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The role of environmental stressors in neurocritical patient outcomes

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The role of environmental stressors in neurocritical patient outcomes

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Table of contents

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Editorial: The role of environmental stressors in neurocritical patient outcomes

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Editorial on the Research Topic
The role of environmental stressors in neurocritical patient outcomes

Neurocritical care occupies a unique nexus wherein demanding physiological management converges with the unpredictability of human environments. In this Research Topic, *The role of environmental stressors in neurocritical patient outcomes*, we sought to shed light on underexplored variables—often outside the traditional scope of intensive care protocol—that have the potential to profoundly impact outcomes in neurologically impaired patients.

The articles in this series reveal how environmental and systemic elements—from oxygenation, nutritional timing, tracheostomy care, and even pesticide exposure—can influence recovery, complications, and survival. Collectively, these studies challenge the conventional borders of neurocritical care and offer practical information for clinical practice.

Zhang et al. research article addressed a very basic procedural milestone in critical care: extubation. A large retrospective cohort examined risk factors for failed endotracheal extubation in neurocritical patients. By determining predictors like longer mechanical ventilation and reduced consciousness, the authors recommend more individualized readiness testing to prevent extubation failure and morbidity.

Complementing this, a synthesis of nursing and clinical care of tracheostomized patients with traumatic brain injury (Mao et al.) emphasized the multidisciplinary teamwork needed for airway care. It outlined how specific nursing interventions—viz., suction routines, stoma care, and communication support—can prevent complications and enhance comfort for patients.

Environmental toxicity was also highlighted in a dramatic case report of insecticide-induced leukoencephalomyelopathy (Li et al.). That hyperthermia was delayed in this lethal case highlights how exposure to agricultural chemicals is one of those rarely spoken but extremely important environmental threats to neurological health, especially in rural or underserved populations.

Meanwhile, the association of hematological markers with outcome was also explored in a study of thrombocytopenia in intracerebral hemorrhage patients (Feng et al.). This study found that platelet count trends can serve as both a biomarker and therapeutic target, again showing how systemic stress responses are mirrored in intracranial vulnerability.

On another level, a bibliometric analysis talked about the most cited articles on hypothermic brain protection (Hu et al.). The study mapped shifting scientific trends and knowledge clusters, offering a meta-perspective on how cooling therapies have shaped neurocritical practices over the past decades.

Nutrition timing constituted another modifiable stressor in a study using a MIMIC-IV database of stroke patients (Wang X. et al.). The authors associated early enteral feeding with reduced 28-day mortality, highlighting the necessity of nutritional planning within the acute period of neurologic recuperation.

This theme of time-dependent care was corroborated in a retrospective single-center study examining the combined effect of mechanical thrombectomy and prolonged mild hypothermia in acute middle cerebral artery occlusion (Wang A. et al.). The findings suggest synergistic effects in the application of both mechanical and environmental modes of treatment for ischemic stroke.

Circumambient oxygenation was also a powerful variable in a MIMIC-IV analysis of non-traumatic subarachnoid hemorrhage (Liu et al.). Transcutaneous oxygen saturation levels during the first 24 h predicted in-hospital mortality, offering an easily accessed but powerful prognostic marker that may be responsive to early environmental and respiratory support interventions.

At a systems modeling level, a predictive model was developed to calculate the likelihood of return of spontaneous circulation and favorable neurological outcomes following in-hospital cardiac arrest (Li and Xing). By consolidating clinical and demographic variables, this tool demonstrates how data-driven frameworks can streamline bedside decision-making along with potentially informing environmental priorities following resuscitation.

Lastly, a network meta-analysis compared screening tools for dysphagia in stroke patients (Jiang et al.). The results emphasize how early and personalized screening prevents aspiration, reduces ICU-acquired infections, and improves outcomes—a testament to how procedural timing and environment can be a therapeutic axis.

Collectively, this Research Topic shines a light on the insidious and unrecognized environmental influences on neurocritically ill patient outcomes. From air quality and sedation to the timing of nutrition and human presence, every modifiable aspect of care can either optimize recovery or impart risk.

We thank all contributors, peer reviewers, and readers for making this Research Topic a robust and thought-provoking exploration of an emerging frontier in neurological care. We hope that these articles will inspire clinicians and researchers alike to further explore and integrate environmental perspectives in neurocritical care protocols.

Author contributions

LM-S: Validation, Data curation, Software, Project administration, Visualization, Formal analysis, Methodology, Investigation, Conceptualization, Funding acquisition, Supervision, Resources, Writing – review & editing, Writing – original draft. TJ: Project administration, Formal analysis, Writing – original draft, Validation, Resources, Data curation, Methodology, Visualization, Supervision, Investigation, Software, Conceptualization, Writing – review & editing, Funding acquisition. VC: Resources, Funding acquisition, Visualization, Project administration, Writing – original draft, Validation, Formal analysis, Data curation, Writing – review & editing, Supervision, Conceptualization, Software, Investigation, Methodology.

Conflict of interest

LM-S was employed by AV Healthcare Innovators, LLC. TJ was employed by ANEUCLOSE, LLC.

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

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A model for predicting return of spontaneous circulation and neurological outcomes in adults after in-hospital cardiac arrest: development and evaluation

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Introduction: In-hospital CA (IHCA) is associated with rates of high incidence, low return of spontaneous circulation (ROSC), low survival to discharge, and poor neurological outcomes. We aimed to construct and evaluate prediction models for non-return of spontaneous circulation (non-ROSC) and poor neurological outcomes 12 months after ROSC (PNO-12).

Methods: We retrospectively analyzed baseline and clinical data from patients experiencing cardiac arrest (CA) in a big academic hospital of Jilin University in China. Patients experiencing CA between September 1, 2019 and December 31, 2020 were categorized into the ROSC and non-ROSC groups. Patients maintaining ROSC >20 min were divided into the good and PNO-12 subgroups.

Results: Univariate and multivariate logistic regression identified independent factors associated with non-ROSC and PNO-12. Two nomogram prediction models were constructed and evaluated. Of 2,129 patients with IHCA, 851 were included in the study. Multivariate logistic regression analysis revealed that male sex, age >80 years, CPR duration >23 min, and total dose of adrenaline >3 mg were significant risk factors for non-ROSC. Before CA, combined arrhythmia, initial defibrillation rhythm, and advanced airway management (mainly as endotracheal intubation) also influenced outcomes. The area under the receiver operating characteristic curve in the prediction model was 0.904 (C-index: 0.901). Respiratory failure, shock, CA in the monitoring area, advanced airway management, and noradrenaline administration were independent risk factors for PNO-12. The AUC was 0.912 (C-index: 0.918).

Conclusions: Prediction models based on IHCA data could be helpful to reduce mortality rates and improve prognosis.

KEYWORDS

cardiopulmonary resuscitation, in-hospital cardiac arrest, neurological function, prognostic model, return of spontaneous circulation

1 Introduction

In-hospital cardiac arrest (IHCA) is a common event facing emergency physicians worldwide. High-quality cardiopulmonary resuscitation (CPR) is crucial to improve patient outcomes. Two key prognostic indicators in IHCA cases are the return of spontaneous circulation (ROSC) and a good neurological prognosis. Unfortunately, IHCA is associated with rates of high incidence, low ROSC, low survival to discharge, and poor neurological outcomes. The financial impact of prolonging life must be considered in countries with high healthcare costs. Therefore, the impact of IHCA on quality of life is paramount worldwide.

A clinical prognosis prediction model should be developed to rapidly and efficiently evaluate the disease and predict outcomes to address this issue. Although various prognostic models have been introduced since 1989, such as the PAM score (1), the CASPRI score (2), the RSSR score (3), and the GO FAR2 score (4), most of these scores focus primarily on parameters related to the acute disease. However, they ignore the important factors associated with chronic disease, limiting their use for accurate diagnosis, treatment, and prognostic evaluation. This study adopts the international Utstein model of the CPR effect evaluation model and collects data to construct short- and long-term prognostic prediction models. Evaluation results showed that the models can help clinicians provide more suitable treatment and predict the prognosis for adult patients with IHCA.

2 Materials and methods

This study used the hospital's digital record system, outpatient medical records, and medical information related to CPR to retrieve data from September 1, 2019, to December 31, 2020. This study included adult patients (aged 18 years and older) who underwent IHCA in various departments including the general ward, emergency room, intensive care unit, operating room, and catheterization room. Patients with no-first CA, incomplete clinical data, congenital heart disease, during pregnancy or perinatal period, and with severe trauma were excluded from the study. We tracked and organized their baseline and clinical data. Based on CPR outcome, patients were categorized into either the ROSC (maintaining ROSC for ≥20 min) or non-ROSC group, which was the primary outcome.

We followed the ROSC group to assess their neurological prognostic status at 12 months mainly by phone interview with the participants or their families. They were divided into two groups by cerebral performance category (CPC), and the detailed evaluation criteria are presented in Table 1 (5).

Participants with a CPC 1–2 status were further categorized into the good neurological outcome group and the others with CPC 3–5 status were categorized into the poor neurological outcome group (PNO-12). PNO-12 was the secondary outcome.

All data were statistically analyzed using SPSS 26.0 or R 4.2. Continuous variables are represented as mean ± standard deviation or median with interquartile spacing (IQR). The normality of the data was based on their distribution. Student's *t*-test was used for normally distributed data, while the Mann–Whitney *U*-test was used for nonnormally distributed data. Count data are expressed as frequency (%), and the chi-square test or Fisher's exact probability method was used for group comparison based on theoretical frequency. A univariate logistic regression analysis was performed for continuous variables, with non-ROSC and PNO-12 as the dependent variable (*Y*). A receiver operating characteristic (ROC) curve was plotted to determine the threshold of the dependent variable using the maximum Youden index method. The dependent variable was then converted into a dichotomous variable (0 or 1). Univariate logistic regression analysis was performed with the variables related to Non-ROSC and PNO-12. Variables with a $P < 0.1$ were included in the multivariate logistic regression model to identify independent influencing factors. Multiple regression models were analyzed using dual variables, and a nomogram prediction model was constructed based on the results. Using bootstrap resampling, the AUC was calculated to evaluate, and a calibration curve was plotted. The C-index and the mean absolute error (MAE) were calculated, and the Hosmer–Lemeshow goodness-of-fit test (H–L test) was performed to evaluate the calibration degree of the model. Additionally, the decision curve analysis method and clinical impact curves were used to assess the clinical applicability of the prediction model. External validation was performed using data from another big academic hospital in Jilin University. The statistical method had been verified by the Administrative Committee for Clinical Research of the First Hospital of Jilin University (num.2023-KS-223).

TABLE 1 Cerebral performance category (5).

CPC level	Illustrations
CPC 1	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis
CPC 4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness
CPC 5	Brain death: apnea, areflexia, EEG silence, etc.

2.1 Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the First Hospital of Jilin University for studies involving humans (Date 2023/09/27, approval num. 2023-649). Informed consent was waived by the board.

3 Results

During the study period, 2,129 patients experienced IHCA. Based on the study criteria, 851 patients were finally included (Figure 1). A total of 564 (66.27%) patients achieved ROSC, and of these, 229 (26.91%) were categorized as PNO-12 (Supplementary Table 1).

Abbreviations: AUC, area under the receiver operating characteristic curve; CA, cardiac arrest; CD, duration of CPR; CPC, cerebral performance category; ETI, endotracheal intubation; CPR, cardiopulmonary resuscitation; H–L test, Hosmer–Lemeshow goodness-of-fit test; IHCA, In-hospital CA; IQR, interquartile spacing; Non-ROSC, non-return of spontaneous circulation; OR, odds ratio; PNO-12, poor neurological outcomes 12 months after ROSC; ROC, receiver operating characteristic; ROSC, return of spontaneous circulation; TDOA, total dose of adrenaline.

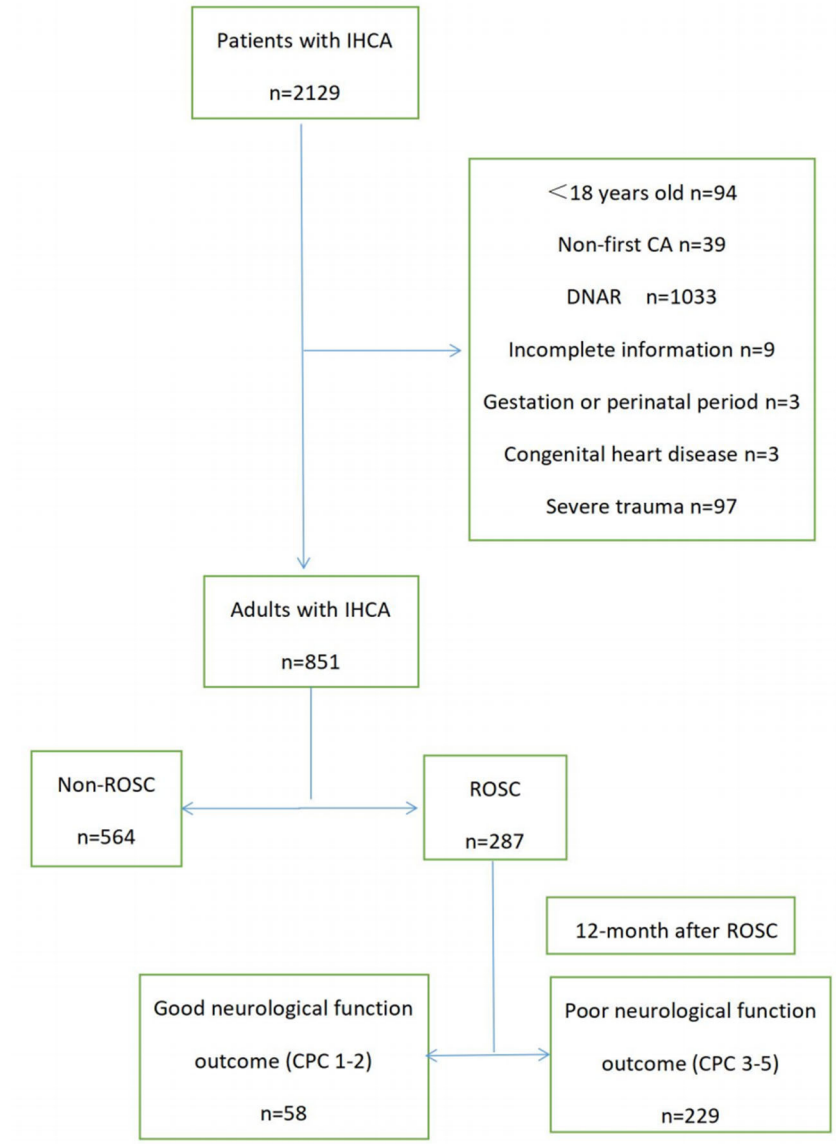

FIGURE 1
Flowchart of the patient selection.

3.1 Development of the predictive model for the primary outcome

Supplementary Table 1 compares the baseline and clinical data between the ROSC and non-ROSC groups. Table 2 shows the dichotomized thresholds for the duration of CPR (CD) and the total dose of adrenaline (TDOA) using the ROC analysis of univariate logistic regression by primary/secondary outcome. All variables with $P < 0.1$ in the results of the univariate logistic regression were included in the multivariate logistic regression analysis (Table 3). The results indicate that male sex [odds ratio (OR) = 2.42, 95% CI: 1.58–3.69, P <0.001], age >80 years (OR = 3.31, 95% CI: 1.57–6.97, $P = 0.002$), CD >23 min (OR = 19.18, 95% CI: 12.01–30.63, P <0.001), and TDOA >3 mg were independent risk factors for non-ROSC. Before CA, arrhythmia (OR = 3.98, 95% CI: 2.43–6.51, $P <$ 0.001), an initial defibrillation heart rhythm (OR = 0.20, 95% CI: 0.11–0.35, $P < 0.001$), and advanced airway management (OR = 0.45, 95% CI: 0.29–0.71, $P = 0.001$) were identified as independent protective factors (Table 3). The predictive model was constructed using R 4.2 (Figure 2A).

3.2 Evaluation and validation of the predictive model for the primary outcome

The discriminative performance of the nomogram model was evaluated by plotting the ROC curves, resulting in an AUC of 0.904 (95% CI: 0.882–0.925), indicating good model discrimination (Figure 2B). Internal validation was conducted using the bootstrap

TABLE 2 Dichotomized thresholds of CPR duration and total dosage of adrenaline using receiver operating characteristic analysis of univariate logistic regression by primary/secondary outcome.

	Cut-off	Sensitivity	Specificity	AUC
CD, min	23.5†/9.5‡	0.830†/0.546‡	0.805†/0.759‡	0.877†/0.654‡
TDOA, mg	3.5†/0.5‡	0.573†/0.686‡	0.882†/0.776‡	0.785†/0.760‡

AUC, area under the receiver operating characteristic curve; CD, CPR duration; TDOA, total dosage of adrenaline.
† Primary outcome.
‡ Secondary outcome.

method, which involved random sampling performed 1,000 times. The C index was 0.901 (95% CI: 0.879–0.922) with an MAE of 0.013. Furthermore, the H–L test (X^2 =12.36, P = 0.136) indicated a good fit and calibration of the model (Figure 2C). The nomogram prediction model demonstrated good clinical applicability, as evidenced by decision curve analysis and clinical impact curves (Figures 2D, E). The external validation, which included 355 participants showed an AUC of 0.900 (95% CI: 0.868–0.933), and the calibration curve showed good consistency (Figures 4A, B).

3.3 Development of a predictive model for the secondary outcome

Supplementary Table 1 compares the baseline and clinical data of the groups with good neurological outcomes and PNO-12. Variables with $P < 0.1$ in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The results showed that respiratory failure (OR = 6.73, 95% CI: 1.33–34.07, P = 0.021), shock (OR = 4.91, 95% CI: 1.51–15.99, P = 0.008), and cardiac arrest (CA) occurring in the monitoring area (OR = 4.42, 95% CI: 1.80–10.88, P = 0.001); advanced airway management (OR = 3.43, 95% CI: 1.24–9.51, P = 0.018); and the use of noradrenaline (OR = 3.19, 95% CI: 1.17–8.66, P = 0.023) were independent risk factors for PNO-12.

Furthermore, cardiac etiology (OR = 0.14, 95% CI: 0.05–0.40, $P < 0.001$) and an initial defibrillation rhythm (OR = 0.39, 95% CI: 0.16–0.92, P = 0.031) were identified as independent protective factors (Table 3). The predictive model is shown in Figure 3A.

3.4 Evaluation and validation of the predictive model for the secondary outcome

The AUC for the nomogram model was 0.912 (95% CI: 0.870–0.954), indicating a good discriminative performance for the model (Figure 3B). The C index was 0.918 (95% CI: 0.875–0.957), and the MAE was 0.032. The H–L test (X^2 =11.10, P=.196) indicated the model was well calibrated (Figure 3C). The prediction model demonstrated good clinical applicability, as evidenced by decision curve analysis and clinical impact curves (Figures 3D, E). The result of the external validation, which included 120 participants, showed an AUC of 0.909 (95% CI: 0.833–0.985), and the calibration curve also showed good consistency (Figures 4C, D).

4 Discussion

In this study, 851 patients with IHCA were included, predominantly consisting of males (543, 63.81%). The median age was 65 (54–74) years. A comprehensive review conducted in the US (6) also reported a mean age of 66 years for patients with IHCA and that 58% of patients with IHCA were male. The ROSC rate in our study was 33.73%, slightly lower than the 35.5% rate reported in a previous study conducted in Beijing (7). The disparity in the level of regional medical development may be a plausible reason for this difference. Male sex and advanced age were identified as independent risk factors for non-ROSC. However, the relationship between sex and PNO-12 was not significant, which is consistent with the results of previous studies (8). Nevertheless, several studies (9) show that advanced age is a risk factor for poor prognosis and even death among patients with an IHCA. This may be due to the decline in physiological function and immunity among older adults or various underlying diseases that make them highly sensitive to the pathophysiological state of ischemia and hypoxia in CA, resulting in poorer tolerance. Additionally, older family members are less likely to receive active treatment due to the influence of traditional ethics, contributing to the poor prognosis of IHCA among older patients in this study.

Respiratory failure and shock before the IHCA were independent factors influencing PNO-12. Both conditions represent the advanced stage of disease progression, indicating the severe condition of the patients. Furthermore, based on the analysis of clinical data from 40,000 patients, Chan et al. (2) concluded that hypotension was a factor contributing to the failure of CPR. Among the 222 patients with arrhythmia before IHCA, 63.96% had a cardiac etiology, suggesting that it may be an independent factor in predicting non-ROSC.

The etiology of IHCA etiology is usually recorded in the Utstein mode based on clinical data and is classified into cardiac and non-cardiac causes. A previous review (6) inferred that unexplained CA is of cardiac origin. In this study, it was determined to be caused by lesions of the heart itself and excluded by definite non-cardiac causes, introducing a degree of subjective bias. The primary cause of IHCA was mainly non-cardiac (58.40%).

A 3-year retrospective study (10) in Denmark demonstrated that patients with CA with a cardiac etiology had a better prognosis rate for neurological outcomes than those with a non-cardiac etiology. Another study (11) found that patients with acute myocardial infarction had a higher survival rate than non-AMI patients. This difference may be attributed to recent advances in coronary intervention technology, including prompt treatment, physical exercise, regular patient monitoring, and comprehensive management of chronic diseases, significantly reducing the incidence of CA.

The location of the IHCA called the "monitoring area," was identified as an independent protective factor that predicted PNO-12. The traditional perception is that patients in a monitoring area

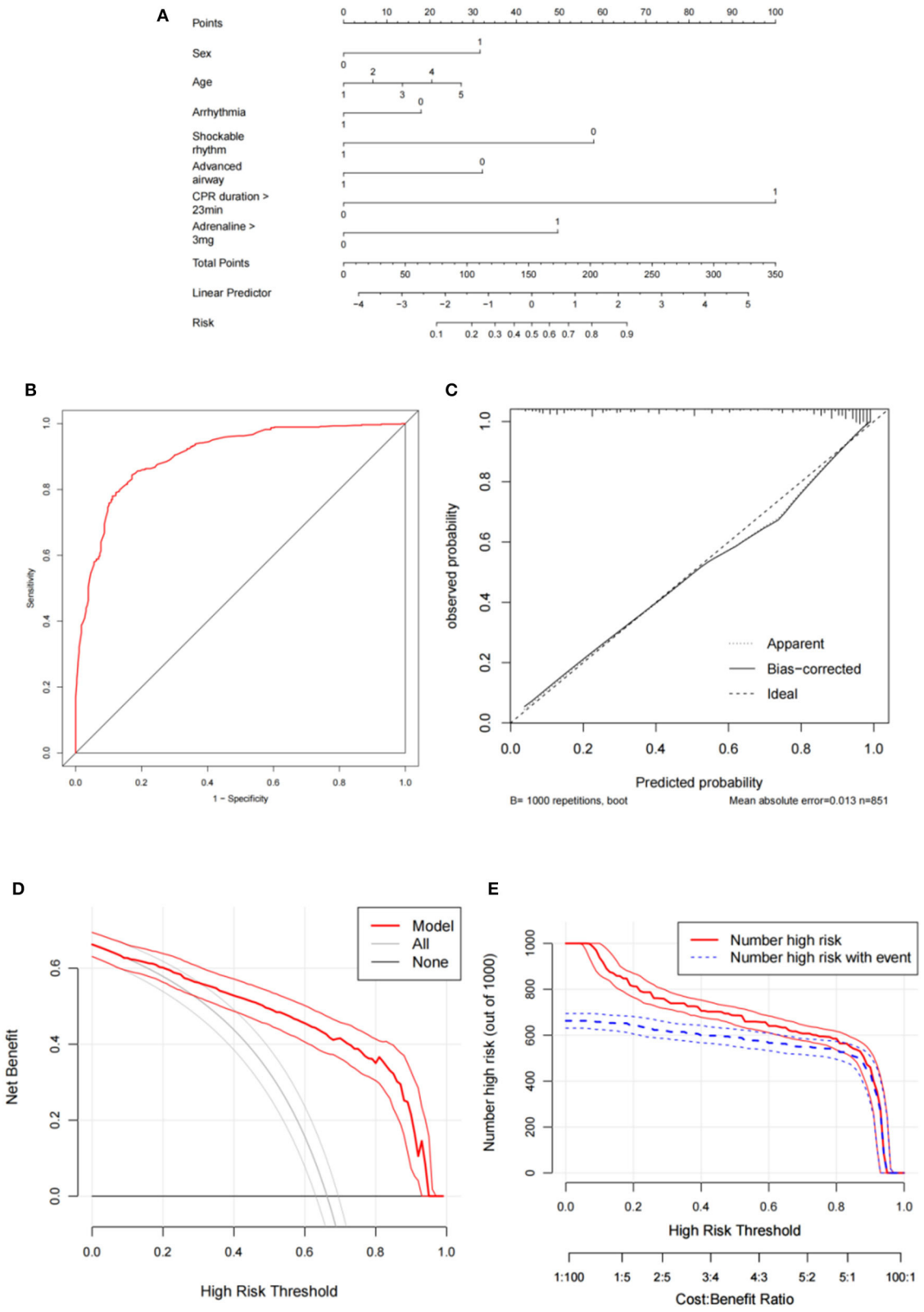

FIGURE 2
Development and evaluation of the predictive model for primary outcome. **(A)** Nomogram; **(B)** Receiver operating curve; **(C)** Calibration curve; **(D)** Decision curve analysis; **(E)** Clinical impact curve. CPR, cardiopulmonary resuscitation.

TABLE 3 Multivariate logistic regression analysis results by primary and secondary outcomes.

Categories	Regression coefficient	Standard error	*P*-value	OR (95%CI)
Primary outcome[†]				
Male	0.88	0.22	<0.001	2.42 (1.58–3.69)
≥80 years	1.20	0.38	0.002	3.31 (1.57–6.97)
Arrhythmia	−0.50	0.25	0.041	0.61 (0.38–0.98)
Defibrillation rhythm	−1.62	0.28	<0.001	0.20 (0.11–0.35)
CD >23 min	2.95	0.24	<0.001	19.18 (12.01–30.63)
AAM	−0.80	0.23	0.001	0.45 (0.29–0.71)
TDOA >3 mg[a]	1.38	0.25	<0.001	3.98 (2.43–6.51)
Secondary outcome[‡]				
Respiratory-F	1.91	0.83	0.021	6.73 (1.33–34.07)
Shock	1.59	0.63	0.008	4.91 (1.51–15.99)
Intensive care	1.49	0.46	0.001	4.42 (1.80–10.88)
Cardiac etiology	−2.00	0.55	<0.001	0.14 (0.05–0.40)
Defibrillation rhythm	−0.95	0.44	0.031	0.39 (0.16–0.92)
AAM	1.23	0.52	0.018	3.43 (1.24–9.51)
Norepinephrine	1.16	0.51	0.023	3.19 (1.17–8.66)

OR, odds ratio; CI, confidence interval; CD, CPR duration; AAM, advanced airway management; TDOA, total dosage of adrenaline; Respiratory-F, respiratory failure.
[†] Primary outcome.
[‡] Secondary outcome.
[a] Dichotomized thresholds.

have a better prognosis than those in general wards because of the resuscitation experience of medical and nursing personnel and the availability of advanced comprehensive emergency equipment. However, the opposing view is that patients in a "monitoring area" are more severely ill, leading to poor prognosis, even with high-quality CPR.

The initial rhythm type of IHCA can be divided into defibrillation and non-defibrillation rhythms. Our results revealed that patients with a defibrillation rhythm had better neurological prognoses than patients with a non-defibrillation rhythm in both predictive models. This finding is consistent with several studies; Hirlekar et al. (12) and Aufderheide et al. (13) also found that patients in CA with non-shockable rhythms have favorable neurological prognoses, ranging from 2 to 15%.

A cohort study involving 114,628 patients with a non-shockable rhythm OHCA (9) demonstrated a significant association between reverting to a shockable rhythm after cycles of CPR and good functional prognoses. Studies conducted in China and abroad have consistently shown that patients with a series of defibrillator shocks during CA exhibit higher rates of ROSC. For acutely ill patients at risk of developing IHCA, monitoring the cardiac rhythm (ECG) and administering appropriate medication and other treatments to reduce mortality rates and improve prognosis is important.

In this study, endotracheal intubation (ETI) was the predominant method of establishing an advanced airway, positively affecting ROSC in patients with IHCA. However, it may also negatively impact neurological outcomes. Brain tissue is highly sensitive to ischemia and hypoxia. Therefore, an advanced airway can fulfill the oxygen demand and improve the metabolic state of the body, particularly the heart and brain tissue, to increase the rate of ROSC. Compared to a balloon mask, an advanced airway can reduce the risk of aspiration to a certain extent.

A study by Aufderheide et al. (13) in prehospital emergency patients showed that establishing an advanced airway was associated with poor long-term neurological outcomes. This may be attributed to unskilled ETI procedures, interrupted chest compression, or inappropriate ventilation. On the contrary, Yeung et al. (10) showed that ETI in patients with IHCA took only 15.8 s and had a high success rate. Furthermore, the decision to perform ETI in patients with IHCA should be made by experienced clinicians to minimize or avoid potential damage caused by the procedures. The benefit of ETI may be greater in patients with a non-defibrillation rhythm than in patients with a defibrillation rhythm (11).

There is no consensus on the optimal time to establish an advanced airway. A single-center retrospective study involving 702 patients in China (14) reported a mean ETI time of 8.8 min, negatively associated with a good neurological prognosis. In contrast, a study found that patients who underwent ETI within 15 min before CPR had worse outcomes than patients who did not (10).

Previous studies consistently show that ROSC and survival rates decrease with increasing CD (15, 16). In this study, the non-ROSC and PNO-12 groups had longer CD (9 min vs. 45 min, $P < 0.001$, respectively; 4.5 min vs. 10 min, $P < .001$, respectively), and these differences were significant. The final results revealed that CD > 23 min independently influenced non-ROSC and was associated with poor prognosis. Timely, continuous, and effective chest

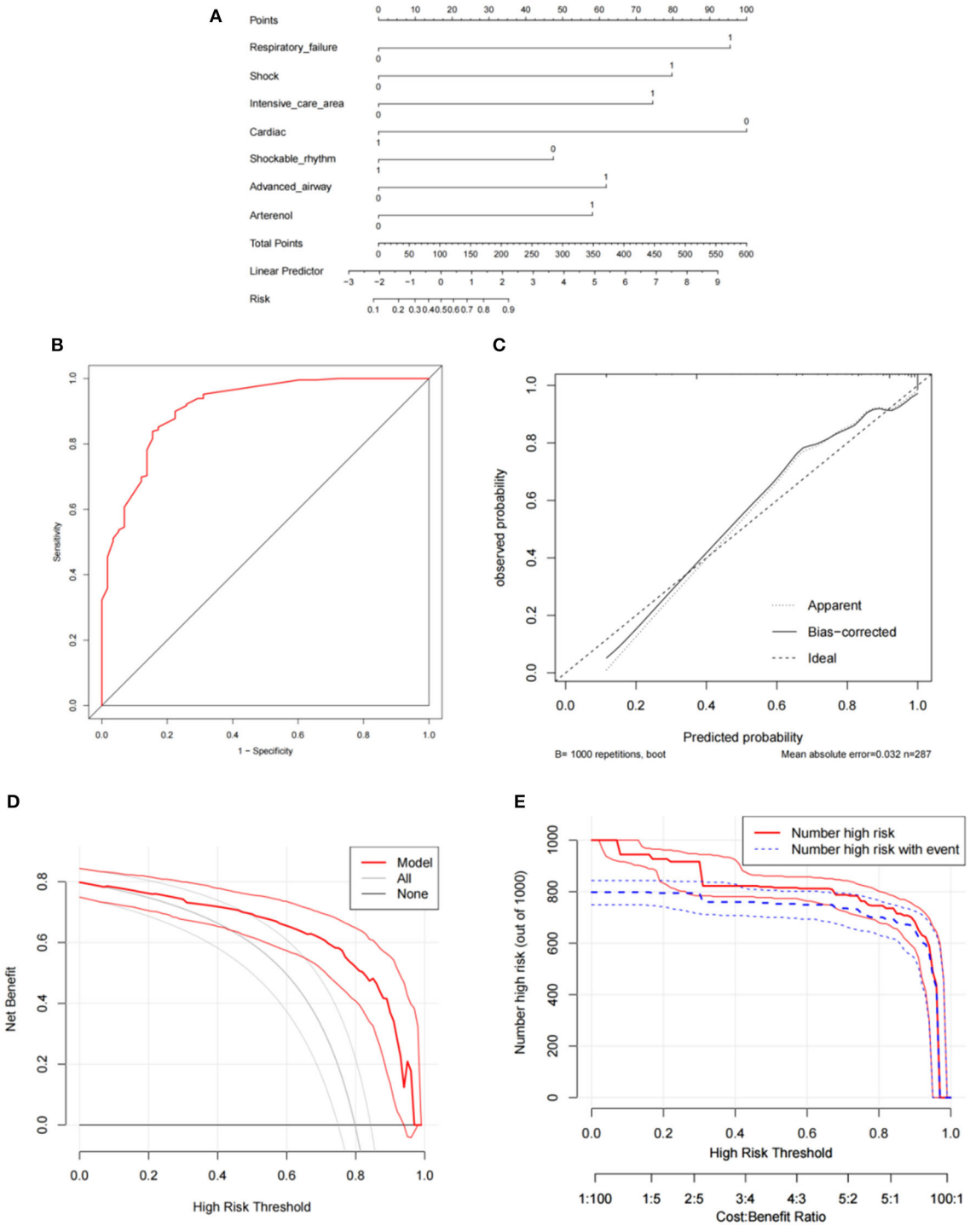

FIGURE 3
Development and evaluation of the predictive model for secondary outcome. **(A)** Nomogram; **(B)** Receiver operating curve; **(C)** Calibration curve; **(D)** Decision curve analysis; **(E)** Clinical impact curve. CPR, cardiopulmonary resuscitation.

compression can improve the ROSC rate. However, prolonged CD leads to irreversible heart, brain, and lung damage caused by ischemia and reperfusion.

