outcomes. Multivariable logistic regression was performed for electrolyte disturbance and favorable GOS outcome. Ordinal logistic regression was used for GOS grade distribution, and multivariable linear regression was used as a sensitivity analysis for overall GOS score. The proportional-odds assumption for the ordinal logistic regression model was assessed using a likelihood-ratio test comparing the proportional-odds model with a model allowing threshold-specific coefficients. Adjusted models included age, primary diagnosis, APACHE II score, admission GCS score, surgery, and mechanical ventilation as covariates. All comparative analyses were interpreted as exploratory because no single primary endpoint was prespecified. Statistical significance was defined as a two-sided *P* value < 0.05 .

Results

Results of expert consultation

Expert profile, engagement, and authority

The panel comprised 20 experts in neurosurgical medicine, neurosurgical nursing, emergency medicine and nursing, critical care nursing, and neurosurgical nursing management. The mean age was 41.45 ± 4.88 years, and the mean duration of professional experience was 20.10 ± 6.24 years. Nearly half of the experts held associate senior professional titles or higher. The response rate was 100% in both consultation rounds. The authority coefficient, which reflects the experts' familiarity with the subject and the basis for their clinical judgments, was 0.833 in the first round and 0.910 in the second round, indicating high self-reported expert authority (Table 1).

Table 1. Authority coefficients of experts across two consultation rounds

Round	Ca	Cs	Cr
Round 1	0.925	0.740	0.833
Round 2	0.960	0.860	0.910

Ca, basis for clinical judgment; Cr, overall authority coefficient, calculated

as $Cr = (Ca + Cs)/2$; Cs, degree of familiarity with the subject

Degree of expert agreement and final protocol formulation

Consensus among the experts was evaluated using Kendall's coefficient of concordance (*W*). After the two consultation rounds, Kendall's *W* values were 0.206 ($\chi^2 = 234.518$, $P < 0.001$) and 0.301 ($\chi^2 = 349.083$, $P < 0.001$), respectively, indicating statistically significant concordance that increased between rounds (Table 2). After the first round, minor adjustments were made in response to qualitative suggestions, including the addition of specific rewarming-equipment requirements and more specific clinical-assessment parameters and the consolidation of health-education items. No further modifications were required after the second round. The finalized TH management protocol comprised 3 first-level items, 15 second-level items, and 41 third-level items (Table 3).

Table 2. Degree of agreement among experts across two rounds

Round	Kendall's <i>W</i>	χ^2	<i>P</i> value
Round 1	0.206	234.518	< 0.001
Round 2	0.301	349.083	< 0.001

A two-sided *P* value < 0.05 was considered statistically significant. *W*, Kendall's coefficient of concordance.

Clinical outcomes evaluation

Participant flow and baseline characteristics

A total of 320 patients were screened for eligibility between January and December 2024. After the exclusion of 68 patients at screening, 252 eligible patients were included in the before-and-after cohort, comprising 123 patients in the historical control group and 129 patients in the TH protocol group. Eight patients were not included in the final analysis because of discharge against medical advice or treatment abandonment ($n = 5$) or missing or incomplete discharge outcome data ($n = 3$). Consequently, 244 patients were included in the final analysis, comprising 120 patients in the historical control group and 124 patients in the TH protocol group (Fig. 2). Table 4 summarizes baseline demographic and clinical characteristics. No statistically significant between-group differences were detected in age, sex, educational level, health insurance type, admission temperature, APACHE II score, admission GCS score, surgery, mechanical ventilation, or primary diagnosis (all $P > 0.05$). Nevertheless, residual confounding could not be excluded because of the non-randomized before-and-after design.