Furthermore, prolonged fatigue during chest compression significantly reduces the quality of CPR and negatively affects outcomes. Currently, there is no consensus on the optimal CD. In China, a CD time of 30 min is mostly used as the standard definition. In comparison, the 2015 European Resuscitation Council guidelines recommend discontinuing CPR for cases of irreversible etiology after 20 min (17). However, the optimal CD for other cases remains unclear. Recently, successful reports following long CD (>30 min) have emerged, raising the possibility that CD

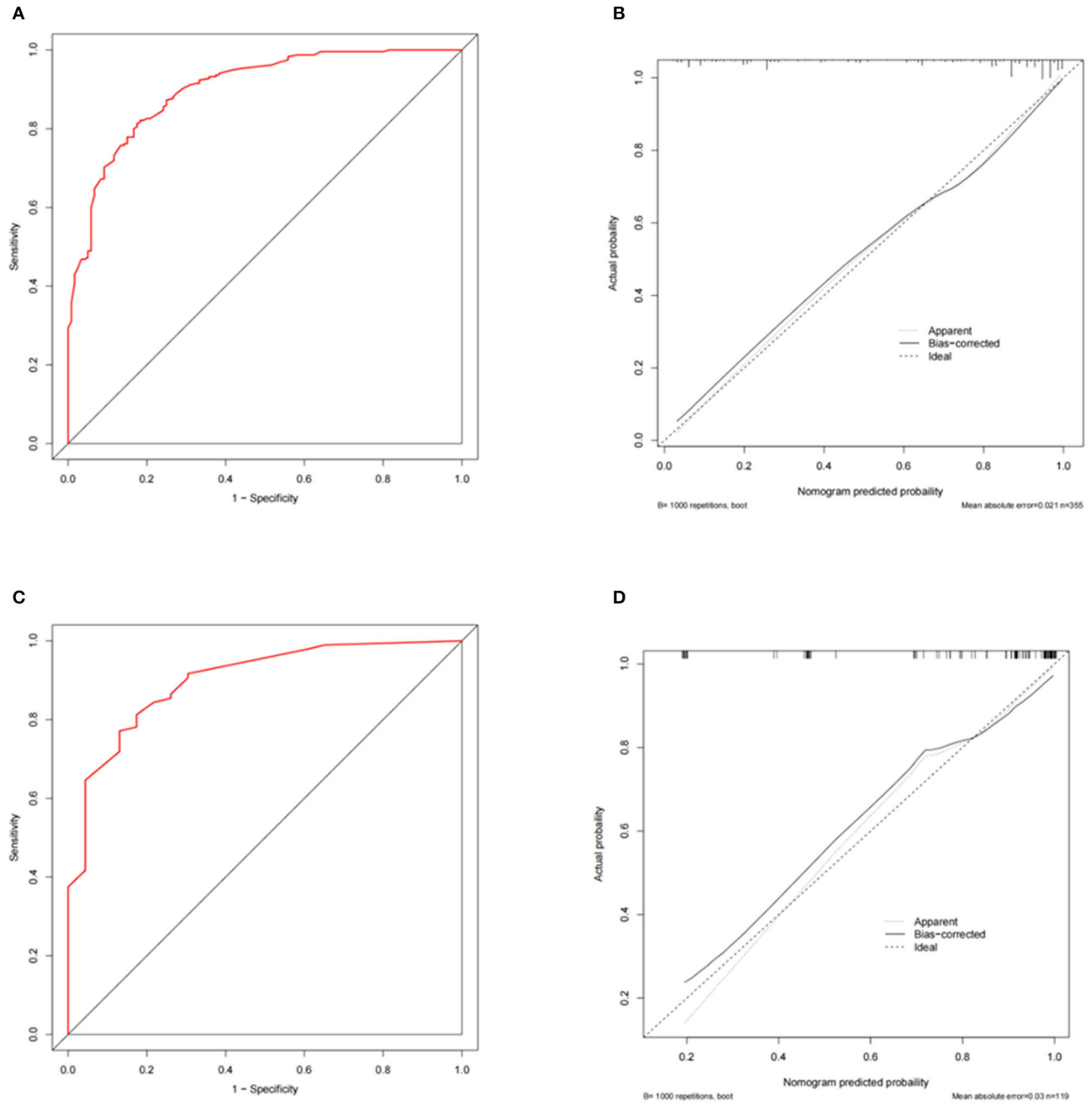

FIGURE 4
External validation of the predictive models for primary and secondary outcomes. **(A, B)** Receiver operating curve and calibration curve for primary outcome; **(C, D)** Receiver operating curve and calibration curve for secondary outcome.

indirectly reflects the severity of the condition and the quality of CPR (18).

Considering individual patient differences and conditions, further multi-center and large-scale clinical studies are necessary to categorize CA-related factors to define the "best threshold" at all levels.

The latest American Heart Association and European Resuscitation Council guidelines recommend the early use of adrenaline, with higher levels of evidence and recommendation (19, 20). Adrenaline strengthens left ventricular and cerebral blood perfusion by exciting α-1 receptors and increasing aortic diastolic pressure, thus improving ROSC and survival rates in patients with CA. However, higher adrenaline (DOA) doses may promote subendocardial vasoconstriction, thus increasing the risk of malignant arrhythmia. With longer CD, increased DOA also leads to a poor neurological prognosis (21). This effect could be due to the simultaneous excitation of the β1 receptor, leading to excessive myocardial oxygen consumption and increased PAMD.

Adrenaline was administered in 662 cases with a median total dose of 3 (IQR: 1, 7) mg in this study. The study findings indicated

that TDOA >3 mg was an independent risk factor for non-ROSC, although it could be insignificant for PNO-12. The disparity in the results may be attributed to several reasons. First, this study was conducted at a single center with a small sample size, which limited the demonstration of the efficacy of adrenaline administration. Second, the study targeted adult patients with IHCA, while similar studies also included patients with OHCA or overall CA.

Recently, some studies (9) used the adrenaline administration rate (total dose/CPR length, mg/min) as an indicator of adrenaline application, reporting that a higher adrenaline administration rate may be associated with a poor neurological outcome after CPR. Furthermore, among IHCA patients who received the same DOA, patients with a body weight of 82.5 kg had a worse prognosis than those with lower body weight. Furthermore, Soar et al. (22) showed that adrenaline better treats patients whose initial heart rhythm is non-shockable.

Noradrenaline is a typical α-receptor agonist, and administration increases aortic and diastolic pressure. In this study, noradrenaline emerged as an independent influencing factor for PNO-12. Callaham et al. (23) reported similar findings in a study showing that noradrenaline had no positive effect on the prognosis of patients with CA, and long-term low-dose administration of noradrenaline could lead to excessive myocardial oxygen consumption, which is associated with death or poor neurological outcomes. In this study, most patients treated with noradrenaline experienced hypotension or shock before and after developing IHCA. Noradrenaline had fewer side effects and a lower incidence of arrhythmia than dopamine (16), and its combination with dobutamine may be more effective and safer (24).

This study has some limitations. First, it was a single-center retrospective study using a small sample size. Second, the analysis was based solely on existing clinical data. Therefore, it is imperative to incorporate supplementary data, such as chest compression quality and specific laboratory indicators, in further studies. This will allow for a comprehensive examination of the clinical characteristics of patients with IHCA and the development of a predictive prognostic model. Consequently, further large-scale and multicenter prospective studies are required to corroborate the results of this study.

5 Conclusions

Most patients with IHCA who underwent CPR were older men. The etiology of IHCA was predominantly noncardiac, and the initial heart rhythm was mainly non-shockable. The continuous ROSC rate was 33.73%, and the good neurological prognosis rate was 6.82%.

Male sex, advanced age, CD >23 min, and TDOA >3 mg were identified as independent risk factors for non-ROSC. Independent protective factors identified before IHCA included arrhythmia, cardiac rhythm of initial defibrillation, and advanced airway intervention. The risk factors for PNO-12 were respiratory failure or shock, occurrence in a monitoring area, advanced airway intervention, and noradrenaline.

Cardiac etiology and initial defibrillation rhythm were identified as independent protective factors. Both models demonstrated good degrees of differentiation, fit, and clinical applicability, allowing for improved prediction of short- and long-term outcomes in patients with IHCA. These models can help clinicians provide more appropriate treatment measures and predict the prognosis for adult patients with IHCA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The First Hospital of Jilin University Institutional Review Board for studies involving humans (Date 2023/09/27, Num.2023-649). Written informed consent was not required to participate in this study in accordance with the local legislation and institutional requirements.

Author contributions

ZL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. JX: Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1323721/full#supplementary-material

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Association between transcutaneous oxygen saturation within 24 h of admission and mortality in critically ill patients with non-traumatic subarachnoid hemorrhage: a retrospective analysis of the MIMIC-IV database

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Background: In critically ill patients, transcutaneous oxygen saturation (SpO_2) upon admission is typically associated with in-hospital mortality. Nevertheless, the available information for patients with non-traumatic subarachnoid hemorrhage (SAH) is limited. In our study, our objective was to assess the correlation between SpO_2 levels and mortality among patients diagnosed with severe SAH.

Methods: In this study, we extracted data from the Medical Information Marketplace in Intensive Care (MIMIC-IV) database, which comprises information on critically ill patients. By employing matching ICD-9 and ICD-10 codes, we identified 3,328 patients diagnosed with SAH. Every individual who was admitted to the intensive care unit (ICU) had their SpO_2 data and various covariates, including age, sex, diagnosis, and duration of stay, recorded upon admission. Subsequently, the patients were categorized into three distinct groups according to their SpO_2 levels: low (≤95%), moderate (95–98%), and high (≥98%). To investigate the association between percutaneous oxygen saturation and mortality in patients with severe SAH, logistic regression, and cubic spline models were utilized. The main outcomes of interest were 28- and 90-day mortality rates. Additionally, subgroup analyses were conducted to evaluate these correlations and assess the consistency of interactions.

Results: A cohort of 864 patients diagnosed with non-traumatic SAH was included in this study. The correlation between SpO_2 and mortality displayed a U-shaped curve when utilizing a finite cubic spline function (non-linearity<0.001), with the nadir in the probability of in-hospital death at 96%. Mortality at 28 and 90days showed an inverse correlation with SpO_2<96% (adjusted odds ratio [OR], 0.8; 95% confidence interval [CI], 0.67–0.95, and 0.76; 95% CI, 0.6–0.96). Conversely, there was a positive correlation between percutaneous oxygen saturation (SpO_2) levels of ≥96% and mortality rates at both 28 and 90days (adjusted OR, 1.17; 95% CI, 1.02–1.35 and 1.2; 95% CI, 1.05–1.39).

Conclusion: In patients with severe subarachnoid hemorrhage, the association between SpO_2 and mortality at 28 and 90 days demonstrated a U-shaped pattern.

When SpO_2 levels were between 95 and 98%, both short- and long-term mortality rates were at their lowest. Patients with significant subarachnoid hemorrhage had a lower chance of survival when their SpO_2 values were either high or low.

KEYWORDS

transcutaneous oxygen saturation, mortality, hypoxia, hyperoxia, subarachnoid hemorrhage, intensive care unit

Introduction

Traumatic subarachnoid hemorrhage (SAH), which accounts for 2–7% of all fatalities (1), is a serious and potentially fatal disorder primarily caused by the rupture of cerebral aneurysms. Compared to ischemic stroke and cerebral hemorrhage, non-traumatic subarachnoid hemorrhage is a more severe type of stroke (2), comprising only 5% of all strokes (3). It has an annual incidence of 8 per 100,000 people (4), occurs relatively early in life (3), and is associated with high mortality, morbidity, and poor prognosis when compared to more common strokes (5). Population-based research indicates that the median age of non-traumatic SAH patients is 55 years, and they have a morbidity and mortality rate of approximately 50% (2, 6, 7). One-third of SAH patients pass away before reaching the hospital, and the remaining patients require ICU care (1, 5). Despite adequate therapeutic care in the ICU, patients with severe SAH continue to experience a significant rate of mortality (8). Reports suggest that 30% of SAH patients die within 48 h of admission, 56% die after the first week, and 76% die after the second week (9).

Transcutaneous oxygen saturation measures how much oxygen is bound to hemoglobin in arterial blood and can be used to monitor cardiovascular disease, determine the respiratory–circulatory condition of ICU patients, and determine whether or not the blood oxygen level is normal (10). SpO_2 has the benefit of being able to continually measure blood oxygen levels, dynamically reflecting the hypoxic or hyperoxic status of ICU patients, as well as being simple to monitor and observe and non-invasive. It also has an advantage over partial pressure of arterial oxygen (PaO_2) and arterial oxygen saturation (SaO_2) (11–15).

The detrimental effects of hypoxia are well-established, and SpO_2 is valuable for monitoring hypoxemia. However, hyperoxia can also have negative consequences (16–22). Increased oxidative stress and inflammation resulting from excessive oxygen supplementation can lead to lung and systemic damage (23). Moreover, studies have demonstrated that elevated levels of oxygen saturation can adversely affect the central nervous system (24). Oxygen therapy lacks a defined standard in many therapeutic situations, and its connection with mortality among individuals with severe subarachnoid hemorrhage remains unknown. While studies have discussed the impact of transcutaneous oxygen saturation on in-hospital mortality in intensive care patients with brain injury (25), patients with severe non-traumatic subarachnoid hemorrhage have not been extensively investigated.

Therefore, this study utilizes data from a large intensive care database to examine the relationship between transcutaneous oxygen saturation and death in patients with critical subarachnoid hemorrhage.

Materials and methods

Study population

The Critical Care Medical Information Marketplace MIMIC-IV (v2.2) database, maintained by the MIT Laboratory of Computational Physiology,[1] was utilized in this study and contains all the necessary data. This database is a comprehensive, open-access, well-documented, and freely available longitudinal single-center database that encompasses inpatient information from cases accepted into the Boston Higher Medical Center in Boston, Massachusetts, United States, between 2008 and 2019. The extraction of unprocessed patient data from the database and its subsequent development for retrospective investigations was validated by the Beth Israel Deaconess Medical Center (Boston, MA, United States) and the Massachusetts Institute of Technology (Cambridge, MA, United States).

It was justified to utilize the MIMIC-IV (V2.2) database for this study for the following reasons: First, all data within the database were carefully de-identified, meaning patient identities were replaced with randomization numbers. This anonymization process is an integral part of MIMIC-IV's design, which aims to facilitate various research and instructional endeavors while upholding patient privacy and simplifying the conduct of clinical research. Consequently, the requirement for informed consent was waived by the Ethics Committee at Beth Israel Deaconess Medical Center. It should be highlighted that this study followed the guidelines stated in the Declaration of Helsinki and adhered to the principles outlined in the Statement to Strengthen Reporting of Observational Studies in Epidemiology (STROBE). Furthermore, author JL has satisfactorily completed the Collaborative Institutional Training Initiative (CITI) course and obtained a passing score on the "Data or Sample Study Only" exam (ID: 52698592), granting her access to the database for extracting the information required to analyze the correlation between mortality and SpO_2 in patients with severe subarachnoid hemorrhage. The diagnosis of SAH determined using the International Classification of Diseases (ICD) includes both the ninth revision (ICD-9) and the tenth revision (ICD-10).

There were 257,366 patients in MIMIC-IV overall from 2008 to 2019, of whom 69,619 were admitted to the ICU. Of these, a total of 3,328 patients were selected based on the following recorded ICD-9 code: 430 and ICD-10 codes: I60, I600 ~ I6012, I6000 ~ I6002, I6020 ~ I6022, I6030 ~ I6032, and I6050 ~ I6052, and 3,328 patients with SAH were included. An analysis was conducted

1 https://physionet.org/content/mimiciv/

that included patients who satisfied the following criteria for selection: (1) it was their first ICU admission; (2) they were over 18 years of age; and (3) SpO_2 recordings were available within 24 h before admission. Exclusion criteria included those as follows: (1) clear evidence of trauma as the cause; (2) ICU stay of less than 24 h; (3) ICU readmission; (4) missing data exceeding 5%; (5) lack of follow-up information; (6) ICU stay of fewer than 48 h with fewer than 24 recorded SpO_2 measures; and (7) patients who had not received oxygen therapy. As a result, this study only comprised 864 patients.

Data acquisition

The MIMIC-IV database was utilized to extract the following variables on the initial day of ICU admission: (1) Demographic variables: age and insurance status. (2) Vital signs: temperature, respiratory rate, heart rate, and oxygen saturation levels were recorded on the first day of ICU admission. (3) Comorbidities: comorbidity index, heart failure, atrial fibrillation, vascular disease, stroke, chronic respiratory disease, liver disease, diabetes mellitus, nephropathy, benign tumors, and metastatic solid tumors. (4) Laboratory tests were performed within the initial 24 h after ICU admission, including white blood cell count, platelet count, serum potassium level, serum sodium level, hemoglobin level, blood glucose level, serum chloride level, urea nitrogen level, creatinine level, anion gap, APTT, and other laboratory markers. If a variable was measured multiple times within the previous 24 h, the mean value was used. (5) Glasgow Coma Scale (GCS), Simplified Acute Physiology Score II (SAPS II), and Acute Physiology Score III (APS III) scores were used to assess the severity of illness upon admission. (6) The duration of ICU stay, overall length of hospital stay, occurrences of death within the ICU, and cases of death during hospitalization. Please note that all the data utilized in this study for analysis and research purposes were exclusively extracted from the MIMIC-IV database.

Endpoints

Endpoints include short-term mortality (28-day mortality) and long-term mortality (90-day mortality).

Statistics

Regarding continuous variables, statistical measures such as the mean, standard deviation, or median (interquartile range) were employed. Based on the normality of the distribution, either independent sample *t*-tests or Mann–Whitney U-tests were conducted for statistical comparison. To compare non-normally distributed variables between groups, the Wilcoxon rank sum test was utilized. They were also reported as the median interquartile range (IQR). Categorical variable hypotheses were examined using the chi-squared test (or Fisher's exact method), presenting the number of cases (%) for each analysis.

Based on 95 and 98%, SpO_2 was split into three groups: 95, 95–98, and 98%. It was investigated how SpO_2 levels correlated with ICU or hospital outcomes.

Using univariate and multivariate logistic regression models, the association between SpO_2 levels and mortality rates at both 28- and 90-day intervals in patients diagnosed with severe SAH was examined. Model 1 referred to an unadjusted model; model 2 referred to a minimum adjusted model, adjusted for demographic factors such as sex, age, and race; and model 3 was a maximum adjusted model: adjusted for sex, age, race, insurance status, heart rate, respiratory rate, temperature, GCS score, atrial fibrillation, congestive heart failure, vascular disease, stroke, chronic lung disease, liver disease, diabetes mellitus, renal disease, benign tumors, white blood cell count, hemoglobin, blood chloride, blood glucose, platelet count, creatinine, anion gap, APTT, and length of hospital stay; and model 4 was a comprehensive and fully adjusted model that considered all variables listed in Table 1, ensuring a thorough examination of their impact on the outcomes.

Additionally, we employed stratified linear regression models, likelihood ratio tests, and curve fitting to establish the correlation between SpO_2 levels and ICU or in-hospital mortality rates. In the study, we had the following data: age (<60 or ≥ 60 years), GCS score (<8 or ≥ 8), SAPS II score (<30 or ≥ 30), and length of ICU stay (<7 or ≥ 7 days). Statistical analysis was conducted using the R software package (R Foundation, http://www.R-project.org) and Free Statistics software version 1.7. A value of $p < 0.05$ was employed as the threshold for determining statistical significance.

Results

Baseline characteristics of the participants

The analysis included 864 consecutive participants (Figure 1). Their SpO_2 levels were categorized into three groups using thresholds of 95 and 98%. Table 1 provides an overview of the baseline characteristics, revealing that the average age of the participants was 64.0 ± 17.1 years, with men accounting for 46.1% of the study population. Participants with high SpO_2 (≥98%) were younger and mostly women. Mortality at 28 and 90 days was 22.1 and 25.5%, respectively. The low SpO_2 (<95%) group had the highest mortality rate, followed by the high SpO_2 (≥98%) group ($p < 0.05$). In the high SpO_2 (≥98%) group, several notable differences were observed when compared to other racial backgrounds. These differences included a higher heart rate, lower systolic blood pressure, elevated body temperature, higher APS III score, lower GCS score, increased white blood cell count, lower hemoglobin level, higher chloride ion level, shorter ICU stay, and shorter overall hospital stay ($p < 0.05$). In the low SpO_2 (<95%) group, participants displayed distinct characteristics, including higher systolic blood pressure, lower diastolic blood pressure, decreased mean arterial pressure, accelerated respiratory rate, higher SAPS II score, elevated BUN level, prolonged ICU stay, and extended overall hospital stay ($p < 0.05$). However, no significant differences were observed among the three groups in terms of complications and relevant parameters ($p < 0.05$).

The impact of percutaneous oxygen saturation on 28- and 90-day mortality rates

In Table 2, the results of univariate logistic regression analysis demonstrated significant correlations between several factors and the

TABLE 1 Baseline characteristics of selected patients grouped by SpO_2 level.

Variables	Total (n = 864)	SpO_2 <95% (n = 62)	SpO_2 (≥95%, <98%) (n = 352)	SpO_2 (≥98%) (n = 450)	p value
*Age, year	64.0 ± 17.1	72.0 ± 14.2	65.3 ± 16.2	61.9 ± 17.7	< 0.001
*Sex, n (%)					< 0.001
Female subjects	466 (53.9)	32 (51.6)	176 (50)	258 (57.3)	
Male subjects	398 (46.1)	30 (48.4)	176 (50)	192 (42.7)	
*Race, n (%)					
White	551 (63.8)	38 (61.3)	272 (77.3)	241 (53.6)	< 0.001
Asian	28 (3.2)	3 (4.8)	7 (2)	18 (4)	
Black	52 (6.0)	3 (4.8)	17 (4.8)	32 (7.1)	
Other	233 (27.0)	18 (29)	56 (15.9)	159 (35.3)	
*Insurance, n (%)					0.007
Medicaid	57 (6.6)	2 (3.2)	25 (7.1)	30 (6.7)	
Medicare	317 (36.7)	37 (59.7)	127 (36.1)	153 (34)	
Other	490 (56.7)	23 (37.1)	200 (56.8)	267 (59.3)	
*HR, beats/min	79.8 ± 14.2	78.5 ± 14.8	78.1 ± 13.4	81.2 ± 14.6	0.006
*SBP, mmHg	124.7 ± 14.3	126.4 ± 20.7	126.0 ± 13.4	123.4 ± 13.9	0.023
*DBP, mmHg	63.9 ± 9.6	61.0 ± 9.6	64.8 ± 9.4	63.6 ± 9.7	0.009
*MBP, mmHg	80.7 ± 9.4	77.8 ± 10	80.9 ± 8.7	80.9 ± 9.7	0.045
RR, beats/min	18.1 ± 3.2	18.9 ± 4	17.9 ± 3.4	18.1 ± 3	0.092
*Temperature, °C	37 ± 0.6	36.9 ± 0.8	36.9 ± 0.5	37 ± 0.6	0.002
*SAPSII	33.4 ± 13.1	40.1 ± 18.3	30.1 ± 11.9	35 ± 12.6	< 0.001
*APSIII	39.0 (28, 56)	42.5 (29, 73.8)	33 (25.8, 46)	44 (30, 61.8)	< 0.001
*GCS	13.9 ± 1.9	13.9 ± 2.3	14.1 ± 1.5	13.8 ± 2.2	0.045
*Charlson index	4 (3, 6)	5 (4, 6)	4 (3, 6)	4 (3, 6)	< 0.001
Myocardial infarct	60 (6.9)	4 (6.5)	22 (6.2)	34 (7.6)	0.776
Congestive heart failure	73 (8.4)	8 (12.9)	31 (8.8)	34 (7.6)	0.348
Peripheral vascular disease	77 (8.9)	7 (11.3)	31 (8.8)	39 (8.7)	0.791
*Cerebrovascular disease	572 (66.2)	47 (75.8)	218 (61.9)	307 (68.2)	0.044
Chronic pulmonary disease	109 (12.6)	12 (19.4)	43 (12.2)	54 (12)	0.252
Mild liver disease	41 (4.7)	2 (3.2)	17 (4.8)	22 (4.9)	0.934
Diabetes	136 (15.7)	13 (21)	51 (14.5)	72 (16)	0.424
Renal disease	65 (7.5)	7 (11.3)	25 (7.1)	33 (7.3)	0.49
Metastatic solid tumor	15 (1.7)	1 (1.6)	5 (1.4)	9 (2)	0.837
*WBC, 10^9/L	12.4 (9.3, 15.9)	12.1 (9.0, 15.8)	11.8 (8.7, 14.9)	13.2 (10.1, 16.8)	< 0.001
*Hemoglobin, g/dL	11.6 ± 2.1	12 ± 1.7	12 ± 2.1	11.2 ± 2	< 0.001
platelets, 10^9/L	202.6 ± 82.3	209.6 ± 78.3	207.2 ± 87.0	198.1 ± 78.9	0.233
*Glucose, mg/dL	135.2 (116.6, 158.8)	143.8 (123.5, 242.9)	132.2 (114.0, 152.9)	136.2 (118.4, 159)	0.007
*Sodium, mmol/L	141.1 ± 4.8	145 ± 6	140.3 ± 4.1	141.8 ± 4.9	< 0.001
Potassium, mmol/L	4.3 ± 0.7	4.2 ± 0.5	4.2 ± 0.7	4.3 ± 0.8	0.546
*Chloride, mmol/L	107.1 ± 5.6	105.4 ± 6	105.5 ± 5	108.6 ± 5.7	< 0.001
*BUN, mg/dL	17 (13, 22.2)	20.5 (16, 28)	17 (13, 23)	16 (12, 22)	< 0.001
*Creatinine, mg/dL	0.9 (0.7, 1.1)	1 (0.8, 1.3)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.023
*Bicarbonate, mmoL/L	24.8 ± 3.3	25.4 ± 4.8	25.3 ± 3	24.3 ± 3.1	< 0.001
Anion gap, mmoL/L	16 ± 3.4	16.2 ± 3	15.8 ± 3.2	16.2 ± 3.6	0.364
*INR	1.3 ± 0.9	1.4 ± 0.7	1.4 ± 1.3	1.2 ± 0.4	0.045
PT, s	12.8 (11.9, 14.4)	13.4 (12.2, 14.9)	12.8 (11.9, 14.4)	12.8 (11.9, 14.1)	0.133
APTT, s	28.5 (25.6, 33.5)	28.9 (26.4, 34.2)	28.4 (25.6, 33.0)	28.6 (25.4, 33.8)	0.57
*ICU LOS (day)	3 (1, 9)	1 (1, 2)	2 (1, 7)	5 (2, 11)	< 0.001
*Hospital LOS (day)	8 (4, 15)	3(1, 9)	7 (4, 12)	10 (5, 19)	< 0.001
*Hospital mortality, n (%)	166 (19.2)	29 (46.8)	44 (12.5)	93 (20.7)	< 0.001
*28-day mortality, n (%)	191 (22.1)	25 (40.3)	65 (18.5)	101 (22.4)	< 0.001
*90-day mortality, n (%)	220 (25.5)	28 (45.2)	73 (20.7)	119 (26.4)	< 0.001

SpO_2, Percutaneous oxygen saturation; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MBP, Mean blood pressure; RR, Respiratory rate; HR, Heart rate; SAPS II, Simplified acute physiology score II; GCS, Glasgow Coma Score; Chronic pulmonary disease, Chronic obstructive pulmonary disease; WBC, White blood cell; BUN, Blood urea nitrogen; INR, International normalized ratio; PT, Prothrombin time; APTT, Activated partial thromboplastin time; ICU LOS, Intensive care unit length of stay; Hospital LOS, Hospital length of stay.

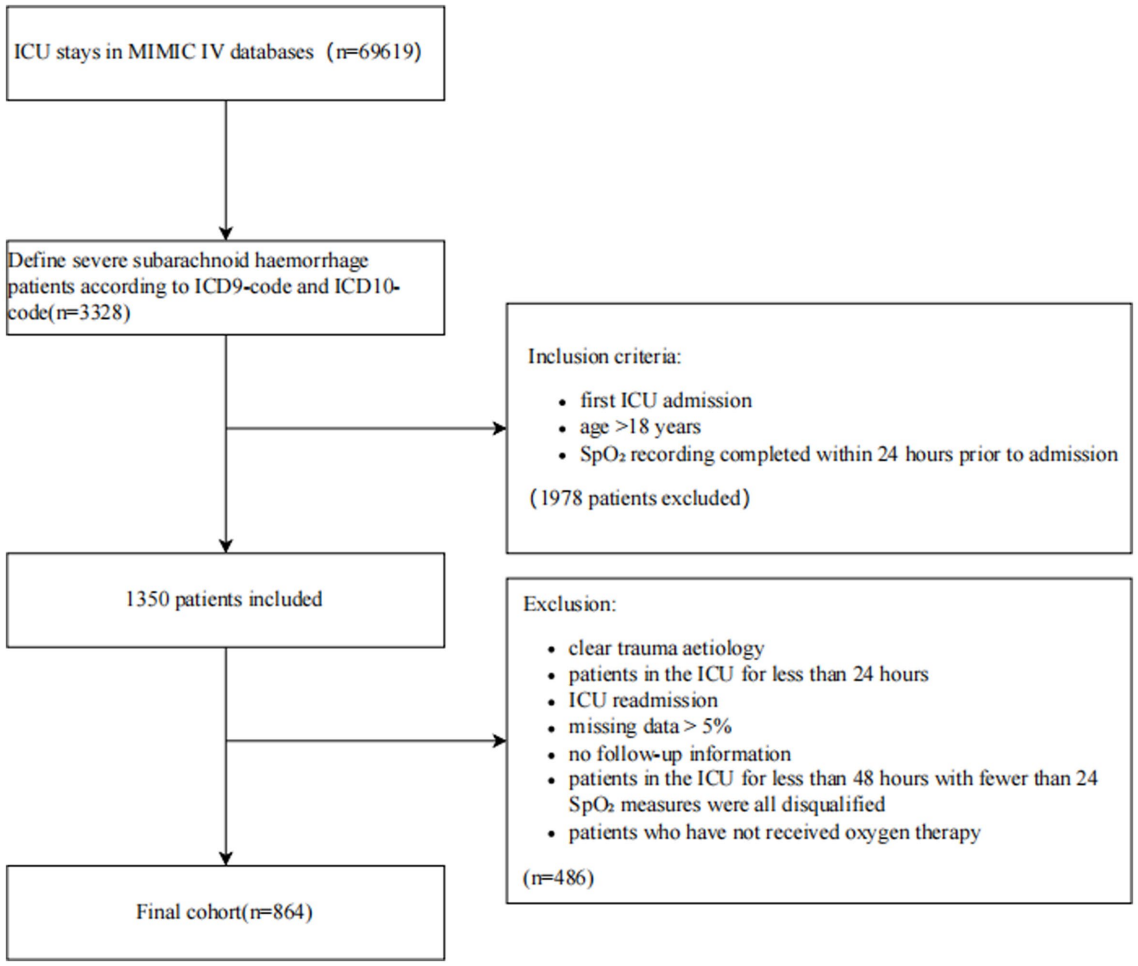

FIGURE 1
Patient selection flowchart. ICD10, Tenth version of the International Classification of Disease; ICD9, Ninth version of the International Classification of Disease; ICU, Intensive care unit; MIMIC-IV, Medical information mart for intensive care fourth edition; SpO_2, Pulse oximetry-derived oxygen saturation.

28- and 90-day mortality rates. These factors included age, insurance status, heart rate, body temperature, respiratory rate, oxygen saturation, comorbidity index, congestive heart failure, chronic respiratory disease, renal disease, metastatic solid tumors, white blood cell count, hemoglobin level, serum sodium, serum chloride, blood urea nitrogen, anion gap, and hospitalization duration ($p < 0.05$).

In the multivariable logistic model, we observed consistent associations between SpO_2 and the 28- and 90-day mortality rates across all four models (Table 3). When analyzing SpO_2 as a continuous variable, we found a negative correlation with mortality rates. Furthermore, when SpO_2 was categorized, the SpO_2 (<95%) group exhibited an increased risk of mortality compared to the SpO_2 (95–98%) group in critically ill SAH patients (adjusted OR, 1.67; 95% CI, 1.08–3.46 for 28-day mortality, and 1.79; 95% CI, 1.02–3.65 for 90-day mortality). In the fully adjusted model, which took into account all covariates listed in Table 1, the SpO_2 (>98%) group showed an increased risk of mortality compared to the SpO_2 (95–98%) group in critically ill SAH patients (adjusted OR, 1.14; 95% CI, 1.01–1.36 for 28-day mortality, and 1.36; 95% CI, 1.12–1.47 for 90-day mortality). However, no significant relationship was found between high oxygen saturation ($SpO_2 > 98\%$) and mortality rates in critically ill SAH patients in the unadjusted model, minimal adjustment model, and maximal adjustment model (which included various demographic and clinical factors).