Comparison of TH process and quality-control indicators

The TH protocol group had more favorable temperature-management process indicators than the historical control group (Table 5). Compared with the historical control group, the TH protocol group had a shorter time from hospital admission to TH initiation (2.1 ± 0.8 vs. 4.5 ± 1.2 h, $P < 0.001$) and a shorter time

to reach the target temperature (3.5 ± 1.0 vs. 5.2 ± 1.5 h, $P < 0.001$). The proportion of patients who reached the target temperature within 4 h was higher in the TH protocol group (76.61% vs. 37.50%, $P < 0.001$). The mean duration of TH maintenance was similar between groups (23.8 ± 1.2 h vs. 23.4 ± 2.5 h, $P = 0.159$). Although the protocol specified a minimum maintenance period of 24 h, the slightly lower mean duration in the TH protocol group reflected minor protocol deviations and variation in the timing of rewarming.

During the maintenance phase, the proportion of patients with unplanned treatment interruptions was lower in the TH protocol group (3.23% vs. 15.00%, $P = 0.001$). During rewarming, the duration of controlled rewarming was longer in the TH protocol group (21.7 ± 3.6 vs. 12.9 ± 1.3 h, $P < 0.001$), and adherence to the rewarming criteria was higher (92.74% vs. 70.83%, $P < 0.001$).

Clinical endpoints: TH-related complications and outcomes

In exploratory unadjusted analyses (Table 6), the TH protocol group had lower incidences of shivering (3.23% vs. 23.33%; OR = 0.11, 95% CI: 0.04–0.32, $P < 0.001$), electrolyte disturbance (12.90% vs. 33.33%; OR = 0.30, 95% CI: 0.16–0.57, $P < 0.001$), deep vein thrombosis (1.61% vs. 7.50%; OR = 0.20, 95% CI: 0.04–0.96, $P = 0.032$), and gastrointestinal dysfunction (3.23% vs. 20.00%; OR = 0.13, 95% CI: 0.05–0.40, $P < 0.001$). Because shivering, deep vein thrombosis, and gastrointestinal dysfunction had few events relative to the number of model parameters, multivariable adjustment was not performed for these outcomes. After multivariable adjustment, electrolyte disturbance remained less frequent in the TH protocol group (adjusted OR = 0.22, 95% CI: 0.11–0.45, $P < 0.001$).

Regarding neurological outcomes, the TH protocol group had a more favorable GOS grade distribution than the historical control group ($P = 0.001$). Ordinal logistic regression showed higher adjusted odds of a better GOS grade in the TH protocol group (adjusted common OR = 2.06, 95% CI: 1.28–3.34, $P = 0.003$). The proportional-odds assumption was not violated ($\chi^2 = 24.18$, df = 33, $P = 0.868$). Favorable neurological outcome, defined as GOS grades IV–V, was also more frequent in the TH protocol group (74.19% vs. 51.67%; OR = 2.69, 95% CI: 1.57–4.61, $P < 0.001$), and the association remained after multivariable adjustment (adjusted OR = 2.70, 95% CI: 1.55–4.73, $P < 0.001$). The overall GOS score was higher in the TH protocol group (3.99 ± 0.97 vs. 3.57 ± 1.07 ; MD = 0.42, 95% CI: 0.16–0.68, $P = 0.001$), and the sensitivity analysis using multivariable linear regression yielded a consistent result (adjusted MD = 0.40, 95% CI: 0.14–0.66, $P = 0.003$).

Discussion

In this before-and-after study, implementation of a Delphi-derived standardized TH management protocol was associated with more favorable temperature-management process indicators, lower incidences of several TH-related complications, and more favorable short-term neurological outcomes in patients with neurocritical illness. Although the biological rationale and potential neuroprotective effects of TH have been well described, translating temperature management into routine practice remains challenging because of variation in implementation. Our findings

Table 3. Finalized therapeutic hypothermia management protocol for patients with neurocritical illness

Protocol items	Importance score (mean $\pm$ SD)	Coefficient of variation (CV)
1. Preparations before implementation	5.00 $\pm$ 0.00	0.00
1.1 Staff and patient preparation	4.80 $\pm$ 0.41	0.09
1.1.1 Patient assessment: Evaluate skin for swelling, breaks, or moisture and assess sensitivity to heat and cold	4.90 $\pm$ 0.31	0.06
1.1.2 Personnel qualifications: Ensure that all participating healthcare professionals complete standardized TH training and competency assessments	4.45 $\pm$ 0.51	0.11
1.1.3 Departmental framework: Establish a multidisciplinary TH team led by an associate chief physician or more senior physician and designated registered nurses; develop institutional TH policies and emergency-response protocols	4.40 $\pm$ 0.60	0.14
1.2 Equipment and supplies	4.80 $\pm$ 0.41	0.09
1.2.1 Monitoring devices: Equip the unit with continuous core-temperature monitors	4.40 $\pm$ 0.50	0.11
1.2.2 Cooling systems: Ensure the availability of physical cooling equipment, including ice packs, conventional cooling blankets, and wraparound cooling pads	5.00 $\pm$ 0.00	0.00
1.2.3 Rewarming supplies: Equip the unit with warming blankets, thermal quilts, insulated gloves, and sock covers	4.95 $\pm$ 0.22	0.05
1.3 Clinical assessment and screening	4.45 $\pm$ 0.51	0.11
1.3.1 Indication screening: Confirm indications, including severe traumatic brain injury with refractory intracranial hypertension, central hyperthermia, post-cardiac arrest coma, extensive cerebral infarction, Hunt-Hess grade IV or V subarachnoid hemorrhage, massive intracerebral hemorrhage, refractory status epilepticus, or severe bacterial meningitis	5.00 $\pm$ 0.00	0.00
1.3.2 Contraindication screening: Evaluate absolute contraindications (e.g., systemic failure, uncorrected shock, uncontrolled active bleeding, or brain death) and relative contraindications (e.g., severe thrombocytopenia, advanced coagulation disorders, or prolonged cardiac arrest)	4.60 $\pm$ 0.50	0.11
1.3.3 Environmental optimization: Maintain a dedicated treatment room with an ambient temperature of 20–24°C, relative humidity of 50–60%, adequate ventilation, and minimal noise	4.55 $\pm$ 0.51	0.11
1.3.4 Baseline clinical measures: Document baseline Glasgow Coma Scale (GCS) score, limb strength, and time of onset, and establish baseline intracranial pressure (ICP) monitoring when indicated	4.40 $\pm$ 0.60	0.14
1.3.5 Risk stratification: Complete standardized baseline risk assessments, including the Braden Scale for pressure injury, nutritional risk screening, and the APACHE II score, with reassessment after clinical changes	4.90 $\pm$ 0.31	0.06
1.4 Risk disclosure and consent	4.70 $\pm$ 0.47	0.10
1.4.1 Education for patients and families: Provide consolidated information about the procedure and expected goals	4.65 $\pm$ 0.49	0.11
1.4.2 Informed consent: Disclose potential procedural risks associated with targeted temperature management and obtain signed informed consent from patients or their legally authorized representatives	4.95 $\pm$ 0.22	0.04
2. Implementation phase	5.00 $\pm$ 0.00	0.00
2.1 Preprocedural initiation	4.80 $\pm$ 0.41	0.09
2.1.1 Cooling-modality selection: Select the appropriate therapeutic cooling method (surface, pharmacologic, or intravascular cooling) according to individual patient characteristics and physician orders	4.50 $\pm$ 0.51	0.11
2.1.2 Equipment setup: Prepare and disinfect cooling equipment; place protective sheets or gel pads to prevent direct skin contact, with particular attention to high-risk areas such as the posterior cervical region	4.90 $\pm$ 0.31	0.06
2.1.3 Pharmacologic preparation: Initiate physician-prescribed sedation and analgesia to suppress shivering	4.90 $\pm$ 0.31	0.06

Table 3. Finalized therapeutic hypothermia management protocol for patients with neurocritical illness (continued)