Figure 2 illustrates the correlation between average SpO_2 and both 28- and 90-day mortality rates. It is noteworthy that both hypoxemia and hyperoxemia are associated with an increased risk of mortality. As a result, we have identified a specific range of SpO_2 values that carries a lower risk of mortality. To account for various factors such as age, sex, race, GCS score, SAPS II score, APS III score, and length of hospital stay, we employed restricted cubic splines to analyze the relationship between SpO_2 and mortality rates in SAH patients. Our findings revealed a non-linear, U-shaped pattern in the relationship between SpO_2 and in-hospital mortality ($p < 0.001$). The nadir of the mortality risk was observed at 96% SpO_2. As the saturation level increased beyond this point, a less pronounced U-shaped curve was observed. It is worth mentioning that, even without precise information on corresponding PaO_2 levels, we can infer that higher oxygen levels are relatively less harmful than hypoxia.

Using a two-part logistic regression model, we identified a critical threshold of 96% for SpO_2 (as shown in Table 4). When SpO_2 levels were below 96%, we observed a negative association with both 28-day and 90-day mortality rates (adjusted OR, 0.8; 95% CI, 0.67–0.95 and 0.76; 95% CI, 0.6–0.96). Conversely, when SpO_2 levels were equal to

TABLE 2 Univariate logistic analysis between oxygen saturation and 28- or 90-day mortality.

Variable	28-day mortality		90-day mortality	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
*Age	1.04 (1.03 ~ 1.05)	<0.001	1.04 (1.02 ~ 1.05)	<0.001
Sex: male subjects vs. female subjects	1.21 (0.88 ~ 1.67)	0.249	1.21 (0.89 ~ 1.64)	0.231
Race, *n* (%)				
White	1		1	
Asian	1.55 (0.67 ~ 3.61)	0.309	1.55 (0.68 ~ 3.51)	0.294
Black	0.7 (0.32 ~ 1.54)	0.38	0.78 (0.38 ~ 1.6)	0.495
*Other	1.41 (0.98 ~ 2.01)	0.061	1.46 (1.04 ~ 2.06)	0.029
Insurance				
Medicaid	1		1	
*Medicare	4.33 (1.8 ~ 10.41)	0.001	4.41 (1.94 ~ 10.04)	<0.001
Other	1.61 (0.67 ~ 3.88)	0.289	1.65 (0.73 ~ 3.76)	0.232
*HR, beats/min	1.01 (1 ~ 1.02)	0.096	1.01 (1 ~ 1.02)	0.023
SBP, mmHg	1.01 (1 ~ 1.02)	0.06	1.01 (1 ~ 1.02)	0.168
DBP, mmHg	0.99 (0.97 ~ 1.01)	0.176	0.99 (0.98 ~ 1.01)	0.401
MBP, mmHg	1 (0.98 ~ 1.02)	0.899	1 (0.99 ~ 1.02)	0.761
*RR, beats/min	1.16 (1.1 ~ 1.21)	<0.001	1.17 (1.12 ~ 1.23)	<0.001
*Temperature, °C	0.87 (0.66 ~ 1.14)	0.308	0.75 (0.58 ~ 0.97)	0.028
*SpO_2, mean ± SD	0.91 (0.86 ~ 0.97)	0.004	0.92 (0.86 ~ 0.98)	0.008
*SAPSII	1.07 (1.06 ~ 1.09)	<0.001	1.07 (1.06 ~ 1.09)	<0.001
*APSIII	1.03 (1.03 ~ 1.04)	<0.001	1.04 (1.03 ~ 1.04)	<0.001
*GCS	0.82 (0.76 ~ 0.89)	<0.001	0.82 (0.76 ~ 0.88)	<0.001
*Charlson comorbidity index	1.28 (1.2 ~ 1.38)	<0.001	1.29 (1.21 ~ 1.38)	<0.001
*Myocardial infarct	1.7 (0.96 ~ 3.01)	0.067	1.77 (1.02 ~ 3.07)	0.041
*Congestive heart failure	2.24 (1.35 ~ 3.72)	0.002	2.21 (1.35 ~ 3.62)	0.002
Peripheral vascular disease	0.92 (0.52 ~ 1.63)	0.769	0.96 (0.56 ~ 1.64)	0.868
Cerebrovascular disease	1.15 (0.81 ~ 1.62)	0.43	1.16 (0.84 ~ 1.61)	0.377
*Chronic pulmonary disease	1.73 (1.11 ~ 2.69)	0.015	1.61 (1.04 ~ 2.47)	0.031
*Mild liver disease	1.89 (0.97 ~ 3.69)	0.061	1.94 (1.02 ~ 3.71)	0.044
Diabetes	1.27 (0.83 ~ 1.94)	0.267	1.44 (0.97 ~ 2.15)	0.074
*Renal disease	3.17 (1.89 ~ 5.32)	<0.001	2.94 (1.76 ~ 4.92)	<0.001
*Metastatic solid tumor	4.16 (1.49 ~ 11.62)	0.007	4.54 (1.6 ~ 12.89)	0.005
*WBC, 10^9/L	1.02 (1 ~ 1.05)	0.044	1.03 (1 ~ 1.05)	0.018
*Hemoglobin, g/dL	0.89 (0.83 ~ 0.97)	0.004	0.89 (0.83 ~ 0.96)	0.002
*Platelets, 10^9/L	1 (0.99 ~ 1)	0.002	1 (0.99 ~ 1)	0.002
Glucose, mg/dL	1 (1 ~ 1)	0.598	1 (1 ~ 1)	0.569
*Sodium, mmol/L	1.07 (1.04 ~ 1.11)	<0.001	1.08 (1.04 ~ 1.12)	<0.001
*Potassium, mmol/L	1.32 (1.08 ~ 1.62)	0.006	1.32 (1.09 ~ 1.61)	0.005
*Chloride, mmol/L	1.04 (1.01 ~ 1.07)	0.004	1.05 (1.02 ~ 1.08)	<0.001
*BUN, mg/dL	1.04 (1.03 ~ 1.06)	<0.001	1.04 (1.03 ~ 1.06)	<0.001
*Creatinine, mg/dL	1.25 (1.04 ~ 1.5)	0.019	1.25 (1.04 ~ 1.5)	0.02
Bicarbonate, mmoL/L	0.97 (0.93 ~ 1.02)	0.286	0.97 (0.92 ~ 1.02)	0.19
*Anion gap, mmoL/L	1.1 (1.05 ~ 1.15)	<0.001	1.1 (1.05 ~ 1.15)	<0.001
INR	1.06 (0.91 ~ 1.24)	0.434	1.1 (0.95 ~ 1.28)	0.218
PT, s	1.01 (0.99 ~ 1.02)	0.431	1.01 (1 ~ 1.03)	0.173
APTT, s	1 (1 ~ 1.01)	0.335	1 (1 ~ 1.01)	0.261
*ICU LOS (day)	0.97 (0.94 ~ 0.99)	0.014	0.97 (0.95 ~ 0.99)	0.011
*Hospital LOS (day)	0.95 (0.93 ~ 0.97)	<0.001	0.95 (0.93 ~ 0.97)	<0.001

SpO_2, Percutaneous oxygen saturation; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MBP, Mean blood pressure; RR, Respiratory rate; HR, Heart rate; SAPS II, Simplified acute physiology score II; GCS, Glasgow Coma Score; Chronic pulmonary disease, Chronic obstructive pulmonary disease; WBC, White blood cell; BUN, Blood urea nitrogen; INR, International normalized ratio; PT, Prothrombin time; APTT, Activated partial thromboplastin time; ICU LOS, Intensive care unit length of stay; and Hospital LOS, Hospital length of stay.

TABLE 3 Multivariate logistic analysis between percutaneous oxygen saturation and 28- or 90-day mortality.

Variable	Non-adjusted model		Minimally adjusted model		Multiply adjusted model		Fully adjusted model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
28-day mortality								
*SpO_2 (%)	0.91 (0.86 ~ 0.97)	0.004	0.94 (0.88 ~ 1.01)	0.07	0.96 (0.89 ~ 1.04)	0.301	0.91 (0.84 ~ 0.99)	0.033
SpO_2 tertiles								
*Low (<95%)	2.98 (1.68 ~ 5.3)	<0.001	2.36 (1.29 ~ 4.28)	0.005	1.77 (1.1 ~ 3.48)	0.06	1.67 (1.08 ~ 3.46)	0.046
Medium (95–98%)	Reference		Reference		Reference		Reference	
High (>98%)	1.28 (0.9 ~ 1.81)	0.168	1.35 (0.93 ~ 1.96)	0.114	1.24 (0.81 ~ 1.92)	0.324	1.14 (1.01 ~ 1.36)	0.502
p for trend	0.85 (0.66 ~ 1.09)	0.201	0.93 (0.72 ~ 1.21)	0.602	0.96 (0.7 ~ 1.31)	0.792	0.75 (0.54 ~ 1.05)	0.094
90-day mortality								
*SpO_2 (%)	0.92 (0.86 ~ 0.98)	0.008	0.95 (0.89 ~ 1.01)	0.1	0.97 (0.9 ~ 1.05)	0.481	0.92 (0.85 ~ 1)	0.041
SpO_2 tertiles								
*Low (<95%)	3.15 (1.79 ~ 5.52)	<0.001	2.5 (1.39 ~ 4.49)	0.002	1.82 (0.93 ~ 3.55)	0.08	1.79 (1.02 ~ 3.65)	0.012
Medium (95–98%)	Reference		Reference		Reference		Reference	
High (>98%)	1.37 (0.99 ~ 1.92)	0.061	1.45 (1.02 ~ 2.07)	0.04	1.38 (0.91 ~ 2.09)	0.129	1.36 (1.12 ~ 1.47)	0.767
p for trend	0.89 (0.7 ~ 1.13)	0.33	0.97 (0.75 ~ 1.25)	0.816	1.03 (0.76 ~ 1.39)	0.86	0.79 (0.57 ~ 1.09)	0.146

Unadjusted: Unadjusted for covariates. Minimally adjusted model: Adjusted for age, sex, and race. Multivariable adjusted model: Adjusted for age, sex, race, insurance status, heart rate, respiratory rate, temperature, GCS score, congestive heart failure, atrial fibrillation, vascular disease, stroke, chronic lung disease, liver disease, diabetes, renal disease, benign tumor, white blood cell count, hemoglobin, platelet count, blood glucose, blood chloride, creatinine, anion gap, APTT, and length of hospital stay. Fully adjusted model: Adjusted for all covariates listed in Table 1. SpO_2, Percutaneous oxygen saturation; OR, Odds ratio; CI, Confidence interval.

or higher than 96%, we found a positive association with 28-day and 90-day mortality rates (adjusted OR, 1.17; 95% CI, 1.02–1.35 and 1.2; 95% CI, 1.05–1.39). These results highlight a clear inflection point at the SpO_2 threshold of 96%, indicating a significant change in mortality risk as SpO_2 levels fall below or rise above this critical value. It is important to note that these associations indicate a change in mortality risk as SpO_2 levels fall below or rise above the 96% threshold.

Sensitivity analysis

Subgroup analyses were performed considering confounding factors such as age, sex, GCS score, SAPS II score, comorbidities (diabetes, myocardial infarction, cerebrovascular disease, congestive heart failure, and renal disease), ICU length of stay, and total length of hospital stay (refer to Figures 3, 4). The results remained robust after these analyses. An interaction was observed between the GCS score and the total length of hospital stay for the 28-day mortality rate. Similarly, an interaction was found among age, GCS score, and total length of hospital stay for the 90-day mortality rate. However, no significant interactions were detected among the other variables ($p > 0.05$). These subgroup analyses strengthen our findings by considering potential confounders and demonstrating the consistency of the results across various subgroups, supporting the reliability of our findings.

Discussion

This study undertook an investigation into the relationship between SpO_2 levels and mortality rates among individuals afflicted with subarachnoid hemorrhage (SAH). Specifically, we investigated the association between average SpO_2 within 24 h of admission and both short-term (28-day) and long-term (90-day) mortality rates. Our findings unveiled an independent correlation between SpO_2 levels and the risk of mortality in SAH patients. Regardless of the approach taken, whether analyzing SpO_2 as a continuous or categorical variable, we observed a significant association between SpO_2 levels and both short-term and long-term mortality rates. Additionally, our analysis using restricted cubic splines indicated a distinctive U-shaped curve in the relationship between SpO_2 and mortality rates. This U-shaped curve suggested that there was a nadir of mortality risk at approximately 96% SpO_2, indicating that mortality rates were the lowest within this range. Notably, the significance of these associations persisted even after meticulous adjustment for potential confounding factors. It is noteworthy that maintaining SpO_2 levels within the range of 95–98% appeared to be beneficial for patient outcomes, as this range was associated with the lowest short-term and long-term mortality rates. Deviations from this optimal range, either above or below, had negative effects on patient survival. Overall, our study emphasizes the independent correlation between SpO_2 levels assessed during the initial 24 h of admission and subsequent mortality rates among individuals diagnosed with SAH. These findings underscore the importance of monitoring and optimizing SpO_2 levels to improve patient outcomes in this specific population. The correlation between SpO_2 and PaO_2 is deemed reliable when SpO_2 levels are within the range of 95–98%. This range effectively reduces the likelihood of underestimating hypoxemia or hyperoxemia occurrences (26). Furthermore, the therapeutic benefits of SpO_2 lie in its capacity to facilitate adjustments in inspired oxygen and ventilator settings according to fluctuations in SpO_2 readings. This obviates the necessity for intermittent arterial blood gas measurements, providing a more streamlined approach to patient management (27).

It was believed that higher blood oxygen saturation (SpO_2) resulted in better patient survival rates. However, our research findings have challenged this assumption. Our findings revealed that the group

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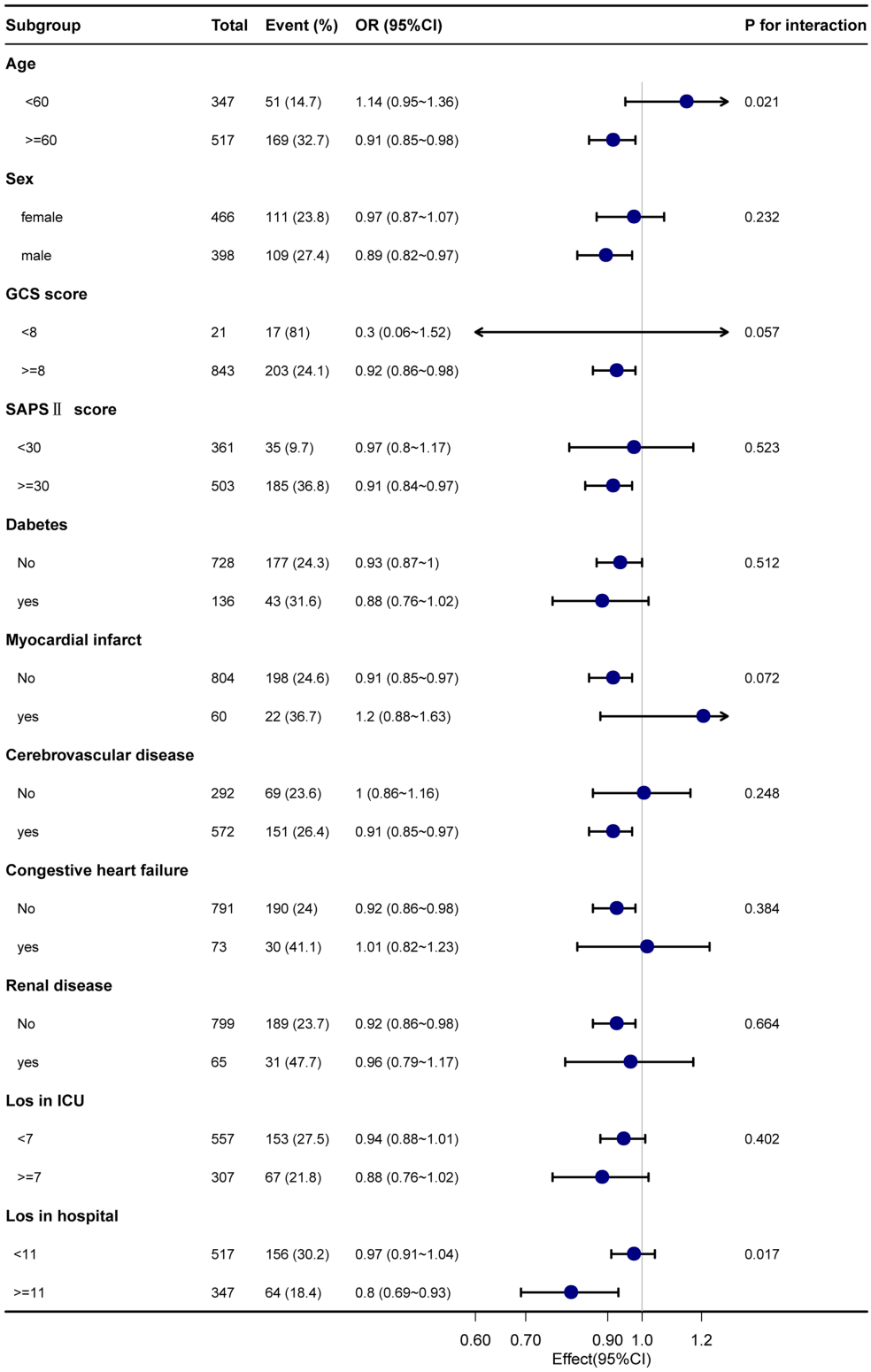

FIGURE 2
Smoothed curves depicting the relationship between $Sp0_2$ levels and the risk of mortality, constructed using a restricted cubic spline model. **(A)** Short-term (28-day) mortality rate; **(B)** Long-term (90-day) mortality rate. The solid black line represents the fitted curve between $Sp0_2$ and mortality, while the gray shaded area indicates the corresponding 95% confidence interval. The model was adjusted for multiple covariates, including age, sex, race, insurance status, heart rate, respiratory rate, temperature, GCS score, congestive heart failure, atrial fibrillation, vascular disease, stroke, chronic lung disease, liver disease, diabetes, renal disease, benign tumor, white blood cell count, hemoglobin, platelet count, blood glucose, blood chloride, creatinine, anion gap, activated partial thromboplastin time (APTT), and length of hospital stay. The blue shadow in the figure represents the relative density curve of overall cases, while the red shadow represents the relative density curve of positive outcome cases. It has been explained in the caption.

TABLE 4 Threshold analysis of SpO_2 on 28- and 90-day mortality in SAH patients in the ICU using a two-segment regression model.

Variable	*n*.total	Non-adjusted model		Multiply adjusted model	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
28-day mortality					
SpO_2 (<96%)	145	0.77 (0.66 ~ 0.91)	0.002	0.8 (0.67 ~ 0.95)	0.012
SpO_2 (≥96%)	719	1.12 (0.97 ~ 1.28)	0.112	1.17 (1.02 ~ 1.35)	0.028
90-day mortality					
SpO_2 (<96%)	145	0.69 (0.56 ~ 0.85)	<0.001	0.76 (0.6 ~ 0.96)	0.02
SpO_2 (≥96%)	719	1.16 (1.02 ~ 1.32)	0.027	1.2 (1.05 ~ 1.39)	0.01

Unadjusted: Unadjusted for covariates. Multivariable adjusted model: Adjusted for age, sex, race, insurance status, heart rate, respiratory rate, temperature, GCS score, congestive heart failure, atrial fibrillation, vascular disease, stroke, chronic lung disease, liver disease, diabetes, renal disease, benign tumor, white blood cell count, hemoglobin, platelet count, blood glucose, blood chloride, creatinine, anion gap, APTT, and length of hospital stay. SpO_2, Percutaneous oxygen saturation; OR, Odds ratio; and CI, Confidence interval.

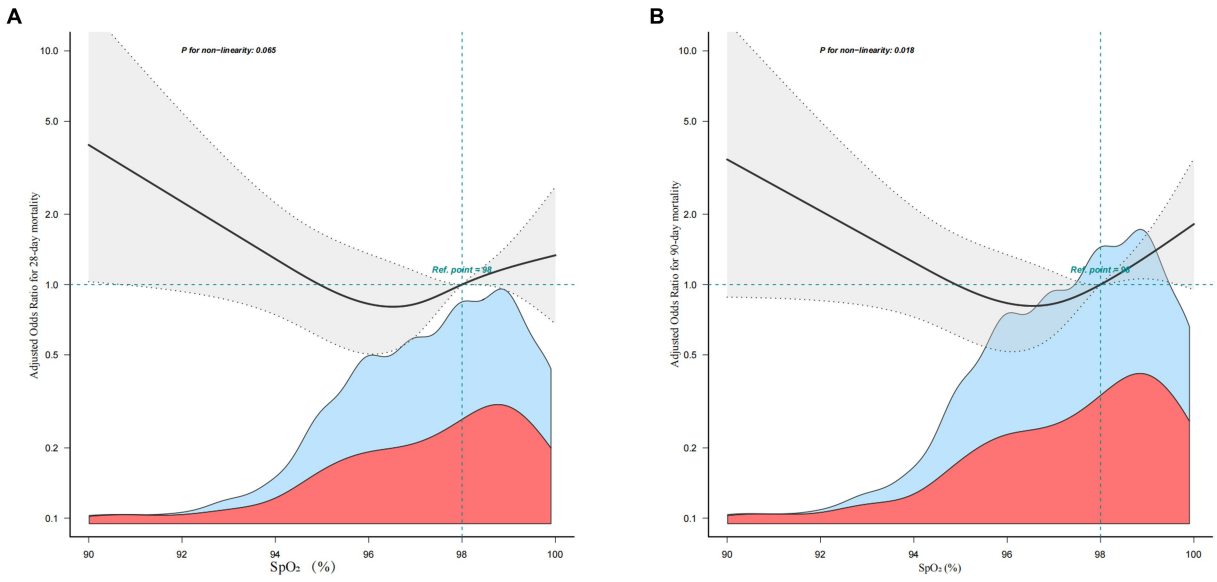

FIGURE 3
The relationship between $Sp0_2$ and 28-day mortality in subgroup analysis.

exhibiting elevated SpO_2 levels had increased rates of both short-term and long-term mortality compared to the group with moderate SpO_2. Similar studies have also reported similar results. For instance, Davis et al. (28) conducted a retrospective study involving 3,420 TBI patients and found a correlation between extremely high oxygen levels [PaO_2 (487 mmHg)] upon admission and worse outcomes. In this study, the optimal PaO_2 range was found to be between 110 and 487 mmHg (28). Another study highlighted the detrimental effects of high oxygen saturation in hospitalized patients, which encompassed prolonged hospitalization and elevated mortality rates within the healthcare setting (29). Furthermore, the lowest mortality rate among TBI patients was observed when SpO_2 ranged from 94 to 98% (30), which aligns with our research findings. Currently, most research and guidelines focus on TBI patients, and there is a lack of specific research on SAH. It is worth noting that these sources emphasize the identification and correction of hypoxia in the ICU but do not address the potential harm of high oxygen levels (31). Previously, it was believed that higher oxygen saturation would lead to better patient survival rates. However, research suggests that patients with oxygen saturation levels between 98 and 100% have lower survival rates compared to those within the range of 96 and 98%.

Elevated blood oxygen levels can induce vasoconstriction in critical arterial territories, including the brain and coronary arteries, thereby aggravating post-SAH cerebral vasospasm (32). From a molecular biology standpoint, excessively elevated blood oxygen levels can lead to the generation of reactive oxygen species (ROS) as byproducts of aerobic metabolism. These ROS have the potential to cause harm to essential biological elements, such as proteins, lipids, and deoxyribonucleic acid (DNA) (33). Prolonged exposure to excessive hyperoxia invariably leads to tissue damage, causing subsequent neuronal injury, and impairment (34). Furthermore, studies have shown that excessive oxygen supplementation can increase oxidative stress and inflammation, potentially causing negative effects on both the lungs and the overall body (23).

Hypoxia is a major contributing factor to adverse outcomes in stroke, and numerous studies have recommended active oxygen therapy (35, 36). Our research has produced comparable findings, indicating significantly elevated mortality rates at both 28- and 90-day

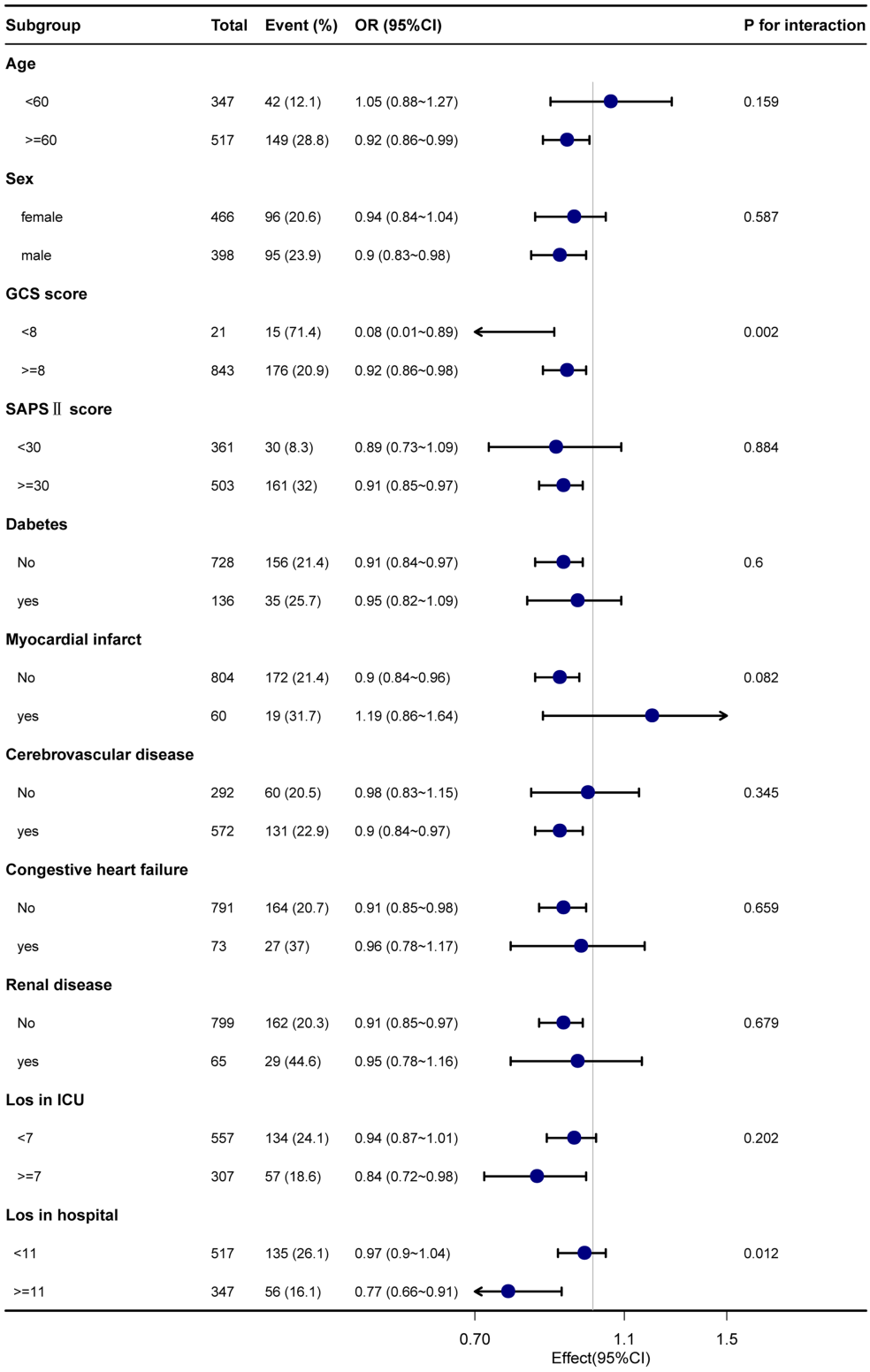

FIGURE 4
The relationship between $Sp0_2$ and 90-day mortality in subgroup analysis.

follow-ups in the low SpO_2 group when compared to the group with moderate SpO_2 levels. It is well known that hypoxia can lead to various problems in different systems of the human body. Many studies have indicated that hypoxia may disrupt the blood–brain barrier, cause irreversible neurological damage, and result in significant impairment (37). The vascular system in SAH is often compromised, leading to inadequate cerebral perfusion, ischemia, hypoxia, and other complications, with hypoxia exacerbating brain tissue damage. From a molecular biology standpoint, hypoxia-induced aberrant metabolism in the brain tissue sets off a cascade of events, including the

development of cerebral edema and disruption of the blood–brain barrier. This creates a cyclical process that perpetuates the detrimental effects (38). Furthermore, hypoxia also causes harm to other systems in the body. Hyperoxia primarily affects the cardiovascular system by manifesting as an elevation in heart rate, increased contractility of the myocardium, impaired diastolic function, and the initial onset of arrhythmias (31). Hypoxia leads to rapid and deep breathing, and over time, respiratory muscles may become fatigued (39). In conclusion, hypoxia causes multi-system damage in SAH patients, impeding their recovery and accelerating mortality.

However, this study has several noteworthy limitations. First, within the MIMIC-IV database, we lacked access to important covariates such as delayed cerebral ischemia, hydrocephalus, intracranial hypertension, and other potential confounding factors. Additionally, there may be residual confounding variables present, as is common in retrospective analyses. Despite employing interpolation techniques, the limited availability of extensive data made it challenging to completely mitigate biases. Furthermore, this study was conducted at a single center, thereby limiting its generalizability to patients from diverse geographic regions. Moreover, the observed relationship between SpO_2 and overall mortality rates established an association rather than a direct causal relationship. Therefore, it is crucial to conduct additional prospective studies to validate the findings and conclusions derived from this research.

Conclusion

In non-traumatic SAH patients, we have observed a U-shaped correlation between the initial SpO_2 levels upon admission and the mortality rates at 28 and 90 days. Additionally, the lowest risks of short-term and long-term mortality were found when the average SPO_2 within the first 24 h of admission was at 96%. Elevated or reduced average SpO_2 levels during the initial 24 h after admission were both linked to higher mortality rates. Nevertheless, it is worth emphasizing that additional prospective studies are required to substantiate these results.

Data availability statement

The data analyzed in this study was obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The following licenses/restrictions apply: To access the files, users must be credentialed users, complete the required training (CITI Data or Specimens Only Research), and sign the data use agreement for the project. Requests to access these datasets should be directed to PhysioNet, https://physionet.org/, DOI: 10.13026/6mm1-ek67.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

JuL: Writing – original draft. ZZ: Writing – review & editing. JiL: Conceptualization, Writing – review & editing. QZ: Data curation, Writing – review & editing. YW: Investigation, Writing – review & editing. JZ: Validation, Writing – review & editing.

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Conflict of interest

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

Publisher's note

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Efficacy analysis of mechanical thrombectomy combined with prolonged mild hypothermia in the treatment of acute middle cerebral artery occlusion: a single-center retrospective cohort study

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Objective: To determine the efficacy of mechanical thrombectomy combined with prolonged mild hypothermia compared with conventional treatment in managing acute middle cerebral artery occlusion, and to explore whether extending the duration of hypothermia can improve neurological function.

Method: From 2018 to June 2023, a retrospective analysis was conducted on 45 patients with acute middle cerebral artery occlusion treated at the NICU of Suzhou Kowloon Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. After thrombectomy, patients were admitted to the neurological intensive care unit (NICU) for targeted temperature management. Patients were divided into two groups: the mild hypothermia group (34.5–35.9°C) receiving 5–7 days of treatment, and the normothermia group (control group) whose body temperature was kept between 36 and 37.5°C using pharmacological and physical cooling methods. Baseline characteristics and temperature changes were compared between the two groups of patients. The primary outcome was the modified Rankin Scale (mRS) score at 3 month after surgery, and the secondary outcomes were related complications and mortality rate. Prognostic risk factors were investigated using both univariate and multivariate logistic regression analyses.

Results: Among 45 patients, 21 underwent prolonged mild hypothermia, and 24 received normothermia, with no significant differences in baseline characteristics between the two groups. The duration of mild hypothermia ranged from 5 to 7 days. The incidence of chills (33.3% vs. 8.3%, $p = 0.031$) and constipation (57.1% vs. 20.8%, $p = 0.028$) was significantly higher in the mild hypothermia group compared with the control group. There was no significant difference in mortality rates between the mild hypothermia and the control group (4.76% vs. 8.33%, $p = 1.000$, OR = 1.75, 95% CI, 0.171–17.949). At 3 month, there was no significant difference in the modified mRS (0–3) score between the mild hypothermia and control groups (52.4% vs. 25%, $p = 0.114$, OR = 0.477, 95% CI, 0.214–1.066). Infarct core volume was an independent risk factor for adverse neurological outcomes.

Conclusion: Prolonged mild hypothermia following mechanical thrombectomy had no severe complications and shows a trend to improve the prognosis of neurological function. The Infarct core volume on CTP was an independent risk factor for predicting neurological function.