Protocol items	Importance score (mean $\pm$ SD)	Coefficient of variation (CV)
2.2 Core-temperature monitoring	4.85 $\pm$ 0.37	0.08
2.2.1 Monitoring-site selection: Use specialized core-temperature probes, prioritizing brain temperature, followed by tympanic, temporal-artery, rectal, bladder, esophageal, or pulmonary-artery measurements	4.75 $\pm$ 0.44	0.09
2.2.2 Monitoring frequency: Maintain continuous temperature recording or document temperature at least hourly throughout TH	4.95 $\pm$ 0.22	0.05
2.2.3 Documentation standards: Record hourly physiologic parameters on the standardized ICU flow sheet	4.90 $\pm$ 0.31	0.06
2.3 Cooling-induction phase	5.00 $\pm$ 0.00	0.00
2.3.1 Target-temperature setting: Set a target core-temperature range of 32.0–36.0°C according to patient-specific neurocritical indications	4.90 $\pm$ 0.31	0.06
2.3.2 Induction rate: Achieve the target temperature within 2–4 h after initiation	4.90 $\pm$ 0.31	0.06
2.3.3 Implementation: Adjust physical and pharmacologic cooling according to physician orders and patient responses	4.85 $\pm$ 0.37	0.08
2.4 Hypothermia-maintenance phase	5.00 $\pm$ 0.00	0.00
2.4.1 Duration: Maintain the target core temperature for at least 24 h; extend maintenance to 24–72 h for extensive cerebral infarction or at least 5 days for severe traumatic brain injury with refractory ICP $\geq$ 20 mmHg	4.95 $\pm$ 0.22	0.05
2.5 Controlled-rewarming phase	4.75 $\pm$ 0.44	0.09
2.5.1 Rewarming criteria: Initiate rewarming under physician guidance when ICP remains below 20 mmHg and imaging confirms resolution of cerebral edema; discontinue TH if severe uncontrolled infection, profound coagulopathy, hemodynamic collapse, or persistent pupillary dilation occurs	4.95 $\pm$ 0.22	0.05
2.5.2 Rewarming rate: Set and monitor a controlled rewarming rate of 0.10–0.25°C/h to reduce the risk of rebound intracranial hypertension	4.90 $\pm$ 0.31	0.06
2.5.3 Gradual weaning: Sequentially remove intravascular or high-efficiency external cooling devices, switch to standard thermal blankets, and taper continuous sedatives or hibernation infusions	4.75 $\pm$ 0.44	0.09
2.5.4 Normothermia target: Complete controlled rewarming to a core temperature of 36.0–37.5°C within 24–48 h	4.80 $\pm$ 0.41	0.09
2.6 Postrewarming normothermia management	4.90 $\pm$ 0.31	0.06
2.6.1 Extended temperature stabilization: Maintain a postrewarming core temperature of 36.0–37.5°C for 3–5 days to prevent rebound fever	4.40 $\pm$ 0.60	0.14
2.7 Multidimensional clinical monitoring	4.40 $\pm$ 0.50	0.11
2.7.1 Vital-sign monitoring: Continuously monitor blood pressure, respiratory rate, oxygen saturation, and electrocardiography	4.95 $\pm$ 0.22	0.05
2.7.2 Neurological and pressure monitoring: Monitor ICP, central venous pressure (CVP), pupillary responses, and GCS hourly	4.80 $\pm$ 0.41	0.09
2.7.3 Laboratory measures: Obtain routine complete blood counts, coagulation profiles, liver and kidney function tests, and blood glucose measurements. Perform arterial blood gas (ABG) analysis every 1–2 h during induction, every 8–12 h during maintenance, and every 8 h during rewarming; maintain pH at 7.35–7.45 and serum potassium at 3.5–5.3 mmol/L	4.80 $\pm$ 0.41	0.09
2.8 Complication monitoring and prevention bundles	4.50 $\pm$ 0.51	0.11
2.8.1 Risk identification: Monitor systematically for shivering, cardiovascular compromise, electrolyte shifts, nosocomial infection, gastrointestinal paralysis, coagulation abnormalities, deep vein thrombosis, pressure injury, and frostbite	4.90 $\pm$ 0.31	0.06

Table 3. Finalized therapeutic hypothermia management protocol for patients with neurocritical illness (continued)

Protocol items	Importance score (mean $\pm$ SD)	Coefficient of variation (CV)
2.8.2 Protocolized management strategies: (1) Shivering: provide prophylactic sedation, use the Bedside Shivering Assessment Scale, and apply combined surface rewarming and pharmacologic control. (2) Cardiovascular compromise: use slow rewarming, continuous electrocardiographic monitoring, and timely vasoactive-agent titration. (3) Electrolyte shifts: monitor electrolytes continuously and replace potassium or calcium as needed to prevent dysrhythmias. (4) Nosocomial infection: enforce aseptic technique, obtain paired sputum and blood cultures, and adjust antimicrobial therapy as indicated. (5) Gastrointestinal paralysis: initiate prokinetic-supported enteral nutrition, with prokinetic laxatives and rehabilitative electrical stimulation if indicated. (6) Coagulation abnormalities: assess for bleeding or ecchymosis, monitor coagulation indices, and administer factor or platelet replacement as indicated. (7) Deep vein thrombosis: use Caprini risk stratification, routine lower-extremity Doppler ultrasonography, compression stockings, and sequential pneumatic compression. (8) Pressure injury: perform serial Braden Scale assessments, scheduled repositioning, and prophylactic silicone dressings. (9) Frostbite prevention: place cotton padding between cooling devices and the skin and assess frostbite severity every 1–2 h using a standard four-stage scale	4.55 $\pm$ 0.51	0.11
3. Clinical outcomes evaluation	5.00 $\pm$ 0.00	0.00
3.1 Patient-centered outcomes	4.95 $\pm$ 0.22	0.05
3.1.1 Proportion achieving the target core temperature within the designated induction window	4.60 $\pm$ 0.50	0.11
3.1.2 Incidence and severity of procedure-related complications	4.95 $\pm$ 0.22	0.05
3.1.3 Proportion with successful controlled rewarming and restoration of normothermia	4.90 $\pm$ 0.31	0.06
3.2 Nursing quality-control indicators	4.90 $\pm$ 0.31	0.06
3.2.1 Protocol adherence among clinical nursing staff	4.90 $\pm$ 0.31	0.06
3.2.2 Incidence, tracking, and reporting of unplanned or accidental TH interruptions	5.00 $\pm$ 0.00	0.00
3.2.3 Accuracy, validation, and completion of standardized hypothermia nursing flow sheets	4.95 $\pm$ 0.22	0.05
3.3 Clinical satisfaction indicators	4.55 $\pm$ 0.51	0.11
3.3.1 Attending physicians' satisfaction with nursing implementation of the TH protocol	4.70 $\pm$ 0.47	0.10
3.3.2 Patient or surrogate satisfaction with ICU nursing care during temperature management	4.90 $\pm$ 0.31	0.06

ABG, arterial blood gas; APACHE II, Acute Physiology and Chronic Health Evaluation II; CV, coefficient of variation; CVP, central venous pressure; GCS, Glasgow Coma Scale; ICP, intracranial pressure; ICU, intensive care unit; SD, standard deviation; TH, therapeutic hypothermia.

suggest that protocolized care processes may help reduce variation in bedside TH delivery.

Delayed achievement of the target temperature is a major practical barrier to TH implementation. The evidence-based guideline from the Neurocritical Care Society emphasizes that targeted temperature management requires not only selection of an appropriate target temperature but also standardized implementation, including cooling methods, temperature monitoring, shivering management, and rewarming procedures.¹ Reviews of TTM practice similarly highlight that variation in induction, maintenance, rewarming, sedation, and fever management may affect the consistency of temperature control.¹² In the present study, the time to target temperature was shorter in the TH protocol group (3.5 vs. 5.2 h), and the proportion reaching the target temperature within 4 h was higher. These findings suggest that protocolized interdisciplinary workflows and continuous temperature monitoring may support more consistent TH delivery.

Standardization of the rewarming phase may also be relevant to the observed differences in clinical endpoints. Rewarming is a critical phase of TH because rapid or poorly controlled rewarming may disturb cerebrovascular pressure reactivity and may be associated with rebound intracranial pressure in patients with traumatic brain injury.^{24,25} Practice-focused reviews of ICU temperature management also emphasize that rewarming should be slow and controlled, with careful monitoring for electrolyte shifts, hemodynamic changes, and temperature rebound.^{26,27} In the present study, the protocol specified controlled rewarming at 0.10–0.25°C/h, and the duration of controlled rewarming was longer in the TH protocol group (21.7 vs. 12.9 h). Although causality cannot be established in this before-and-after design, these findings suggest that standardized rewarming may support more consistent bedside temperature management.