KEYWORDS

mild hypothermia, occlusion, ischemia/reperfusion, neurological function, mechanical thrombectomy

Introduction

Interventional thrombectomy has been proven effective for patients with acute ischemic stroke due to major vessel occlusion (1). However, vessel recanalization does not necessarily provide a favorable outcome (2, 3). Due to prolonged time windows and cerebral ischemia/reperfusion injury, approximately 64% of patients with stroke cannot live independently after mechanical thrombectomy (4). Continuous brain damage is still evident in MRI diffusion imaging within 24 h after recanalization (5). Therefore, it is crucial to protect the brain after recanalization, and hypothermia is one of the important strategies (6, 7). In the 1940s, hypothermia was proven beneficial for neurological prognosis following whole-brain ischemia after cardiac arrest and post-traumatic brain injury (8, 9). Similarly, clinical trials on patients with ischemic stroke suggest that hypothermia can alleviate brain edema in the infarct area, reduce intracranial pressure, and lower the mortality rate (10–14). It can also rescue the ischemic penumbra, limiting the growth of the core infarct volume (15). However, the optimal parameters of hypothermia in patients with ischemic stroke, including treatment temperature and duration, remain controversial.

Regarding the temperature, mild hypothermia and moderate hypothermia exhibited the same effects in rat models. Mild hypothermia was superior to moderate hypothermia in terms of side effects and induction (16, 17), mild to moderate hypothermia (32–35°C) can provide protection with much fewer side effects (18). A clinical trial by Hermann et al. (19) which used hypothermia (33.0 ± 1.0°C) combined with decompressive craniectomy, was terminated due to severe adverse reactions, suggesting that moderate hypothermia is detrimental for patients with acute middle cerebral artery stroke. In some clinical trials, mild hypothermia improved neurological prognosis without severe adverse reactions and complications (20, 21). A meta-analysis of numerous studies on post-stroke hypothermia indicated that moderate hypothermia leads to more adverse reactions compared with mild hypothermia (22). It seems that mild hypothermia can achieve the desired effects and is safer. Existing evidence suggests that for every 1°C decrease in body temperature, the side effects increase correspondingly (23).

Animal models of stroke have demonstrated that the protective effects of hypothermia on the brain depend on the timing of initiation and duration of hypothermia (24–26). Moreover, hypothermia needs to be initiated within 1 h to be effective (27), but it is difficult to achieve in most patients with acute stroke. Some scholars believe that the optimal duration of hypothermia for hypoxic–ischemic injury depends on the severity of the injury and when hypothermia is applied. Within a certain range, delays in inducing hypothermia can be compensated by longer durations of hypothermia to achieve the same neuroprotective effects (23, 28, 29), but more studies are needed in this regard. Clinically, the optimal duration of hypothermia is yet unclear, but in patients with global cerebral ischemia and traumatic brain injury (TBI), a longer duration of hypothermia is associated with better outcomes (29–31).

We aimed to explore whether extending the duration of hypothermia can compensate for the damage caused by treatment delays. From 2018 to June 2023, we used prolonged (5–7 days) mild hypothermia (34.5–35.9°C) for treating patients with acute ischemic stroke after thrombectomy. By comparing the mortality rates and prognosis scores of the two groups, we provide insights into the diagnosis and treatment of the disease.

Methods

Patients

After obtaining approval from the Ethics Committee of Suzhou Kowloon Hospital, affiliated with Shanghai Jiao Tong University School of Medicine (HG-2023-021), we retrospectively analyzed data from patients diagnosed with acute ischemic stroke who were treated with mechanical thrombectomy at Suzhou Kowloon Hospital from January 2018 to June 2023 ($N = 178$). The inclusion criteria were as follows: (1) aged between 30 and 80 years; (2) presenting with signs of acute stroke upon admission and confirmed unilateral middle cerebral artery occlusion on computed tomography angiography (CTA); (3) National Institutes of Health Stroke Scale (NIHSS) score of ≥10, with the level of consciousness at 1a ≥1; (4) ischemic area >30 mL on computed tomography perfusion (CTP). Exclusion criteria were as follows: (1) undergoing decompressive craniectomy; (2) secondary hemorrhage affecting more than one-third of the infarct area with mass effect; (3) rapid improvement of symptoms; (4) hypothermia not initiated or lasted less than 5 days; (5) unilateral or bilateral pupil dilation during the course of the disease; (6) history of intracranial surgery; (7) severe coagulation disorders or cardiac/pulmonary diseases, rendering the patient unable to tolerate hypothermia. Among patients meeting the inclusion criteria, those who underwent prolonged mild hypothermia were classified as the mild hypothermia group ($N = 21$), and those who received normothermia treatment during the same period were classified as the control group ($N = 24$).

Mechanical thrombectomy

Mechanical thrombectomy was performed by experienced neurointerventional physicians. Intracranial mechanical thrombectomy (IMT) was conducted using direct aspiration or stent

retriever techniques. For cases where reperfusion was not achieved post-thrombectomy, other options, like balloon dilation or stent placement, were available to ensure effective blood flow restoration (modified thrombolysis in cerebral infarction score, mTICI score of 2b/3).

Mild hypothermia treatment

All patients underwent continuous bladder temperature monitoring using a dual-lumen 16Fr 15 mL catheter (Well Lead Medical Co., Ltd., Guangzhou). After mechanical thrombectomy, all patients were treated by neurocritical care physicians in the neurological intensive care unit (NICU). The patients underwent mechanical ventilation in a sedated and analgesic state, continuously monitored for electrocardiography, and underwent post-pyloric feeding via a nasoduodenal tube, subclavian deep vein catheterization, and continuous but invasive arterial pressure monitoring. A micro-infusion pump continuously released midazolam and remifentanil for ongoing sedation and analgesia while preserving patients' spontaneous breathing and coughing ability.

In the mild hypothermia group, before induction, a hibernation mixture (chlorpromazine 200 mg, promethazine 200 mg, and pethidine hydrochloride 150 mg, combined with 39 mL of saline to reach a total volume of 50 mL) was continuously infused using a micro-infusion pump. A wrap-around cooling blanket was used for the mild hypothermia group (Changchun ANTAI Medical Instruments Co., Ltd. ZLJ-2000I) to rapidly reach the target temperature. The mild hypothermia treatment was maintained for at least 5 days. Rewarming was conducted as slowly as possible, at a rate of 0.10–0.25°C/h, setting the wrap-around cooling blanket temperature to increase by 1°C every 8 h. After rewarming, the dose of sedatives, analgesics, and hibernation mixture was reduced. The hibernation mixture was discontinued once patients' body temperature returned to normal. Arterial blood gas analysis was performed every 4 h during the rewarming phase. In the control group, medications and ordinary cooling blankets were used to maintain the core temperature at 36–37.5°C. If the temperature was not controlled using this method, a cooling blanket was used to cool down to normal temperature.

Conventional treatment

Postoperatively, tirofiban was administered at a continuous infusion rate of 0.1 μg/kg/min for 24 h. At 20 h postoperative, oral administration of aspirin 0.1 g and clopidogrel 75 mg qd was initiated. Each patient was injected with the same dose of edaravone dexborneol and butylphthalide for 2 weeks. Atorvastatin 40 mg qd was administered through the nasogastric tube postoperatively. Mannitol, concentrated sodium, human serum albumin, and other medications were administered based on the patients' condition. During the treatment period, arterial blood gas analysis was conducted q12h, and complete blood count, coagulation profile, electrolytes, and biochemistry panel were measured at least once every 2 days. All patients underwent daily cranial CT scan in the first 3 days, followed by cranial CT every 3 days after 72 h. Chest CT was conducted every 3–5 days to assess pulmonary infection. Routine bedside transthoracic echocardiography was performed. Fingertip blood glucose was measured q4h, and continuous insulin infusion was administered to maintain blood glucose within the normal range. Enteral nutrition suspension was administered uniformly via a nasogastric feeding pump. A lower limb deep vein ultrasound was conducted weekly to ensure the absence of deep vein thrombosis. Pulmonary multifrequency vibration and lower limb pneumatic compression were used to prevent thrombus formation.

Data collection, statistics, and outcomes

Baseline data included age, gender, underlying diseases [hypertension, diabetes, atrial fibrillation (AF) Coronary artery disease, and smoking history], delays in initiating mild hypothermia, NIHSS score, Glasgow Coma Scale (GCS) score, core infarct volume, and ischemic penumbra volume on CTP. The primary outcome measure was the modified Rankin Scale (mRS) score at 3 months post-treatment, obtained through telephone follow-ups or hospital medical records. Secondary outcomes included complications, such as chills, hypotension, pulmonary infection, hypokalemia, arrhythmias, deep vein thrombosis, constipation, and hemorrhagic transformation. Hypotension was defined as transient or sustained use of vasopressors. The diagnosis of pulmonary infection was made based on changes in chest CT or positive microbiological culture and concurrent increase in inflammatory markers. Arrhythmias included bradycardia, tachycardia, and AF with rapid ventricular response. AF must have necessitated pharmacological intervention. Constipation was defined as the absence of bowel movement for 3 days or more or the need for prokinetic or laxative medications. These data were obtained from medical records.

Statistical analyses were performed using SPSS 26. Independence between groups was ensured for data analysis, and normal distribution tests were conducted before comparisons. Quantitative data conforming to normal distribution were analyzed using an independent sample *t*-test. Non-normal data were analyzed using non-parametric tests. For qualitative data with $n > 40$, a corrected chi-square test was used when at least one expected value (T) was between 1 and 5, and Pearson's chi-square test was used when all T-values were greater than 5. Data following a normal distribution are presented as mean ± SD, while non-normal data are presented as interquartile range (IQR). Univariate analysis and multivariate logistic regression analysis were used to determine the factors affecting the poor neurological outcome. Clinical factors with $p < 0.05$ in univariate analysis were included in multivariate logistic regression analysis. All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

Patients' characteristics

Between 2018 and 2023, 178 patients with acute stroke underwent mechanical thrombectomy at the Shanghai Jiao Tong University School of Medicine. Based on inclusion and exclusion criteria, 53 patients who met the study's requirements were included. Among them, eight patients were excluded due to the lack of CTP data, lost follow-up data, or not maintaining the target temperature during the mild hypothermia period. The normothermia treatment

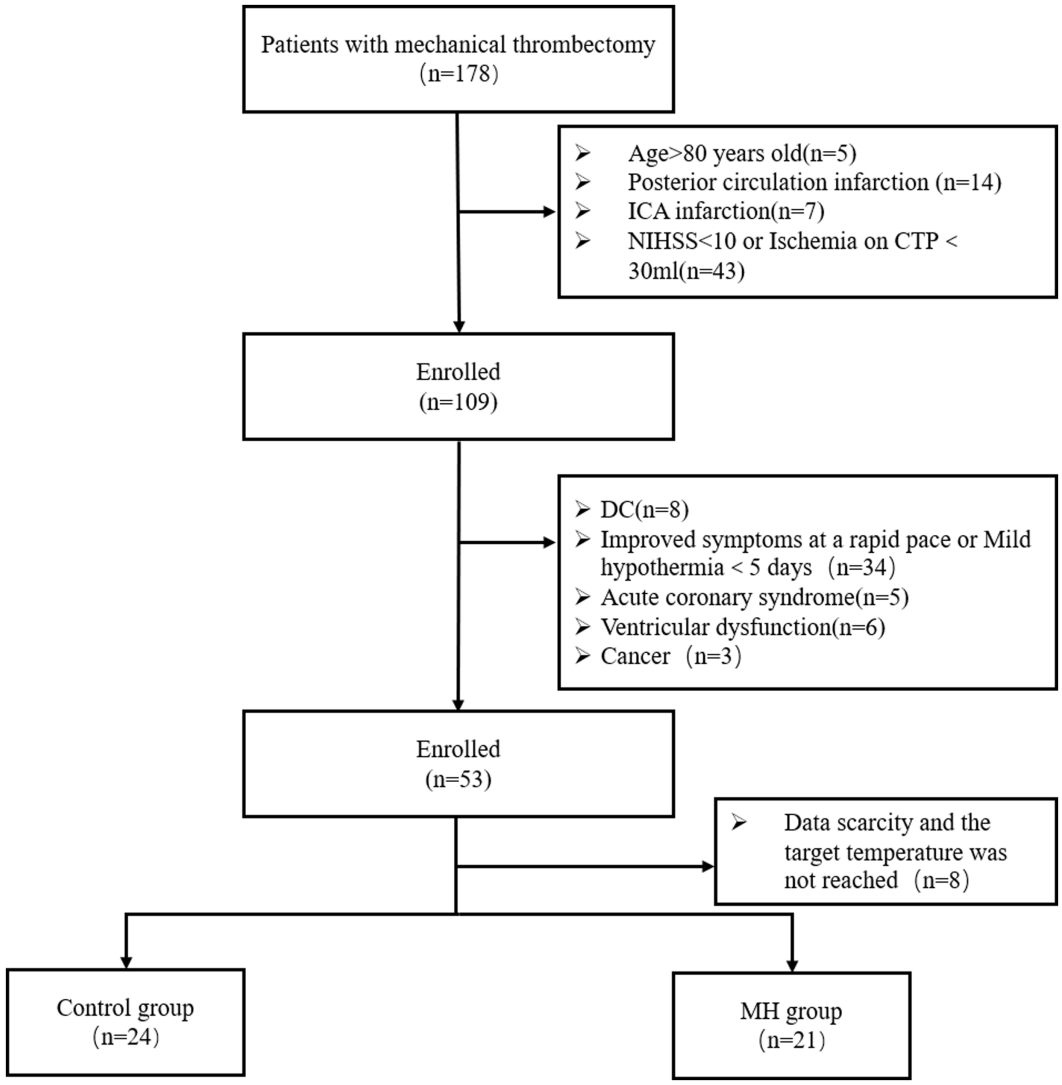

FIGURE 1
Flow chart of patient profile.

group ($n = 24$) was considered the control group, and the mild hypothermia group ($n = 21$) was considered the treatment group (Figure 1). The age of patients was similar between the groups (Table 1). Males (32/46, 69.6%) were more prevalent than females. AF was more common in the control group [11/24 (45.8%) cases] compared with the mild hypothermia group [6/21 (28.6%) cases]. There were no significant differences in the baseline characteristics of patients (Table 1).

Temperature management

Figure 2A presents body temperature changes in both patient groups 8 h after hospital admission. In the mild hypothermia group, patients reached the target temperature within 2–6 h of initiating hypothermia. There was no significant difference in the baseline temperature between the groups (36.9 ± 0.4°C in the mild hypothermia group vs. 36.7 ± 0.3°C in the control group, $p = 0.07$). Figure 2B shows the temperature change curves for both groups during 12 days of hospital stay. This graph reveals that the duration of hypothermia in the mild hypothermia group was maintained for 5–7 days.

Complications

The incidence of chills, hypokalemia, constipation, and pneumonia was higher in the mild hypothermia group compared with the control group (Table 2). There was a significant difference in the incidence of chills in the mild hypothermia group compared with the control group (33.3% vs. 8.3%, $p = 0.031$). No patients in the mild hypothermia group needed the termination of treatment due to uncontrollable chills. Chills were well-controlled with enhanced sedation and muscle relaxants. The incidence of constipation in the mild hypothermia group was significantly higher than in the control group (57.1% vs. 27.8%, $p = 0.028$). The incidence of hypokalemia was 52.4% (11/21) in the mild hypothermia group and 29.2% (7/24)

10.3389/fneur.2024.1406293

in the control group. Hypokalemia was corrected to normal ranges either through nasogastric or intravenous supplementation. There were no cases with severe hypokalemia whose hypokalemia was difficult to correct or necessitated the termination of hypothermia. All seven instances of hemorrhagic transformation were minor bleedings without significant mass effect. After detecting bleeding on CT scan, aspirin and clopidogrel were immediately discontinued, and neutral treatment was adopted. The rate of pneumonia in the mild hypothermia group was higher than that in the control group (71.4% vs. 54.2%), but this difference was not statistically significant ($p = 0.233$). Due to the inclusion of AF episodes in the arrhythmia category and the higher number of patients with AF in the control group, the incidence of arrhythmia was higher in the control group compared with the mild hypothermia group (38.1% vs. 54.2%), yet without statistical significance ($p = 0.281$).

Mortality rates

At 3 month, the mortality rate was 8.33% (2/24) in the control group. Two male patients aged 79 and 78 years died in this group. Due to recurrent pulmonary infections, these patients re-entered the NICU for mechanical ventilation and ultimately chose to discontinue treatment and were discharged due to severe infection and

TABLE 1 Baseline characteristic of the patients.

Characteristic	HM group (n = 21)	Control group (n = 24)	p-value
Age, y, mean ± *SD*	60.1 ± 10.7	61.4 ± 12.5	0.933
Men, *n* (%)	14(66.7)	18(75)	0.775
Infarct volume on CTP, ml, median (IQR)			
Infarct core	14.3(11.9–21.4)	22.4(13.3–28.9)	0.065
Ischemic penumbra	78.5(68.4–92.8)	75.7(59.7–83.8)	0.191
NIHSS, median (IQR)	15(10.5–18)	14(11.3–17.8)	0.863
GCS, median (IQR)	11(8.5–12.5)	10(9–12)	0.640
Premorbid mRS, median (IQR)	0(0–0)	0(0–0)	0.181
Infarct related artery, *n* (%)			0.526
M_1	13(61.9)	17(38.1)	
M_2	8(70.8)	7(29.2)	
Underlying diseases, *n* (%)			
Hypertension	15(71.4)	14(58.3)	0.360
Diabetes mellitus	3(14.3)	6(25)	0.601
Atrial fibrillation	6(28.6)	11(45.8)	0.233
Coronary artery disease	2(9.5)	6(25)	0.355
Smoking	11(52.4)	11(45.8)	0.661
Onset to IMT time, h, median (IQR)	5(4–6.2)	6(4.5–7.8)	0.390

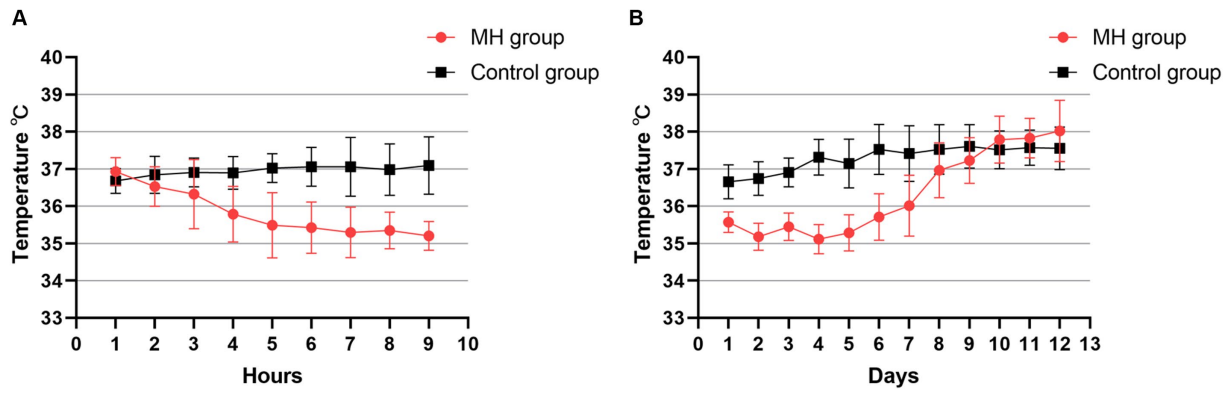

FIGURE 2
(A) Line plot of temperature changes in the two groups during the first 8 h of the first day of hypothermia initiation. Temperature was the bladder temperature recorded hourly by the patient. **(B)** Temperature changes were recorded continuously for 12 days after starting hypothermia. Each point in the graph consists of the daily mean temperature and the value of the standard deviation for all patients in the two groups.

respiratory failure. In the mild hypothermia group, the mortality rate was 4.76% (1/21). A 72-year-old female patient died in this group. The cause of death was similar to the aforementioned cases.

Outcome

The mRS scores were evaluated 3 month, the proportion of mRS0-3 was counted. The number of patients with mRS0-3 was 11/21 (52.4%) in the mild hypothermia group and 6/24 (25%) in the control group (Figure 3). The proportion of mRS0-3 was higher in the mild hypothermia group compared with the control group, but the difference was not statistically significant ($p = 0.114$; OR = 0.477, 95% CI, 0.214–1.066).

TABLE 2 Complications.

Complications	HM group (n = 21)	Control group (n = 24)	P-value
Chills, n (%)	7(33.3)	1(8.3)	0.031
Hypotension, n (%)	4(19.0)	4(16.7)	1.000
Pneumonia, n (%)	15(71.4)	13(54.2)	0.233
Hypokalemia, n (%)	11(52.4)	7(29.2)	0.113
Arrhythmias, n (%)	8(38.1)	13(54.2)	0.281
DVT, n (%)	1(4.8)	2(8.3)	1.000
Constipation, n (%)	12(57.1)	5(20.8)	0.028
Hemorrhagic transformation, n (%)	2(9.5)	5(20.8)	0.335

Multivariate logistic regression analysis for poor prognosis

Univariate logistic regression analysis showed that age, onset to IMT time, infarct core, NIHSS and hypothermia therapy were statistically significant ($p < 0.05$). Multivariate logistic regression analysis showed that the infarct core was an independent factor affecting the poor mRS Score ($p = 0.039$; OR = 1.227, 95%Cl, 1.010–1.491) (Figure 4).

Discussion

Hypothermia, in most clinical trials, as a treatment method for intracranial reperfusion injury has not demonstrated significant improvement in the prognosis of neurological function. However, there is a delay in initiating hypothermia treatment. Whether extending the duration of hypothermia can improve neurological function was the primary aim of our retrospective analysis. Combining numerous reports on hypothermia and our previous experience, the target temperature for hypothermia treatment was shifted from deep or moderate hypothermia to mild hypothermia. Mild hypothermia not only retains the therapeutic effect but also reduces adverse reactions. Additionally, most patients with acute stroke are elderly and may not tolerate moderate hypothermia. As mild hypothermia may not effectively reduce intracranial pressure, we excluded patients needing decompressive craniectomy for extensive infarct cerebral edema. We aimed to protect neurons and improve neurological function, not primarily to reduce intracranial pressure. Hence, we chose mild hypothermia (34.5–36°C) to explore its neuroprotective effect. The patients included in our study all had varying degrees of consciousness impairment and could not undergo interventional

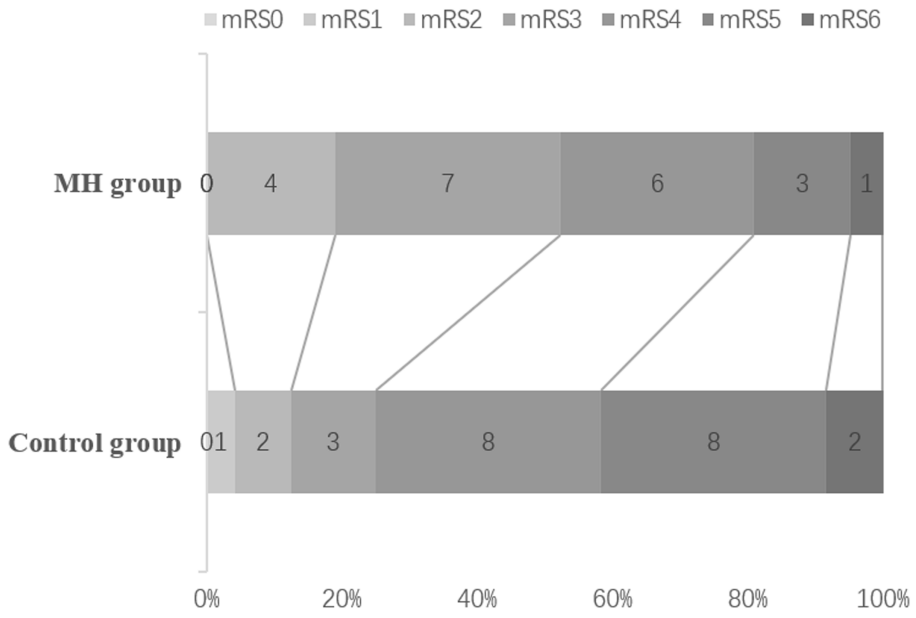

FIGURE 3
mRS at 3 months. The rates of mRS 0–3 in the MH, and control groups were 52.4% (13/21), 25% (6/24), respectively, but there was no statistical difference (P = 0.114; OR = 0.477, 95%Cl, 0.214 ~ 1.066). The mortality rates in the MH and Control groups were 4.76% (1/21), 8.33% (2/24), respectively.

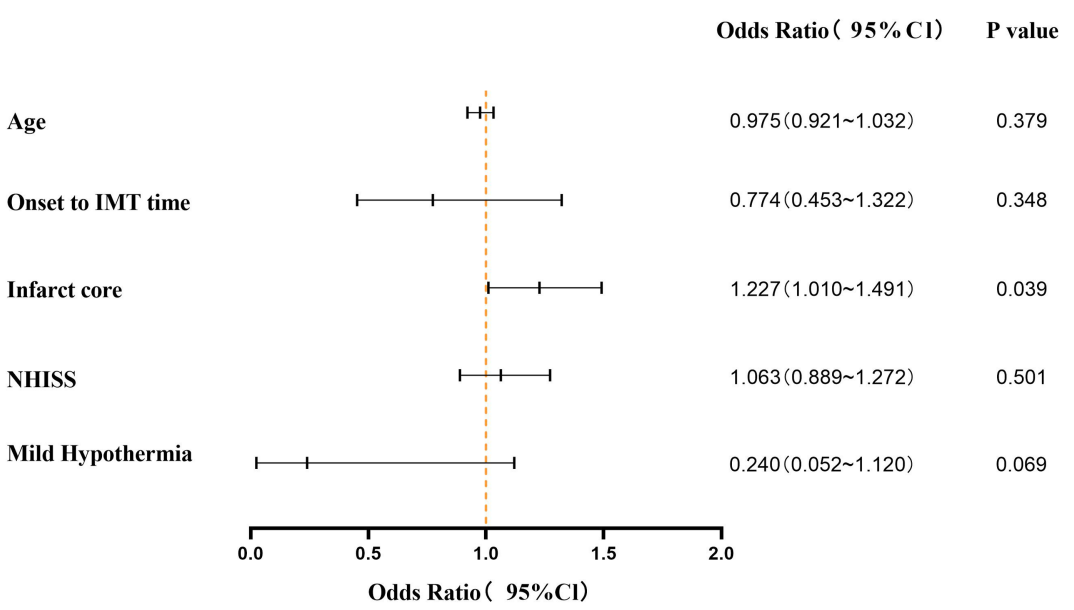

FIGURE 4
Multivariate logistic regression analysis for poor outcome (mRS>3).

thrombectomy with local anesthesia, thus necessitating general anesthesia. This helped family members to accept prolonged hypothermia when the patient returned to the NICU after the surgery. Although there have been instances of hypothermia treatment in conscious states (32, 33), we have not yet attempted prolonged hypothermia.

Prolonged mild hypothermia treatment at 34.5–35.9°C was safe in our study, with no severe complications. The incidence of chills was significantly higher in the mild hypothermia group compared with the control group (33.3% vs. 8.3%, $p = 0.031$). However, this was controlled in the short term by increasing the dosage of the hibernation mixture, deepening sedation and analgesia, and using muscle relaxants. Surface cooling for mild hypothermia treatment inherently causes physiological chills, but timely alleviation or elimination of chills is the key to successful hypothermia. There was a significant statistical difference in the incidence of constipation between the groups (57.1% vs. 20.8%, $p = 0.028$) (Table 2). The higher incidence of constipation in the mild hypothermia group could be due to the use of higher doses of anesthetic drugs, leading to reduced gastrointestinal motility and constipation. There were no cases of severe abdominal distension under hypothermia treatment. The incidence of pneumonia (71.4% vs. 54.2%) and hypokalemia (52.4% vs. 29.2%) were higher in the mild hypothermia group than in the control group but without statistical significance. Among patients with pneumonia in the mild hypothermia group, seven experienced varying degrees of atelectasis, which might be associated with prolonged sedation, analgesia, and hibernation state during hypothermia. Additionally, intravenous sedatives or muscle relaxants might have been necessary to promptly alleviate chills, thereby increasing the depth of anesthesia. Excluding the three deceased patients, pulmonary infections were generally controllable and did not lead to unmanageable infections. In two previous clinical trials investigating short-term hypothermia therapy (34, 35), ICTuS-L used an endovascular cooling technique after intravenous thrombolysis, and COOLAID has surface cooling and intravascular cooling in two ways. While both of these clinical trials targeted a hypothermic state of 33°C and lasted for 24 h, it is noteworthy that the systemic nature of cooling led to an inevitably high incidence of pneumonia [ICTuS-L (50% vs. 10%) and COOLAID (35% vs. 9%)]. While the incidence of pneumonia was higher in prolonged mild hypothermia in our study compared with these two short-term hypothermia. Although it has been reported that the incidence of pneumonia in intensive care units is approximately 70% even under normal temperature conditions (36), temperature changes in the two groups reveals that patients which in mild hypothermia group may experience more severe inflammatory responses compared to the control group after rewarming, the baseline body temperature of patients in the hypothermia group after rewarming was approximately 1°C higher than that of the control group (Figure 2B). Through a retrospective analysis of cases, we found that the elevated incidence of pneumonia in the mild hypothermia group led to fever, and in some cases, even hyperthermia. The immunosuppression under hypothermic conditions, along with prolonged sedation, analgesia, and intubation with mechanical ventilation, may contribute significantly to the high prevalence of pulmonary infections. It is worth further exploring whether modulating the immune system or administering antibiotics earlier during long-term mild hypothermia therapy could reduce the incidence of pneumonia.

All three deceased patients succumbed to recurrent pulmonary infections. They were readmitted to NICU for mechanical ventilation and ultimately died due to respiratory failure and exacerbated infection. The ages of these patients ranged from 72 to 79 years, and they had poor baseline conditions. Two males aged 79 and 78 died in the control group, and a 72-year-old female died in the mild hypothermia group. In the post-acute phase, the inability of patients to care for themselves and prolonged bed rest often make pneumonia a major factor in increasing their mortality. Whether prolonged mild hypothermia is unsuitable for elderly patients requires further subgroup analyses and larger sample sizes. Eight patients (38.1%) in

the mild hypothermia group and 13 patients (54.2%) in the control group had a history of AF (Table 1). Since AF was also considered an arrhythmias, the control group had a higher proportion of arrhythmias. Hypotension occurred more frequently in the mild hypothermia group (19%) compared with the control group (16.7%). In the mild hypothermia group, the primary causes of hypotension were sedatives, analgesics, and hibernation mixture during the hypothermia induction phase, with no instances of hypotension during the rewarming phase. In the control group, some patients experienced hemodynamic instability during AF episodes, leading to hypotension. Hypothermia can affect coagulation and platelet function, but coagulation and platelet dysfunction generally occur at temperatures below 33°C (37–39). Due to the use of heparin during the surgery, postoperative use of tirofiban, and bridging with antiplatelet medications, this study did not include coagulation function and thromboelastography.

Although surface cooling is relatively easy to implement, it is systemic cooling, which inevitably brings more side effects. In our study, even mild hypothermia (34.5–35.9) were associated with significantly higher rates of chills, decreased gastrointestinal function, and a relatively higher incidence of pneumonia, which will prolong the treatment time and Cost of hospitalization, it can be fatal in elderly patients. Endovascular cooling techniques would be more accurate and tolerable but less widely available. Selective cooling of the head surface will avoid systemic complications, but in patients with an intact skull, the target temperature cannot be achieved.

Although several clinical studies suggested that mild hypothermia may improve neurological outcomes and reduce infarct volume, only three clinical studies indicated that mild hypothermia can significantly improve the neurological prognosis of patients with acute cerebral infarction (21, 40, 41). In our study, mRS score of 0–3 ratio was higher in the mild hypothermia group than in the control group (52.4% vs. 25%, $p = 0.114$), which is consistent with the results of most clinical trials. Due to a higher proportion of good prognosis compared with the control group, we believe that prolonged hypothermia may improve neurological outcome. Hypothermia treatment is not a single therapeutic modality but a comprehensive intervention, including prolonged sedation and analgesia, mechanical ventilation, meticulous airway management, and extensive monitoring of various indicators, requiring an expert medical and nursing team.

Limitations

Our study was a single-center retrospective cohort study. Due to the low incidence rate of the disease, it was challenging to collect a large sample size, making it difficult to draw definitive conclusions. One of the indicators of mild hypothermia therapy is brain temperature. Bladder temperature does not represent intracranial temperature. Especially when the cooling method is surface cooling. Using an intracranial pressure (ICP) monitor allows more accurate monitoring of brain temperature, ICP, and cerebral perfusion pressure (CPP) values. However, this requires consent. Additionally, this was a retrospective analysis, not a prospective randomized controlled study. Neurointensivists in the selection of patients for the mild hypothermia group may have introduced a selection bias, potentially affecting the results.

Conclusion

This study indicates that prolonged mild hypothermia following mechanical thrombectomy had no severe complications and shows a trend to improve the prognosis of neurological function. Larger infarct core volume predicted worse neurologic outcome. These findings must be validated in multicenter randomized controlled trials (RCTs).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Suzhou Kowloon Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent from the patients or patients legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AW: Data curation, Formal analysis, Investigation, Writing – original draft. XM: Investigation, Writing – review & editing, Formal analysis, Validation. QC: Data curation, Supervision, Writing – review & editing. YC: Conceptualization, Supervision, Writing – review & editing. QZ: Supervision, Investigation, Writing – review & editing. DJ: Conceptualization, Supervision, Investigation, Resources, Writing – review & editing. ZW: Supervision, Funding acquisition, Writing – review & editing.