TH is associated with physiologic stress and potential systemic complications, making protocolized surveillance essential. Shiv-

Table 4. Baseline demographic and clinical characteristics of the two groups (N = 244)

Variable	Historical control group (n = 120)	TH protocol group (n = 124)	P value
Demographic characteristics			
Age, years, mean $\pm$ SD	54.7 $\pm$ 15.30	53.3 $\pm$ 14.76	0.467
Sex, n (%)			0.742
Male	76 (63.33)	76 (61.29)	
Female	44 (36.67)	48 (38.71)	
Educational level, n (%)			0.887
Illiterate	4 (3.33)	6 (4.84)	
Elementary school and below	10 (8.33)	8 (6.45)	
Junior/vocational high school	14 (11.67)	14 (11.29)	
High school or higher	92 (76.67)	96 (77.42)	
Health insurance type, n (%)			0.488
Self-funded	20 (16.67)	17 (13.71)	
Employee insurance	50 (41.67)	65 (52.42)	
Publicly funded medical care	12 (10.00)	8 (6.45)	
Commercial insurance	20 (16.67)	20 (16.13)	
Rural cooperative medical care	18 (15.00)	14 (11.29)	
Clinical characteristics			
Primary diagnosis, n (%)			0.548
Traumatic brain injury	28 (23.33)	36 (29.03)	
Stroke/cerebral infarction	36 (30.00)	42 (33.87)	
Subarachnoid hemorrhage	49 (40.83)	39 (31.45)	
Post-cardiac arrest coma	3 (2.50)	4 (3.23)	
Meningitis	3 (2.50)	1 (0.81)	
Status epilepticus	1 (0.83)	2 (1.61)	
Surgery, n (%)	75 (62.50)	70 (56.45)	0.336
Mechanical ventilation, n (%)	88 (73.33)	85 (68.55)	0.411
Initial temperature at admission, n (%)			0.141
< 36°C	16 (13.33)	10 (8.06)	
36–37.5°C	82 (68.33)	80 (64.52)	
> 37.5°C	22 (18.33)	34 (27.42)	
APACHE II score, mean $\pm$ SD	13.93 $\pm$ 2.67	14.32 $\pm$ 2.69	0.247
Admission GCS score, mean $\pm$ SD	8.28 $\pm$ 2.15	7.85 $\pm$ 2.18	0.131

Data are presented as n (%) or mean $\pm$ SD. Continuous variables with normal distributions were compared using independent-samples *t* tests, and categorical variables were compared using Pearson chi-square or Fisher exact tests, as appropriate. A two-sided *P* value < 0.05 was considered statistically significant. APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale; SD, standard deviation; TH, therapeutic hypothermia.

ering is a common and clinically important complication because it increases oxygen consumption, energy expenditure, and induction time, thereby counteracting the intended metabolic effects of hypothermia.²⁸⁻³⁰ In this study, the lower incidence of shivering in the TH protocol group may have been related to standardized shivering assessment, prophylactic sedation and analgesia, and timely bedside intervention. Electrolyte disturbances may also occur

during cooling and rewarming because of intracellular shifts, cold-induced diuresis, and redistribution during rewarming.^{26,27} A recent review suggest that hypothermia may increase the risk of selected infections, particularly pneumonia and sepsis.³¹ Therefore, structured infection screening and proactive complication surveillance remain important components of protocolized temperature management. The lower rates of electrolyte disturbance and

Table 5. Temperature-management process indicators in the two groups

Process indicator	Historical control group (n = 120)	TH protocol group (n = 124)	P value
Time from admission to TH initiation, h, mean $\pm$ SD	4.5 $\pm$ 1.2	2.1 $\pm$ 0.8	< 0.001
Time to target temperature, h, mean $\pm$ SD	5.2 $\pm$ 1.5	3.5 $\pm$ 1.0	< 0.001
Target temperature achieved within 4 h, n (%)	45 (37.50)	95 (76.61)	< 0.001
Maintenance phase			
Duration of TH maintenance, h, mean $\pm$ SD	23.4 $\pm$ 2.5	23.8 $\pm$ 1.2	0.159
Unplanned treatment interruptions, n (%)	18 (15.00)	4 (3.23)	0.001
Rewarming phase			
Duration of controlled rewarming, h, mean $\pm$ SD	12.9 $\pm$ 1.3	21.7 $\pm$ 3.6	< 0.001
Adherence to rewarming criteria, n (%)	85 (70.83)	115 (92.74)	< 0.001

Continuous process variables were compared using independent-samples *t* tests. Proportions were compared using Pearson chi-square tests. A two-sided *P* value < 0.05 was considered statistically significant. h, hours; SD, standard deviation; TH, therapeutic hypothermia.

gastrointestinal dysfunction in the TH protocol group may reflect differences in structured monitoring and early intervention rather than any single component of care.

Several limitations warrant consideration. First, the observational before-and-after design inherently carries a risk of temporal confounding and other unmeasured changes in clinical practice over time. Although multivariable-adjusted analyses were performed to reduce the influence of measured baseline differences, residual confounding cannot be excluded. Second, the cohort included patients with heterogeneous neurological etiologies, including traumatic brain injury, stroke, subarachnoid hemorrhage, and post-cardiac arrest coma. The optimal target temperature, duration of hypothermia, and rewarming strategy may therefore vary according to the underlying pathophysiological condition. In addition, some safety outcomes, such as deep vein thrombosis, had few events, which limited reliable multivariable adjustment and may have reduced the precision of effect estimates. Deep vein thrombosis ascertainment also differed between the two periods because routine lower-extremity Doppler surveillance was performed in the TH protocol group, whereas Doppler ultrasonography in the historical control group was performed only when clinically indicated; therefore, the between-group deep vein thrombosis comparison should be interpreted cautiously. Third, temperature-related process indicators may have been influenced by measurement bias because the historical control group underwent intermittent axillary temperature measurement, whereas the TH protocol group underwent continuous core-temperature monitoring and standardized TH documentation. In addition, target-temperature selection was not standardized in the historical cohort, and target-temperature distributions could not be reliably reconstructed retrospectively. Therefore, comparisons of time to target temperature and target achievement within 4 h should be interpreted cautiously. Fourth, the resource requirements of the standardized TH protocol may limit its generalizability. Implementation requires continuous core-temperature monitoring, dedicated temperature-management equipment, and trained clinical personnel. Furthermore, the protocol may not be applicable to all critically ill patients, particularly those with uncorrected shock, active bleeding, or other contraindications to temperature modulation.

Finally, neurological outcomes were assessed using GOS scores at hospital discharge. Although the GOS is a widely accepted five-point functional-outcome scale for severe brain injury,²³ discharge GOS reflects short-term neurological status and may not fully capture long-term functional recovery or changes in functional independence over time.³² Moreover, previous clinical trials and evidence syntheses of temperature management in cardiac arrest and traumatic brain injury populations have shown that the effects of hypothermia or specific target-temperature strategies may differ by disease context and patient selection.³³⁻³⁵ Future prospective multicenter studies with longer follow-up are needed to determine whether the observed associations persist over time.

Conclusions

A standardized TH management protocol may help address common implementation challenges, particularly delayed induction and rapid rewarming. By standardizing temperature-control procedures and complication-prevention measures, the protocol may provide a practical framework for consistent neurocritical temperature management. Prospective multicenter studies are needed to evaluate safety and longer-term neurological outcomes.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/NSSS.2026.00013>.