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Conflict of interest

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

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Relationship between enteral nutrition timing and 28-day mortality in critically ill stroke patients in the MIMIC-IV database

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Background: The ideal timing for commencing enteral nutrition (EN) in critically ill stroke patients in the intensive care unit (ICU) remains a subject of debate, with ongoing controversy regarding the impact of early EN (EEN) initiation. In this study, we investigated the association between the timing of EN initiation and 28-day mortality using data from the MIMIC-IV database.

Methods: This study employed a retrospective cohort design using the MIMIC-IV database to identify stroke patients who received EN during their hospital stay. The main focus of this investigation was to examine 28-day mortality among these patients following hospital admission. Various demographic, clinical, laboratory, and intervention variables were considered as covariates. The Cox regression analysis was employed to assess the correlation between the timing of EN initiation and 28-day mortality, and restricted cubic splines (RCS) analysis was used to test for non-linear correlation. Patients were then stratified into two cohorts depending on the timing of EN initiation: within 2 days ($n = 564$) and beyond 2 days ($n = 433$). A multivariate Cox regression analysis was used to investigate the difference in 28-day mortality between the groups.

Results: A total of 997 participants were included in this study, with 318 (31.9%) dying within 28 days. We observed that the timing of EN initiation correlated with 28-day mortality, but this correlation was not significant after adjusting for covariates (crude HR: 0.94, 95% CI: 0.88–1, $p = 0.044$; adjusted HR: 0.96, 95% CI: 0.9–1.02, $p = 0.178$). The RCS analysis showed that the correlation was not non-linear. Notably, in the multivariate regression models, early EN initiation was associated with a higher mortality rate compared to late EN initiation [odds ratio (OR) = 1.34, 95% CI: 1.06–1.67, $p = 0.012$]. After adjusting for various confounding factors in the multivariate Cox regression models, we identified that patients in the early EN group had a 28% higher risk of mortality than those in the reference group (OR = 1.27, 95% CI: 1–1.61, $p = 0.048$). These associations remained consistent across various patient characteristics, as revealed through stratified analyses.

Conclusions: Early commencement of EN in critically ill stroke patients may be linked to a higher risk of 28-day mortality, highlighting the need for further investigation and a more nuanced consideration of the optimal timing for commencing EN in this patient population.

KEYWORDS

stroke, enteral nutrition, mortality, MIMIC-IV database, intensive care unit (ICU)

Background

Stroke is a major global health concern and is responsible for causing a substantial number of fatalities and disabilities (1). In recent years, China alone has reported millions of new stroke cases and related deaths (2). Critically ill stroke patients often experience reduced consciousness levels, severe dysphagia, and impaired gastrointestinal function, making them susceptible to malnutrition (3, 4). Malnourishment or nutritional vulnerability in stroke patients is associated with higher mortality rates, increased complications, and a poor functional prognosis (3–5). Guidelines suggest that critically ill stroke patients with reduced consciousness levels or prolonged severe dysphagia receive early enteral tube feeding within 72 h from the onset of symptoms (6, 7).

However, the optimal timing for initiating EN in severe stroke cases is still debated. Some studies have shown improved outcomes with early tube feeding within 7 days (8), while others suggest that initiating enteral nutrition within 3 days in comatose stroke patients does not improve nutritional status and may increase the likelihood of diarrhea (9). Consequently, this study aims to provide further insights into the relationship between the timing of enteral nutrition initiation and 28-day mortality in severe stroke patients, utilizing data from the MIMIC-IV database.

Methods

Study population

The present retrospective study utilized patient data from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) cohort, a single-center, longitudinal cohort spanning from 2008 to 2019. The MIMIC-IV database contains various patient information, including demographics, vital signs, laboratory results, diagnoses, medication details, and follow-up information. The data extraction code is available on GitHub (10) (http://github.com/MIT-LCP/mimic-iv). This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (11).

Inclusion and exclusion criteria

This study included stroke patients, both ischemic and hemorrhagic, who received enteral nutrition (EN) during their initial ICU admission. Stroke diagnoses were based on ICD-9 or ICD-10 (International Classification of Disease, Ninth and Tenth Versions), with stroke consistently listed as the primary diagnosis. The inclusion criteria were as follows: (1) patients aged 18 years or older; (2) those with an ICU stay lasting 24 h or more; and (3) only patients in their initial ICU stay were considered. The exclusion criteria were as follows: (1) patients younger than 18 years, (2) patients with an ICU stay of fewer than 24 h, (3) patients with contradictions to enteral nutrition, such as gastrointestinal bleeding or intestinal obstruction, and (4) patients with a wait time for enteral nutrition beyond 15 days.

Data extraction

Structured Query Language (SQL) was used for data extraction. The following variables, collected within 24 h of ICU admission, were extracted:

1. **Patient's basic information**: Sex, admission age, race, admission time, ICD code, EN start time, height, weight, body mass index (BMI), and 28-day mortality.
2. **Vital signs**: Temperature, mean blood pressure (MAP), heart rate, and SpO2.
3. **Severity of illness scores**: The Sequential Organ Failure Assessment (SOFA) score, the Simplified Acute Physiology Score II (SAPS II), the Glasgow Coma Scale (GCS), and the Charlson comorbidity index. If a patient was intubated and could not provide a verbal score for the GCS, it was estimated from the eye and motor scores, as reported in previous studies (12).
4. **Laboratory test results**: WBC count, creatinine levels, hematocrit (HCT), and albumin levels.
5. **Treatment modalities**: Mechanical thrombectomy and thrombolysis.
6. **Commodities**: Myocardial infarction, peripheral vascular disease, dementia, COPD, malignant cancer, renal disease, cancer, severe liver disease, gastrointestinal bleeding, or intestinal obstruction, identified by ICD codes.

Variable definition and outcomes

EN initiation time was defined as the duration between the start of enteral nutrition (EN) and the time of ICU admission. We calculated the initiation time for various EN solutions, including Ensure, Impact, and Vivonex, among others. The main objective of this study was to investigate 28-day mortality as the primary outcome.

Statistical analysis

Baseline patient characteristics were stratified based on different EN initiation time groups. Continuous data are expressed as either the mean ± standard deviation or median (inter-quartile), while categorical variables are expressed as numbers (percentages), as appropriate. Statistical comparisons between the two groups included the use of the chi-square test or Fisher's exact test for categorical variables, and continuous variables were examined using the analysis of variance test or rank-sum test.

Abbreviations: MIMIC-IV, Medical Information Mart for Intensive Care-IV; EN, Enteral nutrition; ICU, Intensive care unit; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; TPN, Total parenteral nutrition; EPN, Early parenteral nutrition; EEN, Early enteral nutrition; WBC, White blood cell; SASPII, Simplified Acute Physiology Score II; BMI, Body mass index; SQL, Structured Query Language; MAP, Mean blood pressure; SOFA, Sequential Organ Failure Assessment score; BUN, Blood urea nitrogen; SD, Standard deviation.

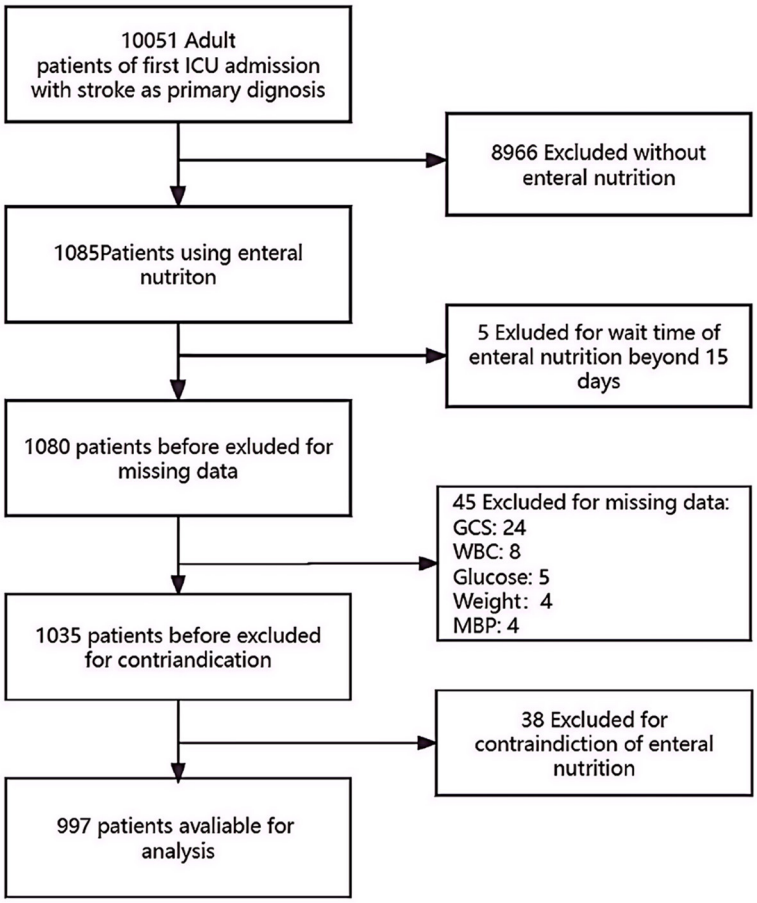

FIGURE 1
A detailed flowchart illustrating the participant recruitment process. GCS, Glasgow Coma Scale; WBC, white blood cell count; ICU, intensive care unit.

We omitted the missing data for glucose levels, GCS, WBC, body weight, and creatinine due to the low percentage of missing data (missing rate below 5%). We also used multiple imputations to handle the missing data for BMI (missing rate: 34.9%) and serum albumin levels (missing rate: 47.8%).

We selected confounders based on clinical relevance and their association with the outcome ($p < 0.2$) or a change in effect estimate of more than 10%. Multivariable Cox regression models were introduced to evaluate the association between early EN initiation and 28-day mortality. Four models were employed in the regression analysis, each adjusted for different sets of variables:

Model 1: Adjusted for sex and admission age.

Model 2: Adjusted for stroke type, BMI, and GCS in addition to variables in Model 1.

Model 3: Adjusted for mechanical ventilation, the Charlson comorbidity index, serum albumin level, glucose, SAPS II, and MAP in addition to variables in Model 2.

Model 4: Adjusted for malignant cancer, diabetes, myocardial infarction, creatinine, WBC, platelets, HCT, thrombolysis therapy, and mechanical thrombectomy in addition to variables in Model 3.

To explore potential non-linear relationships between the timing of EN initiation and 28-day mortality, a restricted cubic spline (RCS) was utilized. Heterogeneity across subgroups was assessed using Cox regression analysis, and interactions were evaluated using a likelihood ratio test.

Statistical significance was determined using a two-tailed test with a threshold of P of <0.05. All data analyses were conducted using the R software package (R version 4.0.3) and Free Statistics software version 1.7.

Results

Baseline characteristics

A total of 10,051 individuals with a primary diagnosis of stroke, either ischemic or hemorrhagic, were identified and admitted to the ICU. Among them, 1,085 patients received enteral nutritional (EN) support. After excluding cases with outlier data (where the wait time for EN exceeded 15 days), contraindications, and missing data, our final cohort consisted of 997 stroke patients who received EN. Of these patients, 318 (31.9%) died within 28 days of their hospital admission. Figure 1 provides a detailed flowchart illustrating the participant recruitment process.

The average age of the 997 patients was 69.4 ± 14.6 years, and nearly half of them were women (49.9%). Table 1 presents the

TABLE 1 Clinical information, and process parameters in patients categorized by EN start-time.

	Total ($n = 997$)	Late EN group ($n = 433$)	Early EN group ($n = 564$)	p
Demographics				
Sex *n* (%)				0.826
Female	498 (49.9)	215 (49.7)	284 (50.4)	
Male	499 (50.1)	218 (50.3)	280 (49.6)	
Age, mean (SD), y	69.4(14.6)	67.4(14.9)	71.0(14.2)	**<0.001**
BMI, kg/m^2	27.2(6.4)	27.1 (6.2)	27.3(6.5)	0.671
Vital signs, mean (SD)				
Heart_rate, bpm	81.1 (13.5)	81.5 (13.9)	80.8 (13.1)	0.391
MAP, mmHg	86.0(10.3)	86.0(10.6)	85.9(10.0)	0.881
Lab test, mean (SD)				
HCT	38.5 (5.5)	38.4 (5.5)	38.6 (5.6)	0.621
Platelets, 10^9/L	236.2 (92.3)	240.8 (98.9)	232.7 (86.8)	0.166
WBC, 10^9/L	13.1 (5.3)	13.2 (5.6)	13.1 (5.0)	0.629
Albumin, g/dL	3.8 (0.6)	3.9 (0.6)	3.7 (0.6)	**0.002**
Glucose, mg/dL	140.2 (40.4)	139.4 (39.1)	140.9 (41.3)	0.569
Creatinine, mg/dL	1.2 (1.1)	1.3 (1.3)	1.2 (1.0)	0.397
Commodities, *n* (%)				
Myocardial infarct	106 (10.6)	52 (12)	54 (9.6)	0.216
Diabetes	234 (23.5)	103 (23.8)	131 (23.2)	0.878
Malignant cancer	56 (5.6)	24 (5.5)	32 (5.7)	0.929
Severity score, mean (SD)				
Charlson comorbidity index	6.8 (2.5)	6.6 (2.6)	6.9 (2.5)	0.128
SAPSii	35.9 (10.8)	35.5 (11.4)	36.2 (10.3)	0.37
GCS	8.1 (3.1)	8.0 (3.1)	8.2 (3.0)	0.178
Stroke sub-type, *n* (%)				**0.015**
Ischemic stroke	370 (37.1)	179 (41.3)	191 (33.9)	
Hemorrhagic stroke	627 (62.9)	254 (58.7)	373 (66.1)	
Interventions, *n* (%)				
Thrombolysis	92 (9.2)	37 (8.5)	55 (9.8)	0.514
Mechanical thrombectomy	96 (9.6)	37 (8.5)	59 (10.5)	0.309
Mechanical ventilation	682 (68.4)	313 (72.3)	369 (65.4)	**0.021**
EN start-time	2.4 (2.0)	3.9 (2.1)	1.2 (0.5)	**<0.001**
28 days Mortality, *n* (%)	318 (31.9)	121 (27.9)	197 (34.9)	**0.019**

SAPS, simplified acute physiology score; MAP, mean arterial pressure; HCT, Hematocrit; WBC, white blood cell count;. GCS, Glasgow coma scale; EN, enteral nutrition; SD, standard deviation. Bold values indicate statistical significance ($p < 0.05$).

baseline characteristics of the included individuals. Compared to the late EN cohort, the early EN cohort had older patients, a higher prevalence of hemorrhagic stroke, a lower prevalence of mechanical ventilation, and lower admission albumin levels.

Effects of EN initiation time on 28-day mortality

In our univariate Cox regression analysis (see Table 2), we observed a decline in 28-day mortality with increasing EN initiation time. Specifically, for each additional day of delay in EN initiation, there was a 6% decrease in the odds of death within 28 days [odds ratio (OR) = 0.94, 95% CI: 0.88–1, $p = 0.044$]. However, this correlation was not significant after adjusting for covariates.

On the other hand, the early EN group had a 34% higher mortality rate than the reference group (OR = 1.34, 95% CI: 1.06–1.67, $p = 0.012$). After adjusting for various confounding factors in the multivariable Cox models (see Table 3), we found that patients in the early EN group had a 27% higher risk of mortality than those in the reference group (OR = 1.27, 95% CI: 1.−1.61, $p = 0.048$).

We performed multivariable-adjusted restricted cubic spline analyses to further explore the association between EN initiation time and 28 days mortality. These analyses did not indicate a non-linear relationship between EN initiation time and mortality (as depicted in Figure 2).

Survival analysis of these two groups showed that patients in the early EN group had poorer overall survival compared to those in the late EN group ($p = 0.012$) (Figure 3).

TABLE 2 Univariate logistic regression evaluating the association between baseline characteristic and 28 days-mortality.

Variable	OR_95CI	*P*
Early EN	1.34 (1.06–1.67)	**0.012**
EN start_time	0.94 (0.88–1)	**0.044**
Female	0.94 (0.75–1.17)	0.582
Admission_age	1.03 (1.02–1.04)	**<0.001**
BMI	0.9933 (0.976–1.0109)	0.453
GCS	0.84 (0.81–0.87)	**<0.001**
Hemorrhagic stroke	0.86 (0.69–1.08)	0.198
Thromblysis	0.97 (0.66–1.43)	0.873
Mechanical thrombectomy	0.82 (0.55–1.22)	0.332
Mechanical ventilation	1.75 (1.34–2.27)	**<0.001**
MAP	0.99 (0.98–1)	0.054
Glucose	1.0066 (1.0042–1.009)	**<0.001**
Hematocrit	0.99 (0.97–1.01)	0.299
Hemoglobin	1 (0.94–1.08)	0.902
Platelets	0.9999 (0.9987–1.0011)	0.894
WBC	1.04 (1.02–1.06)	**<0.001**
Albumin	0.66 (0.55–0.79)	**<0.001**
Creatinine	1.17 (1.09–1.25)	**<0.001**
Myocardial_infarct	1.46 (1.06–2)	**0.019**
Diabetes	1.12 (0.87–1.44)	0.383
Malignant cancer	1.69 (1.14–2.51)	**0.009**
SAPSII	1.04 (1.03–1.05)	**<0.001**
Charlson comorbidity index	1.15 (1.11–1.2)	**<0.001**

SAPS, simplified acute physiology score; MAP, mean arterial pressure; HCT, Hematocrit; WBC, white blood cell count; GCS, Glasgow coma scale. Bold values indicate $p < 0.05$.

Sensitivity analysis

In our multivariable Cox models, we meticulously adjusted for various confounding factors to assess the relationship between early EN initiation and 28-day mortality. Notably, the association remained consistent across all models (see Table 3). To further investigate the robustness of our findings, we conducted subgroup analyses based on various confounding factors such as age, sex, GCS, BMI, stroke type, thrombolysis, and thrombectomy (see Figure 4). We found a significant interaction in the subgroup of patients who underwent thrombolysis, which may be attributed to the small sample size in this group. No significant interactions were detected within any of the other subgroups (all $p > 0.05$) (Figure 4).

To mitigate potential bias, we redefined the early EN group as involving patients who started EN within the first day of admission ($n = 211$) and the late EN group as those who started EN after 1 day of admission ($n = 768$). After meticulous adjustments for various confounding factors in our multivariable Cox models, participants in the early EN group exhibited a higher risk of mortality (OR = 1.24, 95% CI: 0.96–1.61, $p = 0.117$) (Table 4).

We then divided the patients into four groups, EN within 1 day ($n = 211$), at 1–2 days ($n = 353$), 2–3 days ($n = 209$), and beyond 3 days ($n = 224$), to explore potential dose-response relationships. We found that that groups receiving EN in 2–3 days and beyond 3 days were associated with lower morality (all $p < 0.05$) compared to the early EN group (those receiving EN in 1 day), while the 1–2 days group did not show a significant difference in morality ($p = 0.26$) (Table 5).

Discussion

This study primarily focused on investigating the correlation between the timing of enteral nutrition (EN) initiation and short-term outcomes in stroke patients admitted to the ICU. Our analysis revealed an independent correlation between EN initiation time and 28-day mortality, suggesting that starting EN within 2 days may be associated with higher mortality, which differs from mainstream views in this field of research.

TABLE 3 Multivariable COX regression models evaluating the association between early EN and 28-days mortality.

Model	crude.OR_95CI	crude.*P*_value	adj.OR_95CI	adj.*P*_value
Model 1	1.34 (1.06–1.67)	0.012	1.23 (0.98–1.54)	0.074
Model 2			1.32 (1.05–1.66)	0.018
Model 3			1.29 (1.02–1.63)	0.032
Model 4			1.27 (1–1.61)	0.048

Model 1: Adjusted for sex and age.
Model 2: Adjusted for sex, age, stroke type, BMI and GCS.
Model 3: Adjusted sex, age, stroke type, BMI, GCS, Mechanical ventilation, Charlson comorbidity index, serum albumin level, glucose, SAPSii, MAP.
Model 4: Adjusted sex, age, stroke type, BMI, GCS, mechanical ventilation, Charlson comorbidity index, serum albumin level, glucose, SAPSii, MAP, malignant cancer, diabetes, myocardial infarction, creatinine, WBC, platelets, HCT, thromblysis therapy, mechanical thrombectomy.

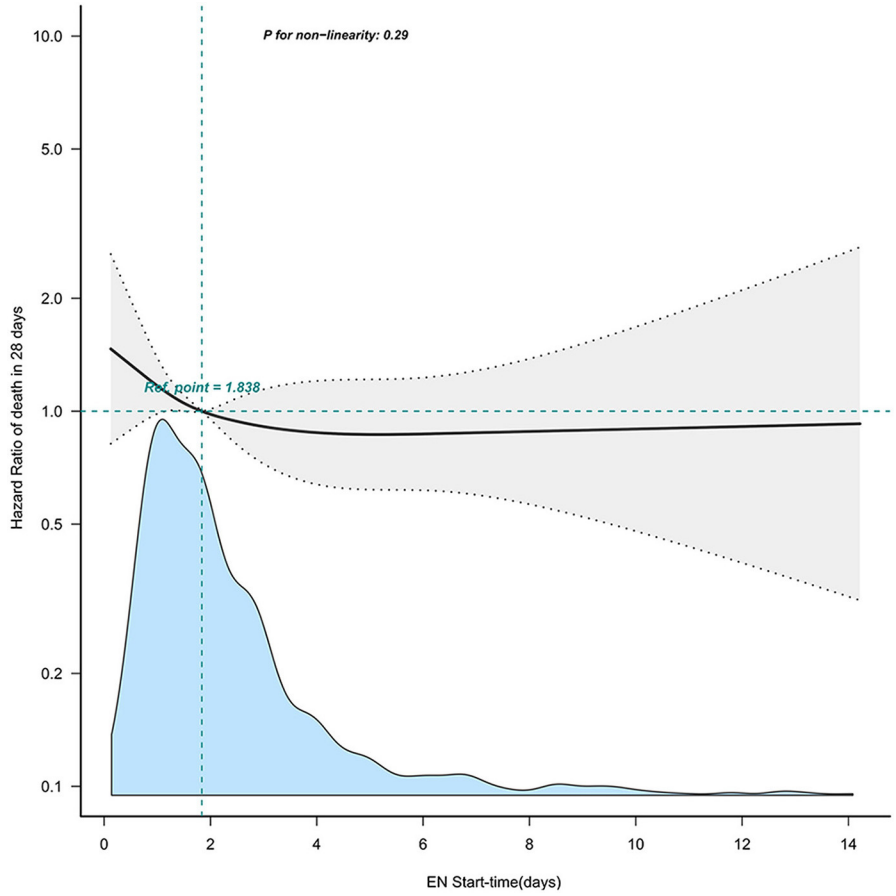

FIGURE 2
The non-linear relationship between EN start time and 28-day mortality. Adjusted confounders in model 4. This curve illustrates the mortality hazard of different EN start times within our cohort, using the median value of 1.8 days as a reference point. EN, enteral nutrition.

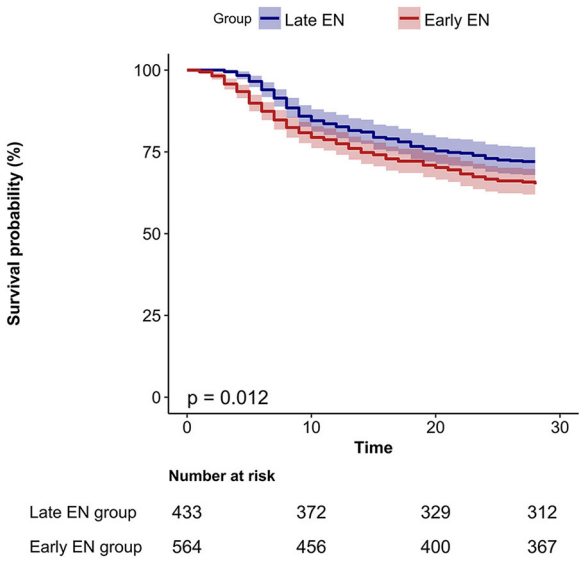

FIGURE 3
The K-M curve of survival in different EN (enteral nutrition) start time groups. EN, enteral nutrition.

These findings emphasize the crucial role of EN initiation timing in determining short-term outcomes for stroke patients receiving enteral nutrition in the ICU. It is essential to carefully consider the optimal time to initiate EN to minimize adverse outcomes. Early enteral nutrition (EN) offers advantages over total parenteral nutrition (TPN) in treating critically ill patients (13). It helps maintain gastrointestinal integrity, prevents intestinal bacterial translocation (14–19), and enhances recovery during the early hyper-metabolic stage (17, 19). It is evident from recent research that early EN is linked to positive outcomes, including lower mortality and fewer infectious complications, in patients with traumatic brain injury and intracranial hemorrhage (13, 18, 19).

However, it is crucial to emphasize that initiating intragastic feeding too early may result in elevated gastric load, hinder gastric emptying, and increase the chances of aspiration pneumonia in critically ill neurological patients (20). This finding has sparked significant debates regarding the ideal timing for commencing EN (21).

A recent meta-analysis comparing early parenteral nutrition (EPN) to early enteral nutrition (EEN) showed that EPN was more effective in lowering mortality and decreasing infectious complications in patients with acute gut-intolerant phase traumatic

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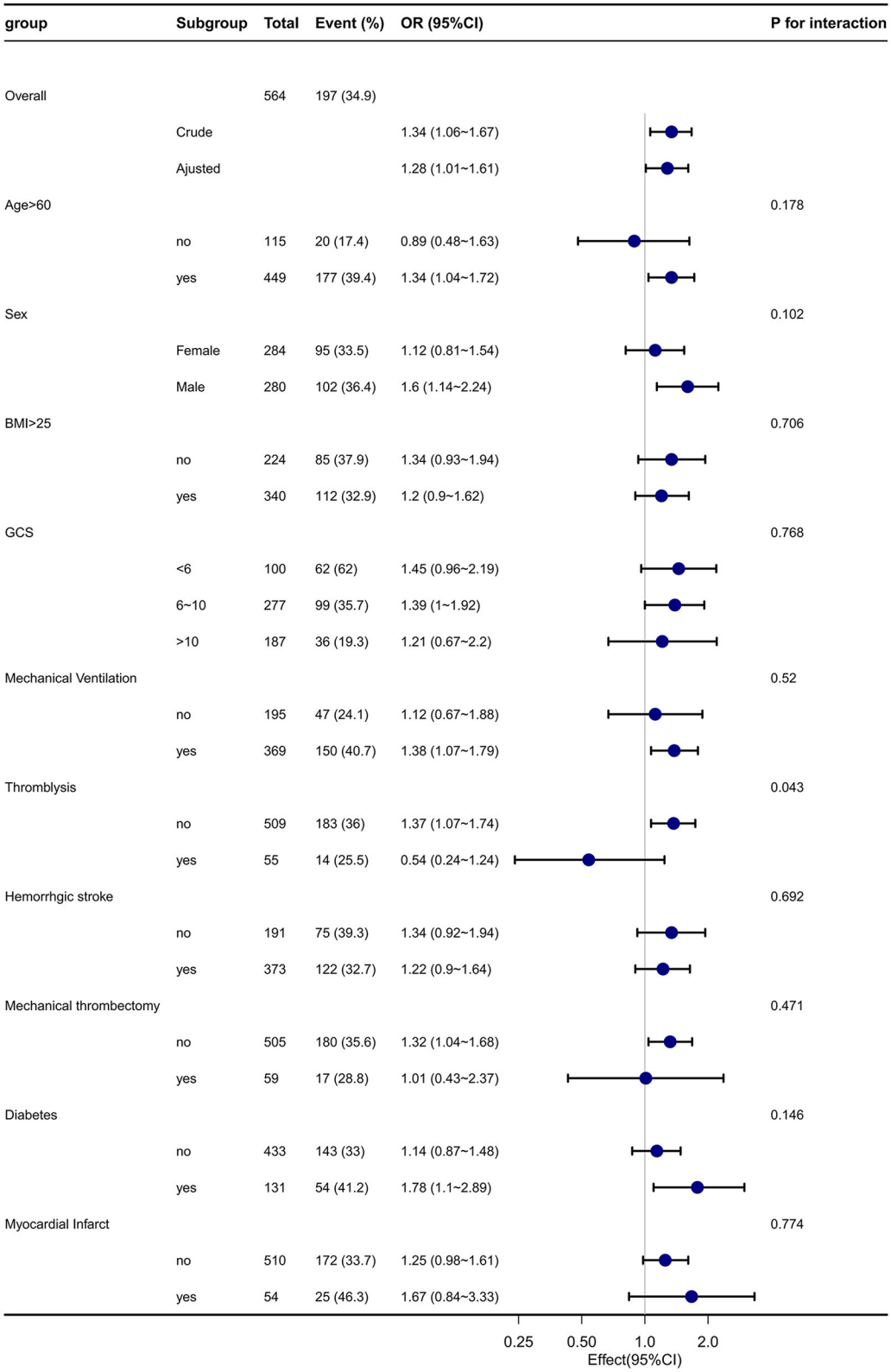

FIGURE 4
Effect size of early EN on 28-day mortality in each subgroup. A subgroup with varied demographics, including age, sex, Glasgow Coma Scale (GCS) scores, BMI, comorbidities such as diabetes and myocardial infarction, and different interventions, was analyzed within the early EN (enteral nutrition) group ($n = 564$), and the late EN (enteral nutrition) group ($n = 433$) was shown as a reference. The results from this subgroup analysis have demonstrated consistent and robust findings. GCS, Glasgow Coma Scale; WBC, white blood cell count; BMI, body mass index; SAPSii, Simplified Acute Physiology Score II; MAP: mean blood pressure Adjusted Charlson comorbidity index, SAPS II, MAP, creatinine, albumin, WBC, platelets, hematocrit, and glucose.

TABLE 4 Multivariable COX regression model evaluating the association between early EN (in 1 day) and 28 days mortality.

Variable	*n*.total	*n*.event_%	crude.OR_95CI	crude.*P*_value	adj.OR_95CI	adj.*P*_value
EN after 1 day	768	239 (30.4)	1 (Ref)		1 (Ref)	
EN in 1 day	211	79 (37.4)	1.35 (1.05–1.74)	0.02	1.24 (0.95–1.61)	0.117

Adjusted confunders in Model 4.

TABLE 5 Multivariable COX regression model evaluating the association between different EN initiation days and 28 days mortality.

EN initiation days	*n*	*n*.event_%	Follow-up. Time	crude.HR_95CI	crude.*P*_value	adj.HR_95CI	adj.*P*_value
≤1 day	211	79 (37.4)	4,445	1 (Ref)		1 (Ref)	
1–2 days	353	118 (33.4)	7,969	0.83 (0.63–1.11)	0.206	0.85 (0.63–1.13)	0.263
2–3 days	209	58 (27.8)	4,808	0.68 (0.48–0.95)	0.026	0.71 (0.5–1)	0.05
>3 days	224	63 (28.1)	5,347	0.66 (0.47–0.92)	0.013	0.7 (0.5–0.99)	0.044
Trend.test	997	318 (31.9)	22,569	0.86 (0.78–0.96)	0.006	0.88 (0.79–0.99)	0.026

Adjusted confunders in Model 4.

brain injuries (21). However, in the case of stroke patients, randomized controlled trials did not show any impact on mortality when comparing early and delayed EN (22).

Furthermore, a study conducted by Yamada et al. found that initiating enteral nutrition too early in comatose stroke patients may not provide nutritional advantages compared to early administration of total parenteral nutrition (TPN), and it might increase the risk of diarrhea (9).

Despite the limited number of studies addressing early EN and its impact on mortality, Cai et al. discovered that administering early EN within 48 h significantly reduced the occurrence of chronic hydrocephalus in severe intracranial hemorrhage patients (23). Similarly, Choi et al. reported that EEN within 72 h was associated with lower 28-day mortality and a reduced occurrence of infectious complications in critically ill neurological patients (24). It is worth noting that the definition of EEN varied among these studies, and our research specifically focused on stroke patients in ICUs.

The potential mechanisms underlying the increased 28-day mortality associated with EEN in critically ill stroke patients remain unclear. However, several possible explanations can be speculated upon. First, initiating early intro-gastric feeding has been associated with an increased likelihood of experiencing gastric complications and developing aspiration pneumonia in critically ill patients with brain injuries (20). These complications can negatively affect patient outcomes and contribute to the observed increase in mortality.

Second, the sympathetic hyperactivation resulting from increased intracranial pressure caused by a stroke can negatively affect gastrointestinal function (25–27). This disruption in the autonomic nervous system may interfere with proper gastrointestinal functioning, leading to complications and potentially higher mortality rates in stroke patients receiving EEN.

Additionally, when comparing EPN and EEN in patients with traumatic brain injuries, research has indicated that EPN is more effective in reducing mortality and infectious complications during the acute gut-intolerant phase (21). This finding suggests that the choice of feeding method can significantly impact patient outcomes, and in certain critical conditions, EEN may not be as effective.