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Table 6. Clinical endpoints in the two groups

Clinical endpoint	Historical control group (n = 120)	TH protocol group (n = 124)	Unadjusted effect estimate (95% CI)	Unadjusted P value	Adjusted effect estimate (95% CI)	Adjusted P value
TH-related complications, n (%)						
Shivering	28 (23.33)	4 (3.23)	OR = 0.11 (0.04–0.32)	< 0.001	—	—
Electrolyte disturbance	40 (33.33)	16 (12.90)	OR = 0.30 (0.16–0.57)	< 0.001	aOR = 0.22 (0.11–0.45)	< 0.001
Deep vein thrombosis	9 (7.50)	2 (1.61)	OR = 0.20 (0.04–0.96)	0.032	—	—
Gastrointestinal dysfunction	24 (20.00)	4 (3.23)	OR = 0.13 (0.05–0.40)	< 0.001	—	—
Clinical outcomes						
GOS grade distribution, n (%)			—	0.001	acOR = 2.06 (1.28–3.34)	0.003
I (death)	4 (3.33)	2 (1.61)				
II (persistent vegetative state)	14 (11.67)	8 (6.45)				
III (severe disability)	40 (33.33)	22 (17.74)				
IV (moderate disability)	34 (28.33)	49 (39.52)				
V (good recovery)	28 (23.33)	43 (34.68)				
Favorable GOS outcome (grades IV–V), n (%)	62 (51.67)	92 (74.19)	OR = 2.69 (1.57–4.61)	< 0.001	aOR = 2.70 (1.55–4.73)	< 0.001
Overall GOS score, mean $\pm$ SD	3.57 $\pm$ 1.07	3.99 $\pm$ 0.97	MD = 0.42 (0.16–0.68)	0.001	aMD = 0.40 (0.14–0.66)	0.003

Data are presented as n (%) or mean $\pm$ SD. Unadjusted comparisons of TH-related complications and favorable GOS outcome were performed using Pearson chi-square or Fisher exact tests, as appropriate. The ordinal GOS grade distribution was compared using the Mann–Whitney *U* test, and the overall GOS score was compared using the independent-samples *t* test. Adjusted analyses used multivariable logistic regression for electrolyte disturbance and favorable GOS outcome, ordinal logistic regression for GOS grade distribution, and multivariable linear regression as a sensitivity analysis for overall GOS score. Adjusted models included age, primary diagnosis, APACHE II score, admission GCS score, surgery, and mechanical ventilation. Adjusted analyses were not performed for shivering, deep vein thrombosis, or gastrointestinal dysfunction because of the small number of events relative to the number of model parameters. A two-sided *P* value < 0.05 was considered statistically significant. acOR, adjusted common odds ratio; aMD, adjusted mean difference; aOR, adjusted odds ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; MD, mean difference; OR, odds ratio; SD, standard deviation; TH, therapeutic hypothermia.

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Conflict of interest

YZ has served as an editorial board member of *Neurosurgical Subspecialties* since August 2024. The authors have no other conflicts of interest related to this publication.

Author contributions

Study concept and design (YO, YL, YZ), study supervision (SL,

LQ, QL), literature search (YO, YL, ML, WL), expert coordination (LQ), protocol development (YO, YL, YZ, SL), protocol implementation (YO, YL, ML), data analysis (ML, WL), drafting of the manuscript (YO, YL), and study quality control (SL, LQ). All authors have made significant contributions to this study and approved the final manuscript.

Ethical statement

The clinical before-and-after evaluation phase was approved by the Medical Ethics Committee of Union Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology on June 3, 2024 (approval No. 20240979-01). The approval covered the use of historical control data and the prospective evaluation of patients receiving the standardized TH

protocol. The protocol-development phase comprised evidence synthesis and Delphi expert consultation and involved no patient intervention or identifiable patient-level data. According to institutional requirements, the Delphi expert consultation did not require separate ethics approval. All participating Delphi experts provided written informed consent before participation. For the retrospective historical control group, informed consent was waived because only existing medical records were analyzed. For patients in the prospective implementation phase, written informed consent was obtained from patients or their legally authorized representatives in accordance with institutional requirements. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request, subject to approval by the institutional ethics committee and applicable privacy and data-protection requirements.

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