Strengths and limitations

Our study boasts several strengths. First, it investigated the association between early enteral nutrition (EN) start time and 28-day mortality in stroke patients admitted to the ICU, providing novel insights into the field. We used RCS to test for non-linear correlations between EN start time and outcomes, which contributed valuable information for the development of EN therapy management strategies for this patient population.

Second, we conducted multiple sensitivity analyses to ensure robustness. Subgroup analyses were conducted based on stroke subtypes, age, sex, GCS score, and thrombolytic/thrombectomy therapy. The consistent results across these subgroups indicate that the relationship between EN initiation time and 28-day mortality remains independent of these factors. An interaction was found in the subgroup of thrombolysis, which may be due to the small sample size, this interaction requires further investigation. Additionally, our Cox regression analyses, adjusted across multiple models, accounted for confounding factors and validated the robustness of the outcomes.

However, our study has limitations. First, the unavailability of the National Institutes of Health Stroke Scale (NIHSS) score in the MIMIC-IV database prevented its inclusion as an important predictor of stroke severity (9). Nonetheless, the GCS score served as an alternative measure of neurological function.

Second, during the wait time for EN, only five patients receive TPN in our cohort, and we did not account for TPN in our analysis. Additionally, the calories received before EN could not be acquired from the MIMIC-IV database.

Third, detailed information such as whether EN feeding was successful was difficult to obtain from the MIMIC-IV database, even though the success rate of feeding is an important factor in 28-day mortality. This limitation could introduce bias into our findings.

Fourth, our study was limited to the United States and a single ICU institution, potentially impacting the generalizability of the findings. Different healthcare settings and practices might influence the applicability of the findings. Future prospective multicenter studies could help validate these results in a more diverse patient population.

Finally, considering that a particular stroke population (9.9%) was analyzed, there may be a selection bias that could affect the results. Conducting future randomized controlled trials would provide more robust evidence to validate these findings.

Conclusion

In conclusion, this study revealed an increased risk of 28-day mortality when EN was initiated within the first 2 days for stroke patients admitted to the ICU. Further research is imperative to understand the significance of this association. Subsequent research confirming these findings could establish a theoretical basis for delineating a specific time window to implement targeted nutritional therapy strategies for stroke patients.

Data availability statement

The data utilized in this study were obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV) Clinical Database (28). Requests for access to these datasets could be directed to PhysioNet (29, 30) and the raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XW: Writing – original draft, Software, Investigation, Formal Analysis, Data curation, Conceptualization. XXi: Writing – original draft, Visualization, Supervision, Resources, Investigation, Formal Analysis, Data curation. XXu: Writing – review & editing, Visualization, Validation, Supervision. LT: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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Conflict of interest

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

Publisher's note

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Advancing stroke patient care: a network meta-analysis of dysphagia screening efficacy and personalization

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Introduction: The increasing incidence of stroke globally has led to dysphagia becoming one of the most common complications in stroke patients, with significant impacts on patient outcomes. Accurate early screening for dysphagia is crucial to avoid complications and improve patient quality of life.

Methods: Included studies involved stroke-diagnosed patients assessed for dysphagia using bedside screening tools. Data was sourced from Embase, PubMed, Web of Science, Scopus, and CINAHL, including publications up to 10 December 2023. The study employed both fixed-effect and random-effects models to analyze sensitivity, specificity, positive predictive value (PPV), and Negative Predictive Value (NPV), each with 95% confidence intervals. The random-effects model was particularly utilized due to observed heterogeneity in study data.

Results: From 6,979 records, 21 studies met the inclusion criteria, involving 3,314 participants from 10 countries. The analysis included six assessment tools: GUSS, MASA, V-VST, BSST, WST, and DNTA, compared against gold-standard methods VFSS and FEES. GUSS, MASA, and V-VST showed the highest reliability, with sensitivity and specificity rates of 92% and 85% for GUSS, 89% and 83% for MASA, respectively. Heterogeneity among studies was minimal, and publication bias was low, enhancing the credibility of the findings.

Conclusion: Our network meta-analysis underscores the effectiveness of GUSS, MASA, and V-VST in dysphagia screening for stroke patients, with high sensitivity and specificity making them suitable for diverse clinical settings. BSST and WST, with lower diagnostic accuracy, require more selective use. Future research should integrate patient-specific outcomes and standardize methodologies to enhance dysphagia screening tools, ultimately improving patient care and reducing complications.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/#recordDetails.

KEYWORDS

dysphagia, swallowing disorders, deglutition, GUSS, MASA

Introduction

In recent years, the incidence of stroke has increased year by year and has become a major disease that seriously endangers national health worldwide (1). Particularly in stroke patients, dysphagia has distinct characteristics compared to dysphagia resulting from other causes. A study highlighted that 56.6% of acute stroke patients presented with dysphagia, which was significantly associated with older age, greater stroke severity, and larger lesion volumes (2). Dysphagia after stroke can lead to severe complications such as aspiration pneumonia, dehydration, and malnutrition, which in turn may result in prolonged hospitalization, increased likelihood of readmission after discharge, and heightened risk of death (3). Early screening for dysphagia after stroke using accurate and appropriate assessment tools can help to identify potential risk factors early and avoid related complications, thereby improving patient outcomes (4). Accurate diagnosis and management of dysphagia are crucial for preventing these complications and improving the quality of life for stroke patients.

In the current landscape of post-stroke dysphagia evaluation, the primary methods encompass instrumental examinations and clinical scale assessments. The Video fluoroscopic Swallowing Study (VFSS) is widely recognized as the "gold standard" in dysphagia diagnosis, providing dynamic imaging under X-ray to meticulously analyze the swallowing movements of the mouth, pharynx, larynx, and esophagus (5, 6). Another notable method, the Fiberoptic Endoscopic Evaluation of Swallowing (FEES), enables direct observation of the nasal, pharyngeal, and laryngeal structures during natural breathing, coughing, speaking, and swallowing activities (7). Yet, it is crucial to acknowledge the inherent limitations of VFSS, including radiation exposure risks and the potential for aspiration during the procedure (8). Additionally, its dependency on specific person environmental factors restricts its widespread application, with the method's high costs further impeding its utility for extensive clinical screening. Both VFSS and FEES are acclaimed for their high accuracy (9). They necessitate specialized equipment and trained professionals, which limits their accessibility in certain patient groups. Specifically, VFSS is not recommended for pregnant women and children due to radiation concerns and is advised against frequent use in general patients (10).

Non-instrumental bedside assessment tools remain the primary method for screening and diagnosing dysphagia in clinical settings, particularly for early evaluation of swallowing disorders. Currently, common swallowing disorder assessment tools include water swallowing test, TOR-BSST©, MASA and GUSS, etc. (11–15). Various studies have shown that the accuracy of swallowing function assessment scales varies, with the Gugging Swallow Screen (GUSS) having a sensitivity of 97% and specificity of 67%, the Mann Assessment of Swallowing Ability (MASA) having 94% sensitivity and 66% specificity, and the Water Swallow Test (WST) having 85% sensitivity and 75% specificity in acute stroke patients, highlighting the need to select appropriate tools for accurate dysphagia diagnosis and management (14, 16, 17). And problems such as over-prediction or under-prediction often exist. Moreover, due to varying pathologies (neurogenic vs. myogenic dysphagia), the effectiveness of these scales can differ (18, 19). There is a lack of comprehensive reviews on the effectiveness of non-instrumental bedside scales specifically for stroke patients. Therefore, our systematic review aimed to determine which non-instrumental assessment methods (clinical or comprehensive) are currently used to screen for dysphagia in stroke and which tool is more accurate for dysphagia screening in stroke patients after gold marker validation.

Methods

This systematic review was registered on the PROSPERO platform with the registration number CRD42023494692 (20). The network meta-analysis (NMA) was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and checklist (21). The PRISMA statement and checklist (Supplementary Files S1, S2) are designed to enhance the transparency and necessity of reporting in systematic reviews.

Eligibility criteria

Inclusion criteria: Studies were included in this systematic review if they met the following criteria: (1) patients diagnosed with stroke by imaging methods such as CTA or MRI; (2) studies utilized bedside screening tools to assess dysphagia; (3) sensitivity and specificity were used as primary outcome measures; (4) studies included patients in the acute phase of stroke; (5) There was sufficient information in English to demonstrate that they described a comprehensive nursing or MDT swallowing assessment to screen for dysphagia in stroke patients.

Studies were excluded if: (1) The study population included non-stroke patients; (2) Outcome indicators reported did not directly diagnose dysphagia; (3) There was no standard comparison to assess the accuracy of the results; (4) Reviews, conference abstracts, commentaries, open letters, editorials, and errata were excluded due to their inherent brevity.

Data sources and search strategies

For data sources and search strategies, a series of relevant keywords were planned based on insights from evidence-based medicine experts. Studies included in this meta-analysis were diagnostic accuracy studies, randomized controlled trials, and prospective cohort studies that reported on the effectiveness or accuracy of dysphagia screening tools in stroke patients. Systematic searches were conducted in typical databases: Embase, PubMed, Web of Science, Scopus, and CINAHL. All publications up to 10 December 2023, were included. Terms related to dysphagia, assessment tools, and accuracy, including MeSH terms and free-text terms, were used to retrieve all relevant literature. The search strategies used in this review are outlined in Supplementary Table S1, summarizing the retrieval information for each database.

Study selection

The study selection and review process was independently conducted by two reviewers, YJ and YC. The initial steps included eliminating duplicates and reading titles to exclude reviews, conference abstracts, letters, protocols, narrative reviews, and editorials. The remaining records underwent preliminary screening

based on titles and abstracts, followed by a comprehensive evaluation through full-text reading. Any differences between the two primary reviewers were resolved through discussion. If unresolved differences persisted, a third reviewer (HJ) was consulted for resolution.

Data extraction

For data extraction from eligible studies, two reviewers (SH and DZ) independently carried out this process using a predefined form. The following detailed information was captured: (1) Author names; (2) Publication year; (3) Demographic characteristics of the study population (age, gender, cohort); (4) Sample size recruited and ultimately included in the analysis; (5) Number of negative and positive samples; (6) Evaluation methods used for comparison; (7) Scales used; (8) Related indices of scale accuracy. In cases where the two primary reviewers had disagreements about data extraction, a third reviewer (YL) arbitrated and made the final decision.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was utilized for evaluating the quality of each study. Two teams independently assessed the quality: Team 1 comprised YJ and YL, while Team 2 consisted of SH and RP. Disagreements were resolved by a third party (HJ). The evaluation was based on four parts: patient selection, index test, reference standard, and flow and timing. QUADAS-2 consists of 14 items, each rated as "yes" for meeting standards, "no" for not meeting or unmentioned standards, and "unclear" for insufficient information. Studies were finally classified as high, medium, or low quality. Publication bias was examined using funnel plots and Egger's regression test, with $p < 0.10$ indicating evidence of publication bias (Supplementary Table S2).

Conceptual mapping of measures

Statistical analysis was conducted using R version 4.3.2. Meta and meta for packages were utilized to aggregate sensitivity, specificity, positive predictive value, and negative predictive value as effect size statistics, each with their 95% confidence intervals (CIs). Considering the study's focus on evaluating various screening tools based on original research, a consistency model was used for NMA and result ranking. Network package and related commands processed data, producing network relationship diagrams, forest plots, radar charts, and funnel plots. Funnel plots were used to identify publication bias, while predictive interval plots (95% CIs and 95% PrIs) assessed the heterogeneity of the combined results. Forest plots and radar charts presented the likelihood of each screening tool being the best choice.

Results

Search results

Our study involved a comprehensive literature search across five independent electronic databases, resulting in the retrieval of 6,979 records. These databases included Embase, PubMed, Web of Science, CINAHL, and Scopus. After eliminating 2,790 duplicates, 4,189 papers remained. Through title and abstract screening, 3,886 studies were excluded. Further full-text review led to the exclusion of an additional 282 studies. Consequently, 21 studies met the inclusion criteria and were incorporated into the systematic review, and 15 were included in the quantitative analysis (11, 12, 14, 15, 22–38) (Figure 1).

Study characteristics

This NMA included 3,314 participants from 10 countries, comprising various types of stroke patients with and without dysphagia. The analysis evaluated the accuracy of 6 assessment tools across 21 studies (11, 12, 14, 15, 22–38). There are 15 studies utilized VFSS or FEES as gold standards for sensitivity and specificity (11, 12, 22, 24, 27–31, 33–38). MASA and SLP were used as comparative baselines in some studies (14, 15, 23, 25, 26, 32). The research involved both cross-sectional and case–control studies, including a multi-center observational study (11, 12, 14, 15, 22–38). Sensitivity and specificity of the various assessment tools ranged from 0.21 to 1.00 and 0.41 to 0.98, respectively. Detailed information about the studies included in the NMA can be found in Table 1.

Study quality

The risk of bias assessment of the studies included in this NMA showed that 7 studies were of high quality and 7 studies were of moderate quality (11, 12, 22, 23, 25–28, 31, 33, 35–38). Most studies had a low risk of bias, with 15 studies enrolling consecutive cases and 19 studies avoiding a case–control design (11, 12, 14, 15, 22, 24–35, 37, 38). Most studies managed to exclude unsuitable patients, interpret test results without knowledge of the reference standard, set predefined thresholds, use the same reference standard for patients, and analyze all included patients. A detailed description of the population, age, and sample size was provided (Supplementary Table S2). The funnel plots for sensitivity, specificity, and accuracy exhibit a symmetrical distribution around the mean effect size, indicating minimal publication bias across the included studies. Slight skewness observed in the specificity plot suggests minor bias, but overall, the symmetry in the data supports the robustness of the meta-analysis findings (Supplementary Figures S1–S3).

Meta-analysis

The network diagram in this study illustrates the inclusion of nine dysphagia assessment tools, with FEES and VFSS prominently positioned as the gold standards, indicated by their central and largest nodes in the network. This prominence reflects their extensive use and frequent comparison with other assessment tools. Conversely, tools such as MASA, V-VST, and GUSS are represented by smaller nodes, suggesting that fewer studies have compared these tools directly with the gold standards. This network visualization underscores the central role of FEES and VFSS in dysphagia screening

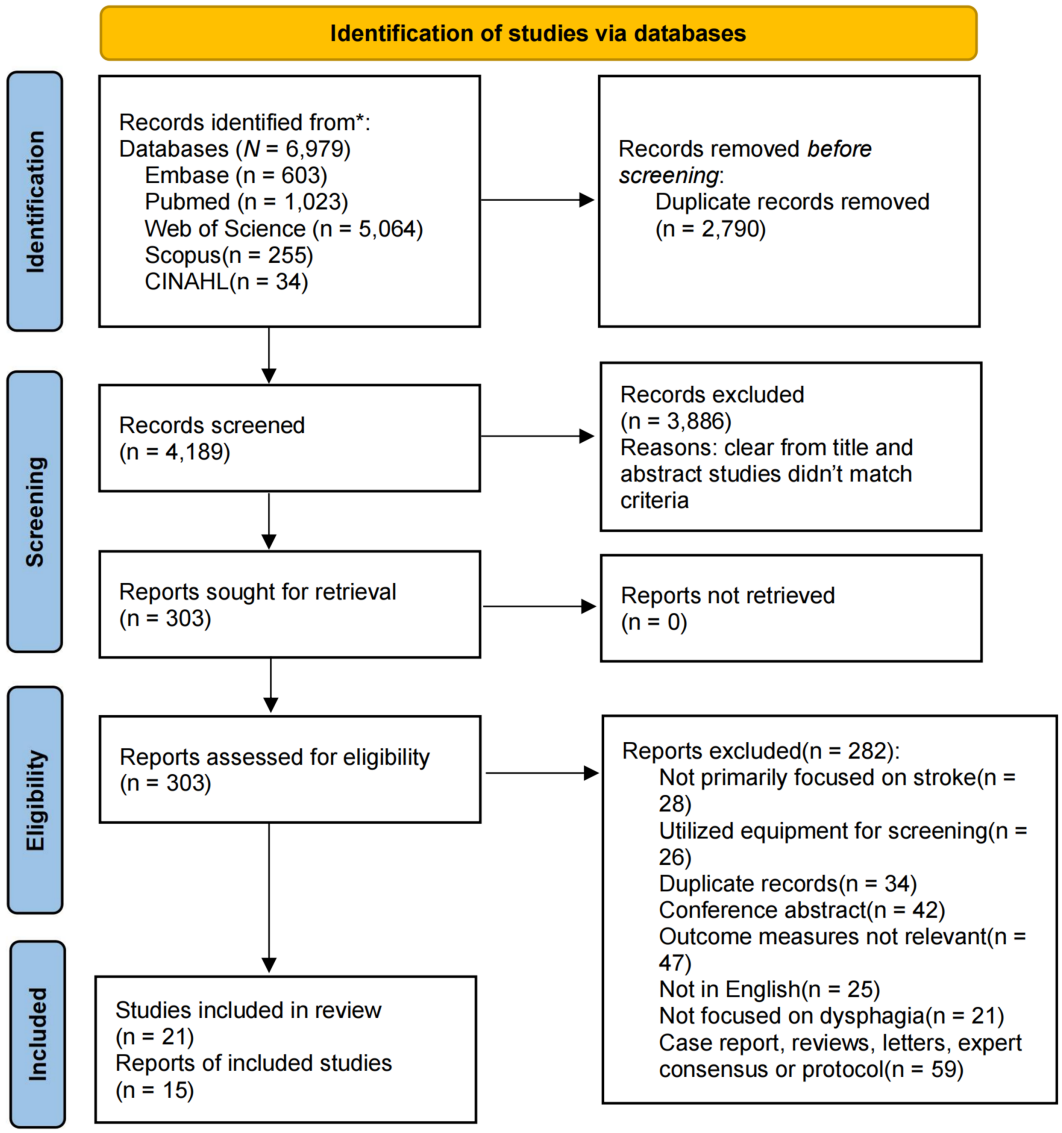

FIGURE 1
Flowchart of the study selection.

while highlighting the relative under representation of other tools in the literature (Figure 2).

Heterogeneity test

The heterogeneity analysis of sensitivity for the GUSS, V-VST, and MASA dysphagia screening tools revealed minimal variability across the five studies evaluated. These tools demonstrated high sensitivity, with a pooled estimate from the mixed-effects model of 0.954 [0.933, 0.975], outperforming BSST (0.903 [0.876, 0.930]), DTNA (0.884 [0.860, 0.907]), and WST (0.788 [0.764, 0.813]) (Figure 3). Similarly, the heterogeneity analysis of specificity (Figure 4) indicated that MASA and V-VST, along with GUSS, exhibited low heterogeneity. MASA and V-VST, in particular, showed more stable and higher specificity, with a pooled estimate from the mixed-effects model of 0.922 [0.884, 0.961]. These findings highlight the robustness and reliability of MASA and V-VST as superior tools for dysphagia screening in stroke patients, offering consistent performance across diverse study settings.

Diagnostic accuracy

The radar chart delineates the performance metrics of various non-instrumental dysphagia assessment tools, bench marked against the gold-standard diagnostic methods VFSS and FEES. GUSS, MASA, and V-VST exhibit superior performance across key parameters, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. GUSS and MASA demonstrate particularly high sensitivity and specificity, underscoring their reliability in detecting and excluding dysphagia. Similarly, V-VST shows robust

TABLE 1 Summary of non-instrumental screening and assessment tools for post-stroke dysphagia.

Study	Country	Study design	Population	Sample size	Sample analyzed	Age (years)	Male *n*, (%)	Reference test	Test
Pacheco Castilho 2020	Brazil	Cross sectional	Stroke	60	60	64.9	33 (55.0)	VFSS	BSST
Umay 2018	Turkey	Cross sectional	Hemispheric stroke	128	113	66.71	61 (54.0)	FEES	GUSS
Simpelaere 2023	Belgium	Retrospective observational study	Acute stroke	115	115	82	66 (57.4)	SLP	MASA
Perry 2001	UK	Cross sectional	Stroke	200	200	71.6	111 (55.5)	SLP	WST
Umay 2018	Turkey	Cross sectional	Acute stroke	174	141	63.27	94 (66.7)	FEES	MASA
Immovilli 2020	Italy	Prospective observational study	Acute Stroke	120	120	67.4	67 (55.8)	FEES	BSST
Gandolfo 2019	Italy	Multicenter observational study	Stroke	249	249	72.6	126 (50.6)	SLP	WST
Sherman 2018	Canada	Retrospective observational study	Ischemic stroke	221	147	68	82 (56.0)	VFSS	DTNA
Warnecke 2017	Korea	Cross sectional	Acute stroke	121	100	73.6	56 (56.0)	FEES	GUSS
Behera 2018	US	prospective observational study	Stroke	225	225	68.4	122 (54.2)	MASA	WST
Edmiaston 2014	US	Cross sectional	Acute stroke	225	225	63	114 (50.9)	VFSS	WST
Somasundaram 2014	Germany	Cross sectional	Left-Hemispheric Middle Cerebral Artery Stroke	67	67	68	45 (67.0)	FEES	WST
Schrock 2011	US	Cohort study	Acute Stroke	283	283	65	144 (51.0)	VFSS	DTNA
Kopey 2011	US	Cross sectional	Acute stroke	350	223	62.5	107 (48.0)	VFSS	WST
Antonios 2010	US	Cross sectional	Acute stroke	150	150	64.5	70 (46.7)	VFSS	MASA
Bravata 2009	US	Retrospective observational study	Acute ischemic stroke	101	101	64.8	67 (66.3)	SLP	DTNA
Martino 2008	Canada	Cross sectional	Stroke	311	311	69.2	183 (58.8)	VFSS	BSST
Cummings 2015	US	Cross sectional	Stroke	49	49	71.7	25	SLP	DTNA
Benfield 2021	UK	Prospective observational study	Acute stroke	47	47	73	24(51.1)	VFSS	DTNA
Toscano 2018	UK	Prospective observational study	Stroke	52	50	74	33(63.5)	FEES	BSST
Rofes 2014	Spain	Retrospective observational study	Stroke	66	66	73.5	37 (56.1)	VFSS	V-VST

BSST, Bedside Swallow Screening Tool; WST, Water Swallow Test; DTNA, Dysphagia Trained Nurse Assessment.

performance with high specificity and sensitivity, complemented by strong PPV and NPV values. Conversely, WST, while maintaining good sensitivity, shows lower specificity, indicating a tendency for over-prediction. BSST and BTNA display comparatively lower sensitivity and specificity, suggesting lesser reliability. Overall, GUSS, MASA, and V-VST align closely with gold-standard benchmarks, highlighting their efficacy and reliability in clinical dysphagia screening for stroke patients (Figure 5; Supplementary Table S3).

Discussion

Accurate screening for dysphagia is crucial in mitigating risks such as aspiration pneumonia and malnutrition (38). This network meta-analysis provides a comprehensive evaluation of various non-instrumental dysphagia screening tools against gold-standard methods (VFSS and FEES) for stroke patients. The findings highlight the efficacy and reliability of these tools, with implications for clinical practice. Furthermore, in this review, the smaller heterogeneity

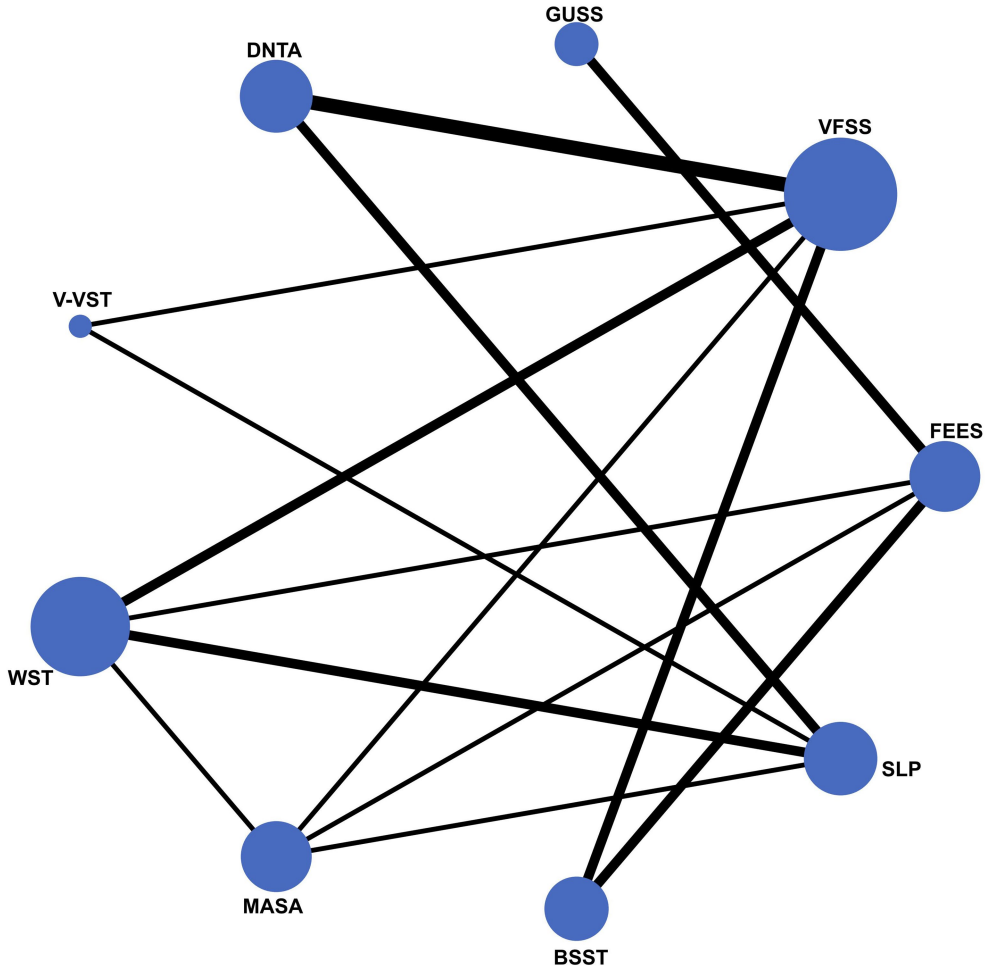

FIGURE 2
Network meta-analysis graph of comparative effectiveness among different screening tools.

observed in the evaluation effects of some screening tools through subgroup analysis of the included studies indicated that the results were consistent in different settings, while the symmetrical distribution in the funnel plot indicated minimal publication bias, which enhanced the credibility of our meta-analysis.

The results of this study highlight the robustness and reliability of GUSS, MASA, and V-VST as primary tools for dysphagia screening. Their consistent performance across different studies underscores their potential for widespread clinical application. This robustness is particularly important in diverse clinical settings, ensuring accurate patient assessments regardless of specific conditions. MASA and V-VST demonstrate the best overall performance for diagnosing dysphagia and screening healthy individuals, though further research is needed on V-VST's comparison to gold standards to support its clinical adoption. Additionally, while GUSS shows high sensitivity, its lower specificity may limit its use in excluding non-dysphagic patients. However, GUSS remains a viable option for early dysphagia screening in acute stroke patients.

MASA, known for its high specificity in dysphagia screening among stroke patients, incorporates 24 comprehensive clinical items (39). These items evaluate oral motor skills, pharyngeal reflexes, laryngeal movement, and the coordination of chewing and swallowing. A score above 178 on MASA suggests the absence of dysphagia. Validated through techniques such as FEES, MASA has demonstrated robust sensitivity and specificity (29). It has been extensively studied in acute stroke settings across diverse regions including the U.S., Belgium, and Turkey, which supports its application in these contexts (14, 22, 32). The high specificity of MASA is significant in clinical practice, particularly in stroke rehabilitation, as it minimizes false-positive rates, thereby ensuring that patients who truly require intervention for dysphagia are accurately identified and managed. Moreover, studies like that by Tomoya Omura (40) report MASA's effectiveness in aspiration detection, potentially aiding in the prevention of aspiration pneumonia. However, its comprehensive nature makes it detailed and time-consuming, posing challenges in fast-paced clinical settings. Professional training, typically provided by speech pathologists, is essential for accurate administration and interpretation of MASA, which may limit its accessibility in general clinical practice (22). MASA's scope of application is expanding beyond stroke patient assessments to include evaluating the effects of treatments like percutaneous auricular vagus nerve stimulation therapy, as studied by Wang et al., and assessing swallowing abilities in sarcopenia patients (22). Integrating this training into clinical practice, especially in busy or resource-limited settings, is challenging

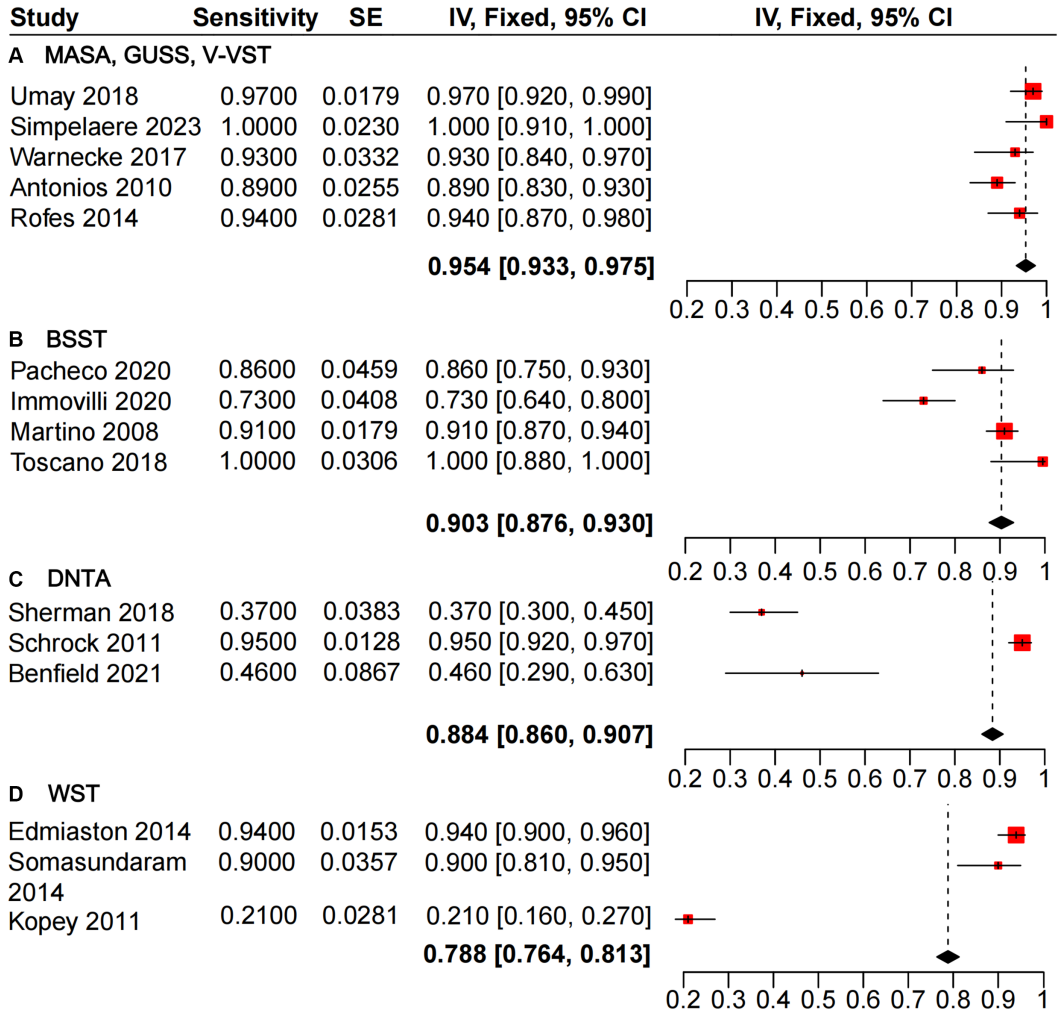

FIGURE 3
Forest plot of sensitivity analysis for non-instrumental dysphagia screening tools.

due to MASA's detailed nature and the time investment required for its administration. These factors can limit MASA's practicality in some healthcare environments, necessitating consideration of the healthcare setting's capacity when choosing to implement MASA for dysphagia assessment.

Comparative analysis reveals that while tools like BSST and WST are useful, they exhibit lower diagnostic accuracy compared to GUSS, MASA, and V-VST. This has practical implications, especially in resource-limited settings where selecting the most reliable tool is critical for accurate patient assessments and avoiding unnecessary interventions. The superior performance of GUSS, MASA, and V-VST suggests they should be preferred in clinical practice, particularly where precise diagnosis can significantly impact patient management and outcomes. In contrast, tools like BSST, WST, and DNTA show inconsistent results across different versions and upgraded evaluation tools for dysphagia screening. For example, Edmiaston and Somasundaram (27, 36) reported WST sensitivity above 0.9 but lower specificity, whereas Kopey (30), using the gold-standard comparison, reported completely opposite findings. This discrepancy may be attributed to Edmiaston and Somasundaram's use of more controlled and standardized procedures, enhancing the reliability of dysphagia detection (27, 36). In contrast, Kopey's use of the less standardized 3-sip test resulted in higher variability and lower sensitivity (30). Additionally, differences in the administrators and managers of WST validation studies and the diverse patient populations included in these studies could contribute to the significant variability in outcomes.

The meta-analysis indicates that BSST, with its high NPV and specificity, could have a unique role in assessing dysphagia in acute stroke patients, such as in assessing swallowing function during rehabilitation. The simplicity and rapid application of BSST make it a practical, non-invasive option during acute hospital admissions (28). However, its effectiveness heavily relies on the practitioner's experience and thorough assessment skills (31). Therefore, standardized training and clear procedural guidelines are essential to maximize its potential. BSST involves a comprehensive set of assessments, including recording patient characteristics, evaluating speech and communication skills, conducting facial and oral motor examinations, monitoring oxygen saturation, performing water swallow tests, and using thickened liquids for evaluation (31). The dependence on clinical experience and detailed evaluation of patient factors, such as alertness, language ability, facial symmetry, and

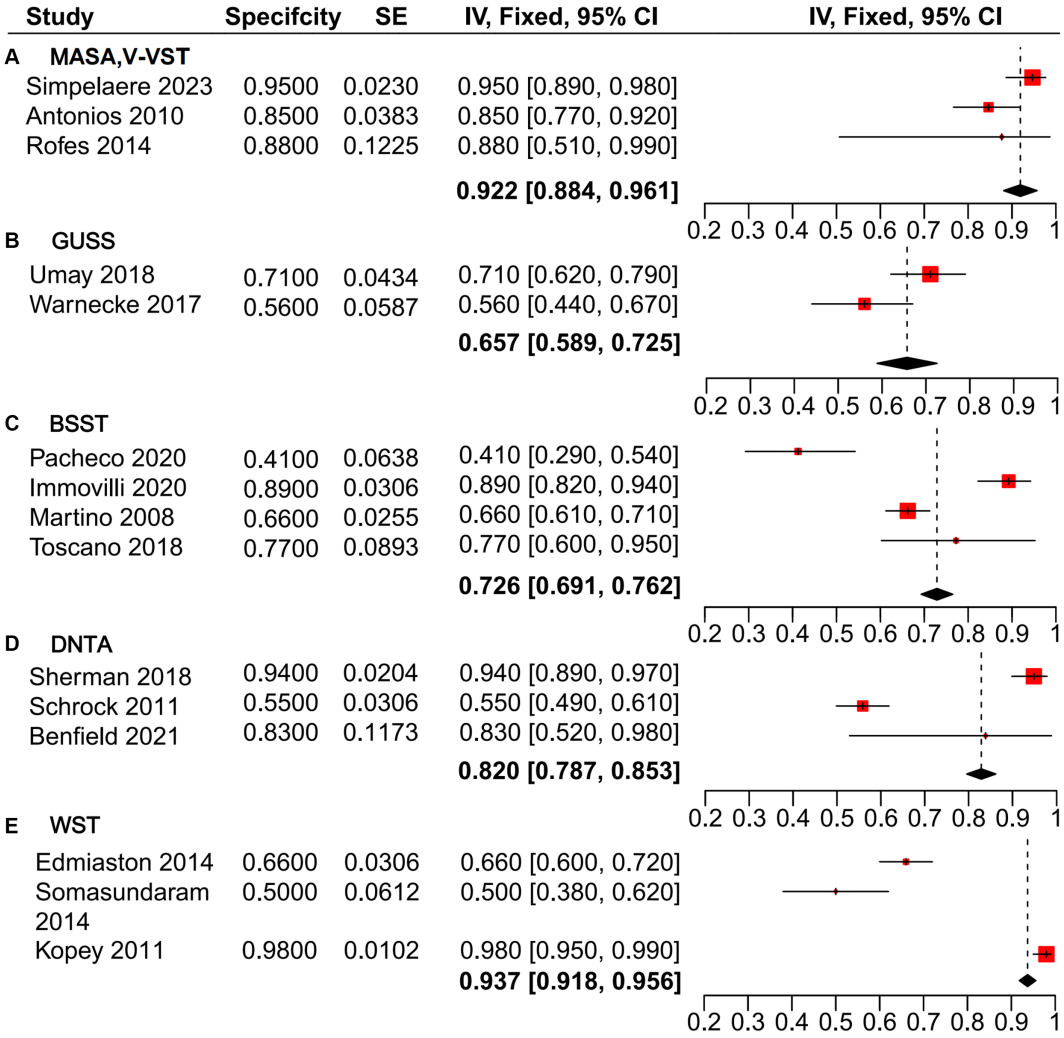

FIGURE 4
Forest plot of specificity analysis for non-instrumental dysphagia screening tools.

apraxia, means BSST lacks uniform content, affecting its reproducibility and practicality across different clinical settings (11). Similarly, DNTA's consistency is compromised due to variability in trained nurses and differing assessment practices. Overall, the heterogeneity in the screening effectiveness of BSST and DNTA is high, likely due to the lack of consistent assessment protocols and the use of varied innovative approaches by different researchers. Our meta-analysis showed that the overall performance of BSST and DNTA was inferior to GUSS, MASA, and V-VST, which may limit the future applicability of BSST and DNTA in research and clinical practice.

Our network meta-analysis underscores the importance of personalized dysphagia screening tailored to patient conditions and stroke stages. Tools like the GUSS, V-VST, MASA and WST offer unique advantages, particularly for acute stroke patients. WST is favored for its simplicity and reliability in initial screenings, while MASA, known for its high accuracy, is more complex and time-consuming, necessitating selective use. A patient-centered approach is essential, with healthcare professionals evaluating each patient's condition, aspiration risk, and cooperation level to ensure accurate diagnosis and patient comfort, thereby enhancing care quality. Integrating tools, such as combining GUSS's high sensitivity with WST's high specificity, can significantly improve diagnostic accuracy, particularly in preventing and managing post-stroke dysphagia and aspiration. However, GUSS and V-VST, despite their safety benefits, can be cumbersome and time-consuming. Clinical assessments often rely on a single scale, each with its strengths and limitations. While combining multiple scales holds promise for improved accuracy, the economic and social impacts of this approach require further exploration. By considering patient conditions and aspiration risks, and integrating diverse tools, healthcare professionals can reduce misdiagnosis risks and provide a more effective foundation for managing post-stroke dysphagia.

Despite the comprehensive nature of this network meta-analysis, several limitations should be acknowledged. First, our study focused on dysphagia screening tools, excluding studies that specifically validated scales with aspiration as the primary patient outcome. This exclusion might have limited our understanding of tools specifically designed to prevent aspiration pneumonia. Future research should address limitations such as the exclusion of aspiration-specific

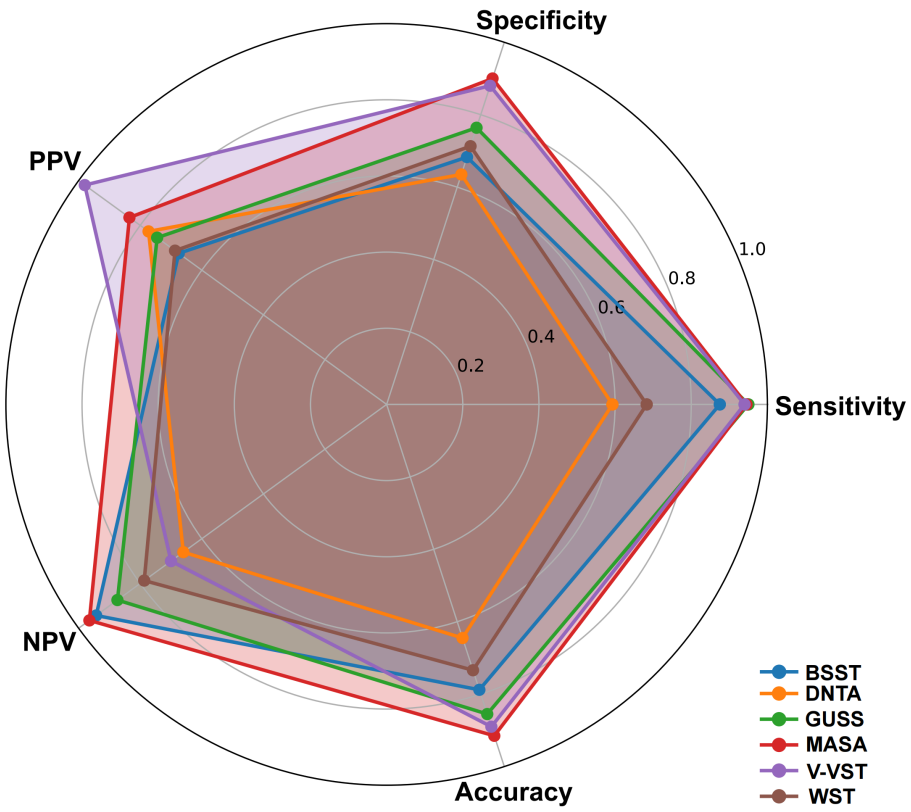

FIGURE 5
Radar chart of performance metrics for non-instrumental dysphagia screening tools using gold standard benchmark.

outcomes and study heterogeneity. Second, since many of the original studies included did not specify whether they included patients with language disorders, this may increase heterogeneity and may lead to some differences in our findings. Although we accounted for these differences through statistical methods, minor inconsistencies may still exist. Lastly, while we aimed to provide a thorough analysis, the reliance on published data means that potential publication bias and incomplete reporting could affect the robustness of our conclusions. Future research should aim to address these limitations by including more diverse patient outcomes and ensuring consistency in study designs and reporting standards.

Conclusion

This network meta-analysis highlights the importance of accurate dysphagia screening tools for stroke patients. GUSS, MASA, and V-VST emerged as the most reliable, demonstrating superior sensitivity and specificity, suitable for diverse clinical settings. While BSST and WST have practical uses, their lower diagnostic accuracy suggests a more selective application. The findings emphasize the need for personalized screening approaches tailored to individual patient conditions and stroke stages. By broadening patient outcomes and standardizing methodologies, future studies can improve the effectiveness of dysphagia screening tools, enhancing patient care and reducing complications.

What is already known on this topic

Dysphagia is a prevalent and serious complication in stroke patients, necessitating early and accurate screening to improve outcomes.

Existing dysphagia screening tools exhibit varied efficacy across different patient populations; however, this study identifies MASA, GUSS, and V-VST as reliable and relatively accurate tools for dysphagia screening.

There is a critical need for personalized screening approaches in dysphagia management post-stroke, highlighting the gap in comprehensive comparative analyses.

What this study adds

- This study provides a direct comparison of 6 non-instrumental bedside dysphagia screening tools, revealing specific strengths and weaknesses in acute stroke settings.
- Our findings quantify the sensitivity and specificity of each tool, offering concrete data to guide clinicians in selecting the most effective screening method for stroke-induced dysphagia.
- The analysis underscores the importance of patient-specific factors and stroke stages in choosing dysphagia screening tools, advancing personalized care approaches.

How this study might affect research, practice, or policy

- This study's insights can inform the development of tailored dysphagia screening protocols, potentially leading to revised clinical guidelines that enhance patient care and outcomes.
- The comparative effectiveness data provided may drive future research toward innovative screening tools and methodologies, particularly those incorporating patient-specific variables and stroke recovery stages.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

YJ: Writing – review & editing, Writing – original draft, Software, Methodology. YC: Writing – original draft, Formal analysis, Data curation. RP: Writing – review & editing, Conceptualization. DZ: Writing – original draft, Data curation. SH: Writing – original draft, Data curation. HJ: Writing – original draft, Supervision, Project administration, Funding acquisition. YL: Writing – original draft, Supervision, Project administration.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1380287/full#supplementary-material

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The 100 most-cited articles in hypothermic brain protection journals: a bibliometric and visualized analysis

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Introduction: A bibliometric analysis is used to assess the impact of research in a particular field. However, a specialized bibliometric analysis focused on hypothermic brain protection has not yet been conducted. This study aimed to identify the 100 most-cited articles published in the field of hypothermic brain protection and analyze their bibliometric characteristics.

Methods: After screening articles from the Web of Science citation database, complete bibliographic records were imported into Python for data extraction. The following parameters were analyzed: title, author's name and affiliation, country, publication year, publication date, first author, corresponding author, study design, language, number of citations, journal impact factors, keywords, Keywords Plus®, and research topic.

Results: The 100 articles were published between 1990 and 2016. The citation frequency for each publication ranged from 86 to 470. Among the 100 articles, 73 were original articles, 18 were review articles, 8 were clinical articles, and 1 was editorial material. These papers were published in 37 journals, with the *Journal of Cerebral Blood Flow and Metabolism* being the most prolific with 15 papers. Eighteen countries contributed to the 100 publications, 51 of which were from United States institutions. In addition, the keywords in the Sankey plot indicated that research in the field of hypothermic brain protection is growing deeper and overlapping with other disciplines.

Discussion: The results provide an overview of research on hypothermic brain protection, which may help researchers better understand classical research, historical developments, and new discoveries, as well as providing ideas for future research.

KEYWORDS

hypothermia, brain protection, surgery, bibliometric analysis, citations highlights

Highlights

- The unique advantage of this study is that it is the first bibliometric study to identify and characterize articles in the field of hypothermic brain protection in all journals of the Science Network (SCIE).
- Most bibliometric studies exclude nonprofessional journals.
- We generated a more comprehensive list of the 100 most-cited articles in the field of hypothermic brain protection by including all journals in the analysis.

Introduction

Hypothermic brain protection is an important technique used in neurosurgery to mitigate ischemic and hypoxic injuries. Moreover, lowering the temperature of the brain tissue can protect neurological function (1). Recent research has focused on understanding the mechanisms of hypothermic brain protection and its ability to protect brain functions (2). Hypothermia inhibits the generation of free radicals, reduces apoptosis, and stabilizes cell membrane integrity (3). Clinical methods for hypothermic brain protection include surface, nasopharyngeal, and intravenous cooling (4). However, hypothermia can also lead to complications, such as immunosuppression and renal failure, highlighting the need for further investigation to determine the optimal hypothermic brain protection protocol (5).

Several related studies in the field of hypothermic brain protection have been published in various journals. Analysis of these articles is crucial to evaluate their impact on basic research, clinical practice, and the surgical profession. Bibliometric analysis is an excellent method to assess this impact (6).

Bibliometrics is a discipline that uses quantitative and statistical methods to analyze scientific literature (7). It provides valuable information and reveals the laws and trends in the development of a particular scientific discipline (8). In neurological surgery, bibliometric analysis has been widely applied to analyze research hotspots and developmental trajectories of various diseases, including cerebral aneurysms, stroke, and traumatic brain injury (9–11). This analysis provides guidance for future research directions and resource allocation in the field of neurosurgery. However, specialized bibliometric analyses have not yet been performed in the field of hypothermic brain protection.

Therefore, this study aimed to identify the 100 most-cited articles published in the field of hypothermic brain protection using bibliometric methods. We analyzed their bibliometric characteristics to provide insights into the developments in this field.

Materials and methods

Ethical considerations

This study analyzed and described previously published articles; therefore, no ethical approval was required.

Data sources and search strategies

The Clarivate Analytics' Web of Science (WOS) (1980–present) citation database was used as the data source to identify articles in the field of hypothermic brain protection and track their citations. Considering the broad range of topics covered in the articles on hypothermia-related brain protection, we conducted a pre-search to determine the best search formula. The last search was conducted on August 21, 2023, using the expressions detailed in Supplementary Table S1. All obtained references, including bibliographic and citation data, were exported from the database and subsequently imported into document management software (Zotero, 6.0.30; https://www.zotero.org/) to remove duplications and screen them. The search strategy produced 1,847 records, listed in descending order, based on the number of citations retrieved from the source database.

Study selection and data extraction

Two independent researchers (Geli and Huang) screened the literature in the database in descending order based on WOS citations. Literature in the field of non-hypothermic brain protection was excluded based on the title and abstract. For uncertain articles, the full text was obtained for accurate inclusion or exclusion determination. During the study selection process, discrepancies between investigators were resolved by a third investigator (Hu). The evaluation was terminated at the 100th paper with the highest number of citations. Finally, the 100 most-cited articles in the field of hypothermic brain protection were listed for further analysis. Complete bibliographic records were exported from the WOS in plain text or Excel (Microsoft Corporation, Redmond, WA, United States) format and imported into Python (version 3.11.5; https://www.python.org/downloads/release/python-3115/) for data extraction.

The following information was extracted using Python and stored in Microsoft Excel (Microsoft Corporation): article title, author, abstract, keywords, year of publication, published journal, cited references, PMID, DOI, total citations, and annual average citations. We also determined the impact factor (IF) of the articles based on the currently published journal citation report (JCR® IF 2023).

Data analysis and visualization

Descriptive statistics of the selected articles were analyzed using Microsoft Excel 2023 (Microsoft Corporation), Python (version 3.11.5), and VOSviewer [version 1.6.20; developed by van Eck and Waltman (12)], a literature knowledge visualization software for constructing a bibliometric network. Before data analysis, the obtained data were standardized. All authors were checked through their institutions or email addresses to eliminate potential confusion from authors sharing the same names and initials, ensuring that they were specific individuals. The names of all institutions, such as universities and research centers, were reviewed and included at the same level, whereas the individual departments or research units under them were removed. Articles from Northern Ireland and Britain were considered to be from the United Kingdom. Different keywords with the same meaning were merged into one term (e.g., head injury and brain injury were collectively classified as brain injury). Some authors in the top 20 articles did not provide keywords ($n=7$), and three independent researchers discussed and determined the keywords for these articles based on Keywords Plus®. All references were standardized to create a unified list. Excel (Microsoft Corporation) was used to list the basic characteristics of the selected documents in a tabular form. The bibliometric network was graphically generated using the VOSviewer software (12). In a network visualization map, different nodes represent different elements such as countries, institutions, authors, or terms. The links between nodes represent relationships such as coauthors, co-citations, or co-occurrences, and are weighted by the total link strength (13). Python (version 3.11.5) and R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) were used to construct radar charts describing article types and

publication years and a Sankey plot was created to describe the relationships among authors, countries, and keywords. The packages used in Python and R are listed in Supplementary Table S2. The research process is shown in Figure 1.

Results

Citations

The 100 most-cited articles from all journals were published between 1990 and 2016, as shown in Table 1, and are listed in descending order based on the total WOS citation count on the search day (1, 14–112). Additionally, the table includes the year of publication, journal name, IF, first author, corresponding author, and average citations per year count based on WOS data.

The citation frequency of these 100 studies ranged from 86 to 470 times (mean = 156), with the average annual citation volume ranging from 2.9 to 19.4 times (mean = 7.3). The median publication year for these articles is 1999. Approximately one-fifth of the articles ($n = 18$) were cited more than 200 times, and only six articles were cited more than 400 times. The most-cited article, titled "Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia" was published by Globus et al. (14) in the *Journal of Neurochemistry* in 1995 and has 470 citations to date.

We also created a network visualization based on the number of citations per article (Figure 2). Globus et al. (14), Clifton et al. (15), Kuboyama et al. (16), Ginsberg et al. (17), Dietrich et al. (18), and Colbourne et al. (19) all received more than 400 citations, making them the largest nodes in the graph. Todd et al. (20) and Erecinska et al. (21) also received a high number of citations.

Years and types of publications

Among the 100 most-cited articles, 1991–1996 had the most publications ($n = 42$) (Figure 3), with the highest number of publications occurring in 1996 ($n = 9$) and a smaller peak occurring

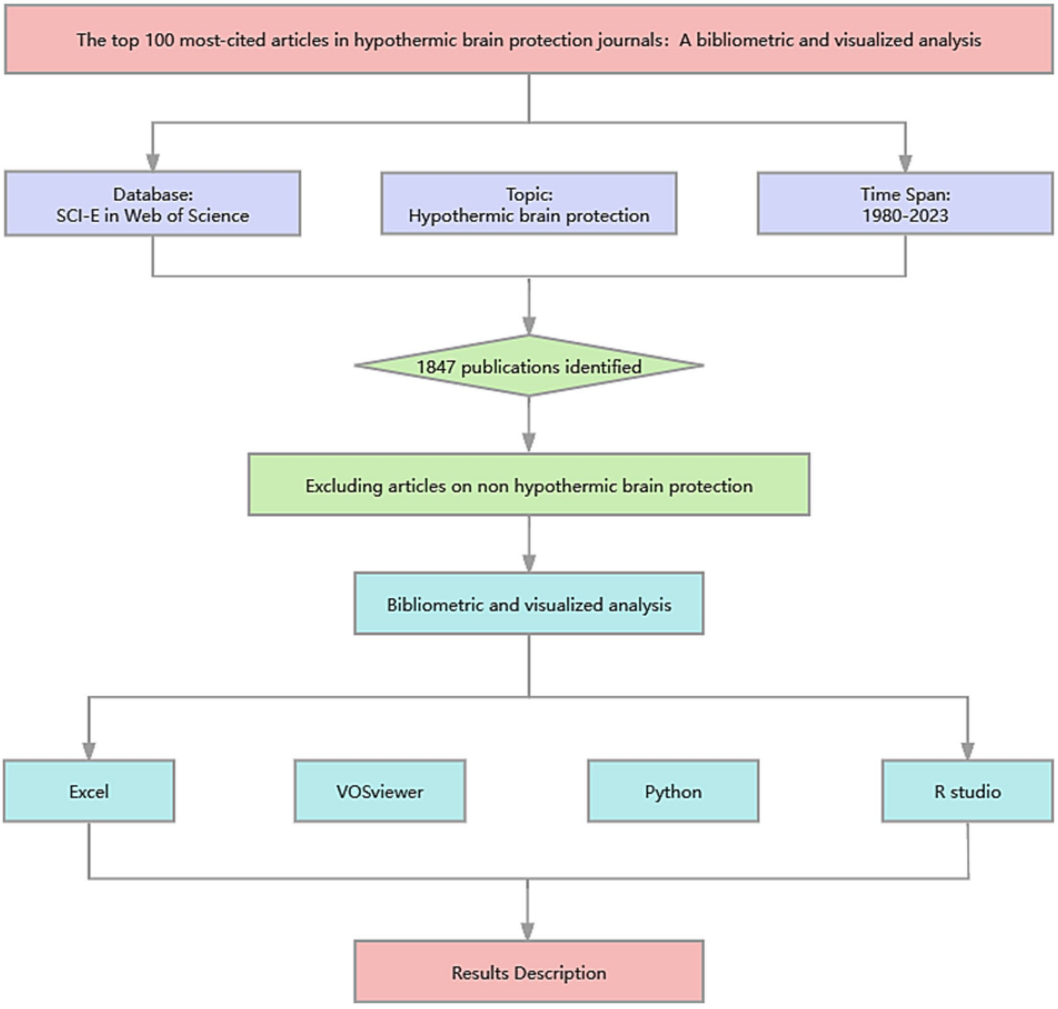

FIGURE 1
Study flow diagram created using ProcessOn.com. The Web of Science (WOS) (1980–present) citation database was used to identify articles in the field of hypothermic brain protection. The search strategy yielded 1,847 records, with the final selection of 100 articles made by the researchers. Data were then standardized and imported into Excel, VOSviewer, Python, and R Studio for bibliometric and visual analyses.

TABLE 1 List of the 100 most-cited articles in hypothermic brain protection journals.

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
1	Glutamate release and free-radical production following brain injury—effects of posttraumatic hypothermia	4.7	470	16.8	Journal of Neurochemistry	Globus, MYT	Globus, MYT	1995
2	Marked protection by moderate hypothermia after experimental traumatic brain injury	6.3	440	13.8	Journal of Cerebral Blood Flow and Metabolism	Clifton, GL	Dr. G. L. Clifton	1991
3	Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac-arrest in dogs— a prospective, randomized study	8.8	417	13.9	Critical Care Medicine	Kuboyama, K	Peter Safar	1993
4	Therapeutic modulation of brain temperature—relevance to ischemic brain injury	6.9	416	13.4	Cerebrovascular and Brain Metabolism Reviews	Ginsberg, MD	Ginsberg, MD	1992
5	Intraischemic but not postischemic brain hypothermia protects chronically following global forebrain ischemia in rats	6.3	410	13.7	Journal of Cerebral Blood Flow and Metabolism	Dietrich, WD	Dietrich, WD	1993
6	Delayed postischemic hypothermia—a 6 month survival study using behavioral and histological assessments of neuroprotection	5.3	409	14.6	Journal of Neuroscience	Colbourne, F	Frederick Colbourne	1995
7	Mild intraoperative hypothermia during surgery for intracranial aneurysm	158.5	345	19.2	New England Journal of Medicine	Todd, MM	Todd, MM	2005
8	Effects of hypothermia on energy metabolism in mammalian central nervous system	6.3	328	16.4	Journal of Cerebral Blood Flow and Metabolism	Erecinska, M	Erecinska, M	2003
9	Protective effects of moderate hypothermia after neonatal hypoxia-ischemia: short- and long-term outcome	3.6	273	10.9	Pediatric Research	Bona, E	Thoresen, M	1998
10	Posttraumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat	12.7	271	9.3	Acta Neuropathologica	Dietrich, WD	Dietrich, WD	1994
11	The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children	6	258	8.1	Journal of Thoracic and Cardiovascular Surgery	Greeley, WJ	Greeley, WJ	1991
12	Brain temperature alters hydroxyl radical production during cerebral ischemia reperfusion in rats	6.3	248	9.2	Journal of Cerebral Blood Flow and Metabolism	Kil, HY	Dr. C. A. Piantadosi	1996
13	Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse	3.5	237	8.2	Journal of Pharmacology and Experimental Therapeutics	Miller, DB	Miller, DB	1994
14	Induced hypothermia in critical care medicine: a review	8.8	233	11.7	Critical Care Medicine	Bernard, SA	Bernard, SA	2003
15	Antegrade cerebral perfusion with cold blood: a 13-year experience	4.6	228	9.5	Annals of Thoracic Surgery	Bachet, J	Bachet, J	1999
16	Treatment advances in neonatal neuroprotection and neurointensive care	48	219	18.3	Lancet Neurology	Johnston, Michael V	Johnston, MV	2011
17	The relationship among canine brain temperature, metabolism, and function during hypothermia	8.8	213	6.7	Anesthesiology	Michenfelder, JD	Michenfelder, JD	1991
18	Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia	11.2	213	11.8	Annals of Neurology	Ma, DQ	Maze, M	2005

(Continued)

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TABLE 1 (Continued)

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
19	Low environmental temperatures or pharmacological agents that produce hypothermia decrease methamphetamine neurotoxicity in mice	2.9	185	6.4	Brain Research	Ali, SF	Ali, SF	1994
20	Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants	8	180	8.6	Pediatrics	Shankaran, S	Shankaran, S	2002
21	Moderate hypothermia mitigates neuronal damage in the rat-brain when initiated several hours following transient cerebral-ischemia	12.7	177	6.1	Acta Neuropathologica	Coimbra, C	C. Coimbra	1994
22	Mild hypothermia reduces apoptosis of mouse neurons *in vitro* early in the cascade	6.3	176	8.4	Journal of Cerebral Blood Flow and Metabolism	Xu, LJ	Giffard, RG	2002
23	Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an anti-inflammatory/antipyretic drug—evidence for chronic encephalopathic processes following ischemia	8.3	176	6.5	Stroke	Coimbra, C	Coimbra, C	1996
24	Posthypoxic cooling of neonatal rats provides protection against brain injury	4.4	174	6.4	Archives of Disease in Childhood-fetal and Neonatal Edition	Thoresen, M	Dr. Marianne Thoresen	1996
25	Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischemia	8.3	174	11.6	Stroke	Hobbs, Catherine	Thoresen, M	2008
26	Chronic histopathological consequences of fluid-percussion brain injury in rats: effects of post-traumatic hypothermia	12.7	169	6.5	Acta Neuropathologica	Bramlett, HM	Bramlett, HM	1997
27	Effect of hypothermia on cerebral blood flow and metabolism in the pig	4.6	168	8.0	Annals of Thoracic Surgery	Ehrlich, MP	Griepp, RB	2002
28	Indefatigable ca1 sector neuroprotection with mild hypothermia induced 6 h after severe forebrain ischemia in rats	6.3	163	6.8	Journal of Cerebral Blood Flow and Metabolism	Colbourne, F	Colbourne, F	1999
29	Brain injury following trial of hypothermia for neonatal hypoxic-ischaemic encephalopathy	4.9	161	14.6	Archives of Disease in Childhood-Fetal and Neonatal Edition	Shankaran, Seetha	Shankaran, S	2012
30	Protective effects of brain hypothermia on behavior and histopathology following global cerebral-ischemia in rats	2.9	158	5.1	Brain Research	Green, EJ	Green, EJ	1992
31	RBM3 mediates structural plasticity and protective effects of cooling in neurodegeneration	64.8	155	19.4	Nature	Peretti, Diego	Mallucci, GR	2015
32	Hypothermia prevents ischemia-induced increases in hippocampal glycine concentrations in rabbits	8.3	152	4.8	Stroke	Baker, AJ	Dr. M. H. Zornow	1991
33	Influence of mild hypothermia on inducible nitric oxide synthase expression and reactive nitrogen production in experimental stroke and inflammation	5.3	148	7.0	Journal of Neuroscience	Han, HS	Yenari, MA	2002
34	Mild hypothermia inhibits inflammation after experimental stroke and brain inflammation	8.3	146	7.3	Stroke	Deng, H	Yenari, MA	2003

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TABLE 1 (Continued)

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
35	General versus specific actions of mild-moderate hypothermia in attenuating cerebral ischemic damage	6.3	145	9.1	Journal of Cerebral Blood Flow and Metabolism	Zhao, Heng	Zhao, H	2007
36	The importance of brain temperature in cerebral injury	4.2	143	4.6	Journal of Neurotrauma	Dietrich, WD	Dietrich, WD	1992
37	Protection against hippocampal ca1 cell loss by postischemic hypothermia is dependent on delay of initiation and duration	3.6	142	4.6	Metabolic Brain Disease	Carroll, M	Carroll, M	1992
38	Co-administration of MDMA with drugs that protect against MDMA neurotoxicity produces different effects on body temperature in the rat	3.5	142	5.3	Journal of Pharmacology and Experimental Therapeutics	Malberg, JE	Karen Sabol	1996
39	Twenty-four hours of mild hypothermia in unsedated newborn pigs starting after a severe global hypoxic-ischemic insult is not neuroprotective	3.6	138	6.3	Pediatric Research	Thoresen, M	Thoresen, M	2001
40	Posttraumatic brain hypothermia provides protection from sensorimotor and cognitive-behavioral deficits	4.2	135	4.8	Journal of Neurotrauma	Bramlett, HM	Edward J. Green	1995
41	Hypothermia for acute brain injury-mechanisms and practical aspects	38.1	134	12.2	Nature Reviews Neurology	Choi, H. Alex	Mayer, SA	2012
42	Hypothermia as a potential treatment for cerebral-ischemia		131	4.4	Cerebrovascular and Brain Metabolism Reviews	Maher, J		1993
43	Systemic inflammatory challenges compromise survival after experimental stroke via augmenting brain inflammation, blood-brain barrier damage and brain oedema independently of infarct size	9.3	130	10.8	Journal Of Neuroinflammation	Denes, Adam	Denes, A	2011
44	Hibernation in ground squirrels induces state and species-specific tolerance to hypoxia and aglycemia: an *in vitro* study in hippocampal slices	6.3	128	5.1	Journal of Cerebral Blood Flow and Metabolism	Frerichs, KU	Frerichs, KU	1998
45	Hypothermia in the management of traumatic brain injury—a systematic review and meta-analysis	38.9	127	6.4	Intensive Care Medicine	Henderson, WR	Henderson, WR	2003
46	Protection in animal models of brain and spinal cord injury with mild to moderate hypothermia	4.2	125	8.9	Journal of Neurotrauma	Dietrich, W. Dalton	Dietrich, WD	2009
47	A comfortable hypothesis reevaluated—cerebral metabolic depression and brain protection during ischemia	8.8	125	4.0	Anesthesiology	Todd, MM	Todd, MM	1992
48	Delayed induction of mild hypothermia to reduce infarct volume after temporary middle cerebral-artery occlusion in rats	4.1	125	4.3	Journal of Neurosurgery	Karibe, H	Philip R. Weinstein	1994
49	Neuroprotection after several days of mild, drug-induced hypothermia	6.3	124	4.6	Journal of Cerebral Blood Flow and Metabolism	Nurse, S	Nurse, S	1996
50	Selective antegrade cerebral perfusion and mild (28°C–30°C) systemic hypothermic circulatory arrest for aortic arch replacement: results from 1002 patients	6	124	11.3	Journal of Thoracic and Cardiovascular Surgery	Zierer, Andreas	Zierer, A	2012
51	Effects of isoflurane and hypothermia on glutamate receptor-mediated calcium influx in brain-slices	8.8	123	4.2	Anesthesiology	Bickler, PE	Bickler, PE	1994

(Continued)

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TABLE 1 (Continued)

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
52	Cirp protects against tumor necrosis factor-alpha-induced apoptosis via activation of extracellular signal-regulated kinase	5.1	123	7.2	Biochimica et Biophysica Acta-Molecular Cell Research	Sakurai, Toshiharu	Fujita, J	2006
53	Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases	7.4	122	5.5	Free Radical Biology and Medicine	Drew, KL	Drew, KL	2001
54	A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat	8.8	122	3.9	Anesthesiology	Sano, T	Drummond	1992
55	Therapeutic hypothermia: neuroprotective mechanisms	3.1	121	7.6	Frontiers in Bioscience-Landmark	Liu, Liping	Yenari, MA	2007
56	Temperature modulation of ischemic neuronal death and inhibition of calcium calmodulin-dependent protein kinase-ii in gerbils	8.3	120	3.6	Stroke	Churn, SB	Robert J. DeLorenzo	1990
57	Resuscitative hypothermia	8.8	119	4.4	Critical Care Medicine	Marion, DW	Marion, DW	1996
58	Mild-to-moderate hypothermia in aortic arch surgery using circulatory arrest: a change of paradigm?	3.4	118	10.7	European Journal of Cardio-Thoracic Surgery	Urbanski, Paul P	Urbanski, PP	2012
59	Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion	5.3	118	5.1	Experimental Neurology	Corbett, D	Colbourne, F	2000
60	Metabolic downregulation—a key to successful neuroprotection?	8.3	118	7.9	Stroke	Yenari, Midori	Yenari, M	2008
61	Cooling combined with immediate or delayed xenon inhalation provides equivalent long-term neuroprotection after neonatal hypoxia-ischemia	6.3	118	8.4	Journal of Cerebral Blood Flow and Metabolism	Thoresen, Marianne	Dingley, J	2009
62	Antegrade selective cerebral perfusion in thoracic aorta surgery: safety of moderate hypothermia	3.1	117	7.3	European Journal of Cardio-Thoracic Surgery	Pacini, Davide	Pacini, D	2007
63	Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury	8.9	117	4.7	Mayo Clinic Proceedings	Albrecht, RF	Lanier, WL	1998
64	Influence of hypothermia on post-ischemic inflammation: role of nuclear factor kappa B (NFkappaB)	4.2	116	6.8	Neurochemistry International	Yenari, Midori A	Yenari, MA	2006
65	Mild posttraumatic hypothermia reduces mortality after severe controlled cortical impact in rats	6.3	115	4.3	Journal of Cerebral Blood Flow and Metabolism	Clark, RSB	P. M. Kochanek	1996
66	Topiramate extends the therapeutic window for hypothermia-mediated neuroprotection after stroke in neonatal rats	8.3	115	6.1	Stroke	Liu, YQ	Silverstein, FS	2004
67	Low-flow hypothermic cardiopulmonary bypass protects the brain	6	114	3.6	Journal of Thoracic and Cardiovascular Surgery	Swain, JA	Julie Swain	1991
68	Posttraumatic hypothermia in the treatment of axonal damage in an animal model of traumatic axonal injury	4.1	112	4.5	Journal of Neurosurgery	Koizumi, H	Povlishock, JT	1998
69	Regulation of therapeutic hypothermia on inflammatory cytokines, microglia polarization, migration and functional recovery after ischemic stroke in mice	6.1	110	15.7	Neurobiology of Disease	Lee, Jin Hwan	Yu, SP	2016

(Continued)

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TABLE 1 (Continued)

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
70	Cooling the injured brain: how does moderate hypothermia influence the pathophysiology of traumatic brain injury	3.1	109	6.8	Current Pharmaceutical Design	Sahuquillo, Juan	Sahuquillo, J	2007
71	A study of brain protection during total arch replacement comparing antegrade cerebral perfusion versus hypothermic circulatory arrest, with or without retrograde cerebral perfusion: analysis based on the japan adult cardiovascular surgery database	6	108	13.5	Journal of Thoracic and Cardiovascular Surgery	Okita, Yutaka	Okita, Y	2015
72	Effects of pH on brain energetics after hypothermic circulatory arrest	4.6	107	3.6	Annals of Thoracic Surgery	Aoki, M	Dr. Jonas	1993
73	Postischemic hypothermia and il-10 treatment provide long-lasting neuroprotection of ca1 hippocampus following transient global ischemia in rats	5.3	106	4.4	Experimental Neurology	Dietrich, WD	Dietrich, WD	1999
74	Moderate posttraumatic hypothermia decreases early calpain-mediated proteolysis and concomitant cytoskeletal compromise in traumatic axonal injury	5.3	102	4.3	Experimental Neurology	Buki, A	Buki, A	1999
75	Protective effects of moderate hypothermia on behavioral deficits but not necrotic cavitation following cortical impact injury in the rat	4.2	101	4.0	Journal of Neurotrauma	Dixon, CE	Hayes, RL	1998
76	Mild hypothermia attenuates cytochrome c release but does not alter Bcl-2 expression or caspase activation after experimental stroke	6.3	100	4.8	Journal of Cerebral Blood Flow and Metabolism	Yenari, MA	Yenari, MA	2002
77	Moderate hypothermia and unilateral selective antegrade cerebral perfusion: a contemporary cerebral protection strategy for aortic arch surgery	4.6	100	7.7	Annals of Thoracic Surgery	Leshnower, Bradley G	Chen, EP	2010
78	Prolonged mild hypothermia therapy protects the brain against permanent focal ischemia	8.3	98	4.5	STROKE	Yanamoto, H	Yanamoto, H	2001
79	Role of hypothermia in the mechanism of protection against serotonergic toxicity. II. Experiments with methamphetamine, p-chloroamphetamine, fenfluramine, dizocilpine and dextromethorphan	3.5	98	3.5	Journal of Pharmacology and Experimental Therapeutics	Farfel, GM	Lewis Seiden	1995
80	Intracerebral temperature in neurosurgical patients	4.8	98	3.1	Neurosurgery	Mellergard, P	Mellergard, P	1991
81	Therapeutic hypothermia for acute stroke	48	96	4.8	Lancet Neurology	Olsen, TS	Olsen, TS	2003
82	Cerebral oxygen-metabolism during hypothermic circulatory arrest in humans	4.1	96	3.2	Journal of Neurosurgery	Ausman, JI	Ausman, JI	1993
83	Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery	8.8	95	4.3	Anesthesiology	Grigore, AM	Newman, MF	2001
84	Delayed, spontaneous hypothermia reduces neuronal damage after asphyxial cardiac arrest in rats	8.8	95	4.1	Critical Care Medicine	Hickey, RW	Hickey, RW	2000
85	Combination of systemic hypothermia and n-acetylcysteine attenuates hypoxic-ischemic brain injury in neonatal rats	3.6	94	5.5	Pediatric Research	Jatana, M	Jenkins, D	2006

(Continued)

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TABLE 1 (Continued)

Ranking	Title	JCR® IF	Total citations	Average citation	Journal	First author	Corresponding author	Published year
86	Mild intraischemic hypothermia suppresses consumption of endogenous antioxidants after temporary focal ischemia in rats	2.9	94	3.2	Brain Research	Karibe, H	Philip R. Weinstein	1994
87	Therapeutic time window of post-ischemic mild hypothermia and the gene expression associated with the neuroprotection in rat focal cerebral ischemia	2.9	94	5.9	Neuroscience Research	Ohta, Hiroyuki	Shintani, Y	2007
88	Hypothetical pathophysiology of acute encephalopathy and encephalitis related to influenza virus infection and hypothermia therapy	1.4	93	4.0	Pediatrics International	Yokota, S	Yokota, S	2000
89	Effect of delayed MK-801 (dizocilpine) treatment with or without immediate postischemic hypothermia on chronic neuronal survival after global forebrain ischemia in rats	6.3	93	3.3	Journal of Cerebral Blood Flow and Metabolism	Dietrich, WD	Dietrich, WD	1995
90	Mild postischemic hypothermia limits cerebral injury following transient focal ischemia in rat neocortex	2.9	93	3.4	Brain Research	Yanamoto, H	Kevin S. Lee	1996
91	Regional alterations of protein-kinase-c activity following transient cerebral-ischemia—effects of intraischemic brain temperature modulation	4.7	89	3.1	Journal Of Neurochemistry	Busto, R	Busto, R	1994
92	Treatment window for hypothermia in brain injury	4.1	88	4.0	Journal of Neurosurgery	Markgraf, CG	Markgraf, CG	2001
93	Behavioral protection by moderate hypothermia initiated after experimental traumatic brain injury	4.2	88	2.9	Journal of Neurotrauma	Lyeth, BG	Lyeth, BG	1993
94	Novel thyroxine derivatives, thyronamine and 3-iodothyronamine, induce transient hypothermia and marked neuroprotection against stroke injury	8.3	88	5.5	Stroke	Doyle, Kristian P	Stenzel-Poore, MP	2007
95	Mild to moderate hypothermia prevents microvascular basal lamina antigen loss in experimental focal cerebral ischemia	8.3	88	4.6	Stroke	Hamann, GF	Hamann, GF	2004
96	Diminished neuronal damage in the rat brain by late treatment with the antipyretic drug dipyrone or cooling following cerebral ischemia	12.7	88	3.3	Acta Neuropathologica	Coimbra, C	Coimbra, C	1996
97	Therapeutic hypothermia alters microrna responses to traumatic brain injury in rats	6.3	87	7.3	Journal of Cerebral Blood Flow and Metabolism	Truettner, Jessie S	Dietrich, WD	2011
98	Role of hypothermia in the mechanism of protection against serotonergic toxicity. I. Experiments using 3,4-methylenedioxymethamphetamine, dizocilpine, CGS 19755 and NBQX	3.5	87	3.1	Journal of Pharmacology and Experimental Therapeutics	Farfel, GM	Lewis Seiden	1995
99	The relationship between intelligence and duration of circulatory arrest with deep hypothermia	6	87	3.1	Journal of Thoracic and Cardiovascular Surgery	Oates, RK	Oates, RK	1995
100	Delayed onset of prolonged hypothermia improves outcome after intracerebral hemorrhage in rats	6.3	86	4.5	Journal of Cerebral Blood Flow and Metabolism	MacLellan, CL	Colbourne, F	2004

JCRIF, Journal Citation Reports Impact Factor; average citations, average number of citations per year since publication.

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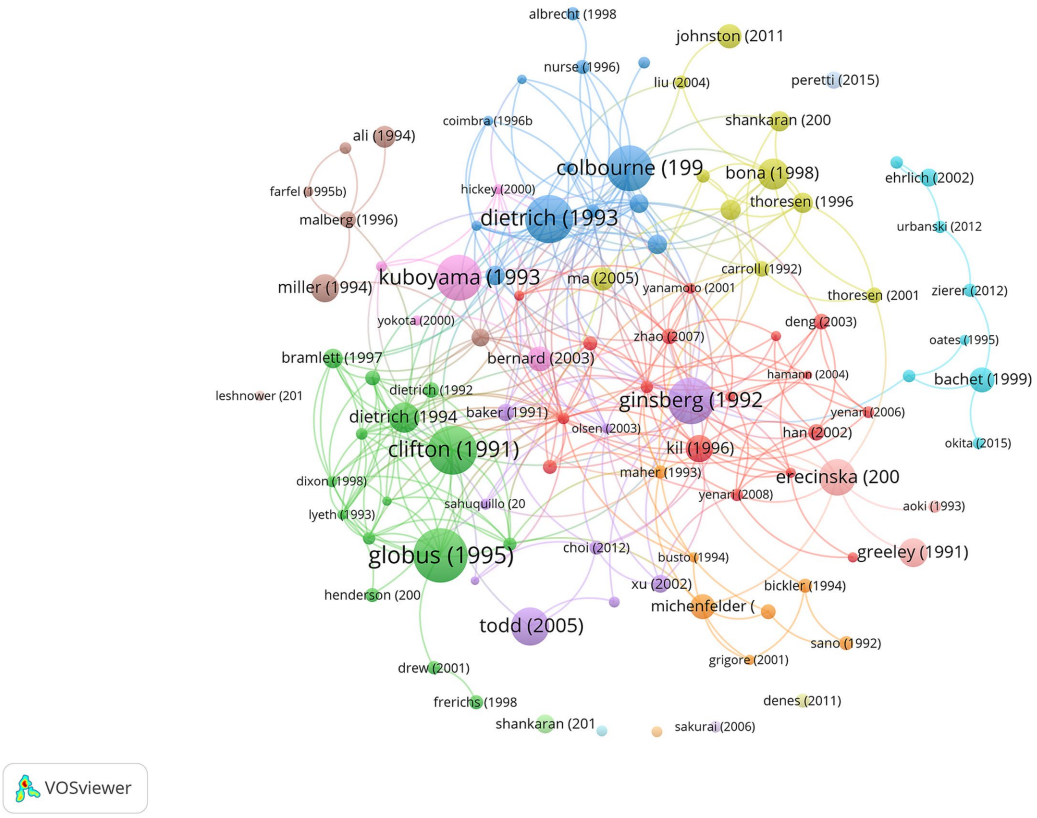

FIGURE 2
Citation of documents in hypothermic brain protection journals created using VOSviewer. Labels and circles were used to represent articles, representing authors' name and year of publication indicated. The size of each label and circle was based on the weight of the article.

in 2007 ($n = 6$). The lowest numbers of publications occurred in 1990, 1997, 2010, and 2016 ($n = 1$). Among the types of published articles, randomized controlled trials were the most common ($n = 73$), followed by reviews ($n = 18$), whereas case reports, clinical studies, and other types of articles were the least common ($n = 9$) (Table 2).

Contributing authors

We established a collaborative network based on the authors who published two or more papers (Figure 4). Dietrich, Ginsberg, and Busto published the most relevant articles; therefore, their nodes were the largest. In addition, we observed close collaboration among multiple authors. For example, Dietrich closely cooperated with Busto, Alonso, and others (Figure 4A). More detailed and specific collaborations between the authors can be found in the author coupling diagram (Figure 4B). There are five main color classifications, with yellow representing authors such as Dietrich, Busto, and Ginsberg, who have the highest collaborations. There are many collaborations among the authors, represented in green, such as Markgraf, Clifton, and Marion. The authors represented in red, such as Yenari, Steinberg, Chan, and Graham, strongly cooperated with each other. The authors represented in blue, such as Colbourne, Wieloch, Corbett, and Yanamoto, strongly cooperated with each other. Purple represents authors such as Thoresen, Loberg, and Chakkarapani, who participated in many collaborations.

Contributing countries and institutions

Visual networks and statistical charts were developed for both countries and their institutions. The 100 most-cited articles included 136 countries/regions and 258 institutions. The maps clearly indicated the presence of clusters. It is evident from the number of publications and international cooperation that the United States has the greatest influence among many countries. In addition, Japan has established strong scientific relationships with countries such as Germany, Canada, and Sweden (Figure 5). Among the countries that published articles, the United States ($n = 51$), the United Kingdom ($n = 8$), and Japan ($n = 8$) had the highest number of published articles, whereas the remaining articles were scattered among other countries (Table 3).

Multiple institutions also formed regional cooperative networks. The University of Miami has close cooperation with the University of Texas, the University of Pittsburgh, and others. Stanford University has close cooperation with Duke University, the University of California, San Francisco University, and others. The Memorial University of Newfoundland cooperates closely with Emory University, Yale University, and others (Figure 6).

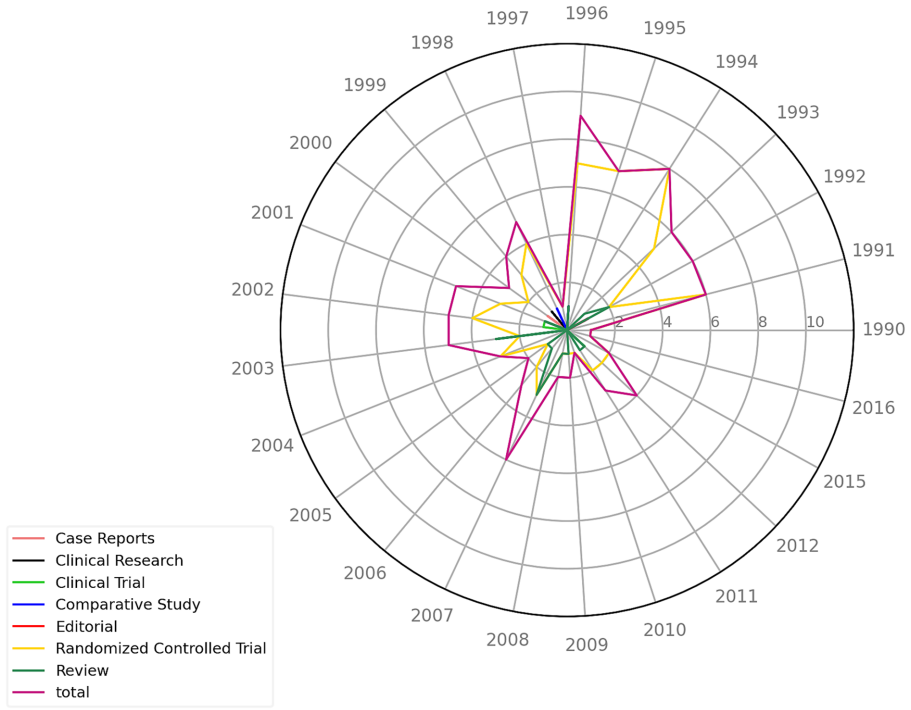

FIGURE 3
The 100 most-cited articles by publication year. The radar chart depicts the publication years of articles, spanning from 1990 to 2016. Each colored line represents a different type of article, with the outermost purple line representing the total number of publications per year.

TABLE 2 Statistics on the types of studies in the 100 most-cited articles.

Study type	Count
Randomized Controlled Trial	73
Review	18
Clinical Trial	3
Comparative Study	3
Clinical Research	1
Case Reports	1
Editorial	1
Total count	100

Journal of publication

Journals with at least two publications and their main characteristics are listed in Table 4. There are 19 journals on the list, and the two journals with the highest publication volumes in the field of hypothermic brain protection are the *Journal of Cerebral Blood Flow and Metabolism* and *Stroke*, with 15 and 10 articles published, respectively. Additionally, five articles were published in *Anesthesiology*, the *Journal of Neurotrauma*, and the *Journal of Thoracic and Cardiovascular Surgery*.

Research topics

The relationships among the authors, countries, and research keywords of the 20 most-cited articles in hypothermic brain protection journals are shown in Figure 7. Other keywords related to hypothermic brain protection with a high frequency of occurrence included hyperthermia, dopamine, ischemia, metabolism, surgery, and trauma.

Discussion

With continuous advances in science and technology, research in the biomedical field is expanding in terms of breadth and depth, leading to an exponential increase in the number of related studies (113). Effectively screening useful information from this vast body of literature poses a major challenge for researchers. Bibliometric analysis, a key tool in modern medical research, allows researchers to quantitatively analyze scientific literature to reveal development dynamics and trends in the research field. Using bibliometric analysis, researchers can better understand the development of a discipline, identify cutting-edge fields and research hotspots, evaluate the impact and quality of academic achievements, and provide valuable references and guidance for future medical research and strategic planning (10).

Hypothermic brain protection is a key area of medical research aimed at reducing brain injury and improving the tolerance to cerebral ischemia, trauma, and other conditions. Hypothermic brain protection techniques have shown potential neuroprotective effects in patients with neurological ischemia or injury (114–116). Although there are challenges to its clinical application, research on hypothermic brain protection is advancing, providing new ideas and methods for improving the treatment of brain injuries and neurological diseases.

The research that is most cited in a specific field is often considered a milestone and can be referred to as "classic (117, 118)." The frequency

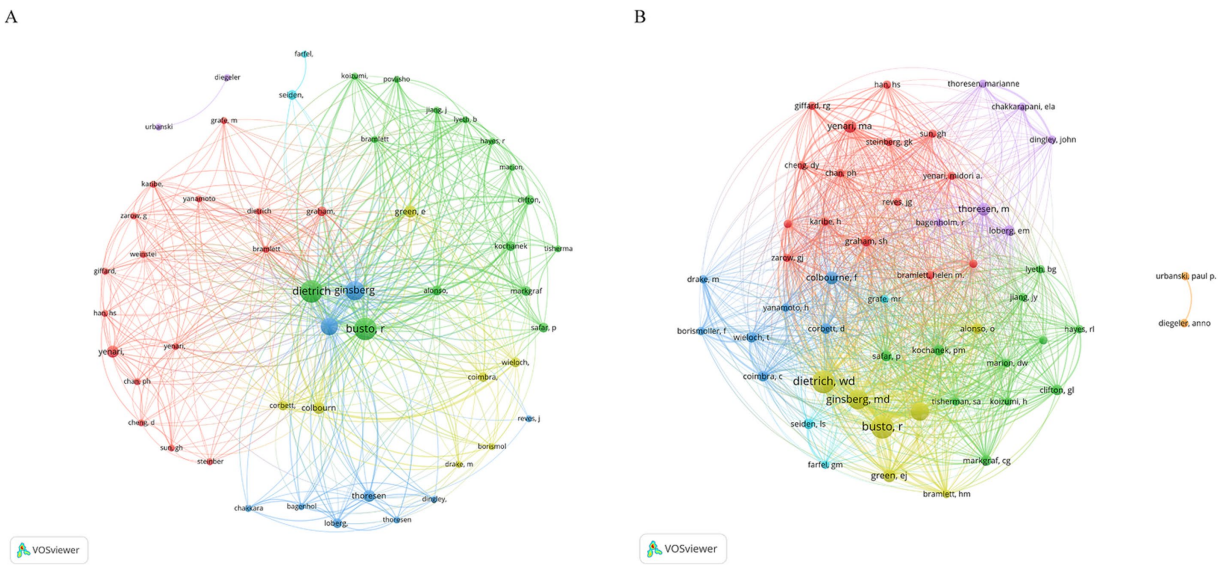

FIGURE 4
The author network visualized using VOSviewer software. The minimum number of documents by any one author is ≥2. Author citation (A) and the bibliometric coupling (B) are shown using labels and circles, showcasing each author's name. The size of the label and circle varied according to the author's weight.

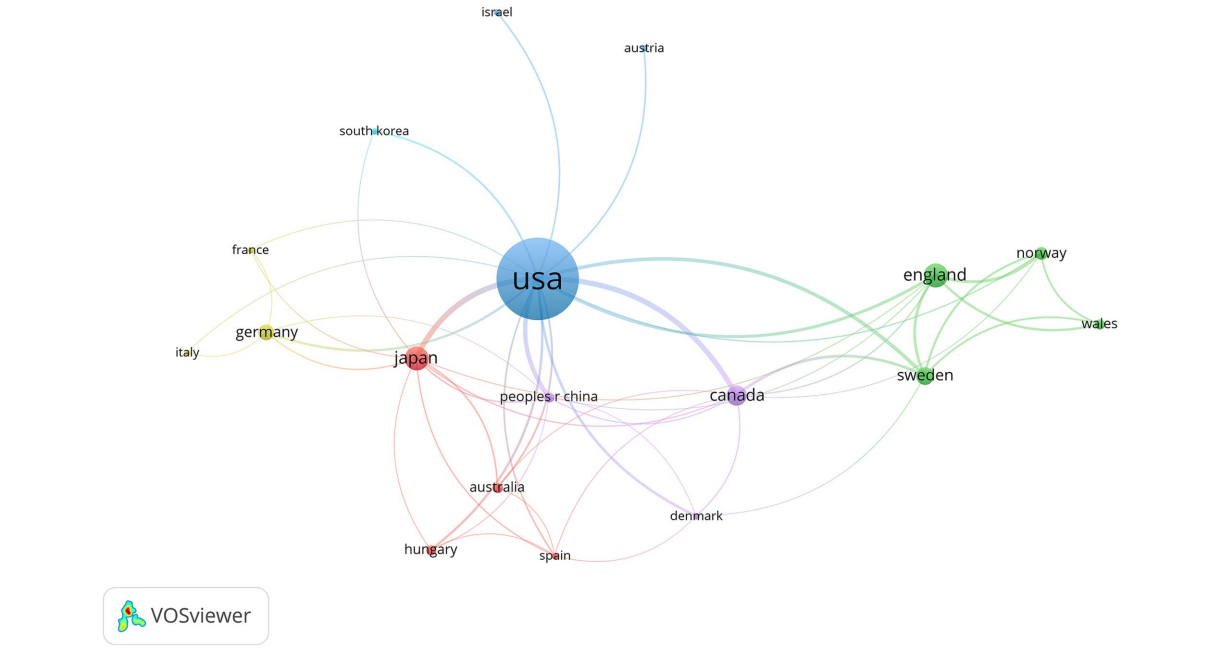

FIGURE 5
Countries cited in the 100 most-cited articles on hypothermic brain protection created by VOSviewer. The minimum number of documents from any one country is ≥1. Countries are represented by labels and circles, with the size of each country's label and circle determined by its weight.

of citations in a paper generally reflects its importance, indicating that it has gained recognition from researchers in the relevant field as well as sparking discussions and guiding new research directions (119, 120). Owing to its pioneering contributions, this study provides important reference values for further analysis. This study identified and analyzed the 100 most-cited articles in the field of hypothermic brain protection, providing an historical overview of the development of the research field over time, defining interesting trends, and potentially offering clues for the future development of basic research and clinical practice in hypothermic brain protection.

Since Busto et al. (121, 122) first proposed the use of mild hypothermia (33–35°C) to treat brain injuries in the 1980s, experts

TABLE 3 Countries of the 100 articles in hypothermic brain protection journals.

Journal	Country	Year	Count
Journal of Cerebral Blood Flow and Metabolism	United States	1981	15
Stroke	United States	1970	10
Anesthesiology	United States	1940	5
Journal of Neurotrauma	United States	1984	5
Journal of Thoracic and Cardiovascular Surgery	United States	1936	5
Acta Neuropathologica	Germany	1961	4
Annals of Thoracic Surgery	United States	1965	4
Brain Research	Netherlands	1966	4
Critical Care Medicine	United States	1973	4
Journal of Neurosurgery	United States	1944	4
Journal of Pharmacology and Experimental Therapeutics	United States	1909	4
Experimental Neurology	United States	1959	3
Pediatric Research	United States	1967	3
Archives of Disease in Childhood-Fetal and Neonatal Edition	United Kingdom	1996	2
Cerebrovascular and Brain Metabolism Reviews	United States	1989	2
European Journal of Cardio-Thoracic Surgery	Netherlands	1987	2
Journal of Neurochemistry	United States	1956	2
Journal of Neuroscience	United States	1981	2
Lancet Neurology	United Kingdom	2002	2

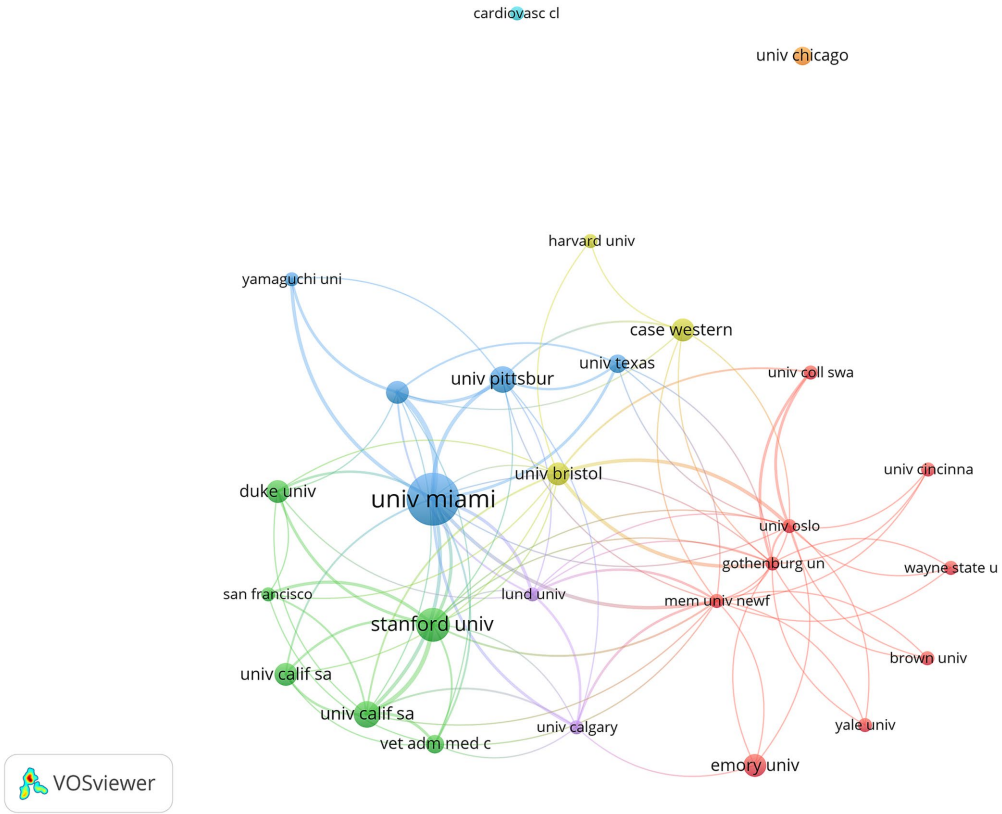

FIGURE 6
Citation of institutions in the 100 most-cited articles in hypothermic brain protection journals created by VOSviewer. The minimum number of documents from any one country is ≥2. Institutions are represented by labels and circles, with the size of each institution's label and circle determined by its weight.

TABLE 4 Journal distribution and main characteristics of the 100 most-cited articles on hypothermic brain protection.

Country	Count
USA	51
Japan	8
UK	8
Canada	6
Sweden	5
Germany	4
Norway	3
Australia	2
China	2
Wales	2
Hungary	2
Italy	1
Israel	1
France	1
Austria	1
Denmark	1
South Korea	1
SPAIN	1
Total count	100

The minimum number of articles from any one journal is ≥2. SJR, SCImago Journal Rank 2022; cites/doc: total citations/total documents; Year: journal establishment year.

have recognized its protective effects on the body, particularly on the brain. The question of whether lowering body temperature to induce hypothermia can effectively shield the brain has sparked interest in clinical and basic research. The 100 most cited articles listed in this study have shown that hypothermia can improve brain function and provide significant protection (1, 14–112). The current mechanisms of hypothermic brain protection include reducing brain energy metabolism, protecting the blood brain barrier, decreasing brain swelling and pressure, preventing lactic acid accumulation, limiting the release of harmful amino acids, blocking the detrimental effects of calcium, inhibiting nitric oxide production, reducing the generation of oxygen radicals, enhancing the elimination of oxygen radicals, suppressing the expression of genes associated with cellular damage, and reducing inflammation and neuronal cell death (2, 123).

Hypothermic brain protection is used to lower a patient's body or brain temperature to decrease brain oxygen consumption and facilitate recovery (124). Mild hypothermia (33–35°C) and moderate hypothermia (28–32°C) are commonly used, and studies have indicated that 33°C is the optimal temperature for treatment (125). Deep hypothermia (17–27°C) is reserved for specific patients (for example, those with aortic stenosis or aortic dissection) due to more severe complications (126).

However, some recent large-scale clinical studies have refuted this view. In a study conducted in 2005 to determine whether hypothermia during craniotomy can improve the prognosis of patients with acute aneurysmal subarachnoid hemorrhage, there was no significant difference in hospitalization time, total hospitalization time, or follow-up mortality in the intensive care unit between the hypothermia group and the normal temperature group during craniotomy (20). Another randomized controlled trial published in 2010 showed no correlation between intraoperative hypothermia or supplementation of protective drugs and neurological prognosis in patients undergoing temporary clipping during cerebral aneurysm surgery (127). At the same time, some systematic reviews also expound similar viewpoints (128–130).

There is a guideline stating that the duration of brain hypothermia should be sufficient to provide brain protection (131). For patients with craniocerebral injury, it is challenging to achieve favorable clinical outcomes with short-term (24–48 h) mild hypothermia treatment. It is recommended that the duration of mild hypothermia treatment for such patients be maintained for at least 3–5 days. Therefore, additional research is required to determine the appropriateness of utilizing low temperatures in varying circumstances, along with the corresponding low-temperature strategy and duration of maintenance.

The most-cited studies in the field of hypothermic brain protection generally describe the effects of posttraumatic hypothermia on neuronal damage in rats with traumatic brain injury (TBI) (14). Research has shown that TBI leads to a significant increase in the glutamate and hydroxyl radical levels in the brain, with a positive correlation between these two factors. Post-traumatic hypothermia effectively suppresses these elevations, indicating a potential link between glutamate release and hydroxyl radical production in the brain after TBI. This groundbreaking discovery has had a significant guiding influence on clinical treatment, making it the most influential article. Six articles, with a total citation count of over 400 in this field, can be referred to as "classics." The six authors and their teams—Globus et al. (14), Clifton et al. (15), Kuboyama et al. (16), Ginsberg et al. (17), Dietrich et al. (18), and Colbourne et al. (19)—have all made significant contributions to further research in the field of hypothermic brain protection.

The temporal distribution of these 100 articles revealed that they were published between 1990 and 2016, whereas the years that produced a relatively large number of highly influential articles were 1991–1996 and 2007. Furthermore, it must be emphasized that the total citation count of publications over the past 3 years may have been underestimated, considering that recently-published articles will take time to attract citations. Over time, an increasing number of recently-published studies have become highly cited (132). Among the 100 articles, the proportion of basic research was the highest ($n = 73$), followed by reviews ($n = 18$), whereas the proportions of clinical research and case reports were low ($n = 8$). These findings indicate that although we have observed the protective effect of hypothermia, we still have only a partial understanding of its mechanism, and the study of the specific mechanism of hypothermic brain protection remains a hot topic (123).

Regarding countries and institutions, most of the 100 most-cited articles in the field of hypothermic brain protection were from the United States ($n = 51$), which also had an overwhelming number of citations, indicating that the United States is the most influential country in this field. The United States has always led the world in the field of hypothermic brain protection research, and its continuously innovative medical technology and cutting-edge research results have inspired tremendous progress. The most-cited authors were from the United States. The University of Miami and Stanford University the institutions with the most cited articles, reflecting their authority in the field of hypothermic brain protection (35, 39). In terms of international cooperation, the United States cooperates closely with multiple countries, whereas Japan cooperates closely with Germany, the United Kingdom, and Sweden. At the institutional level, Stanford

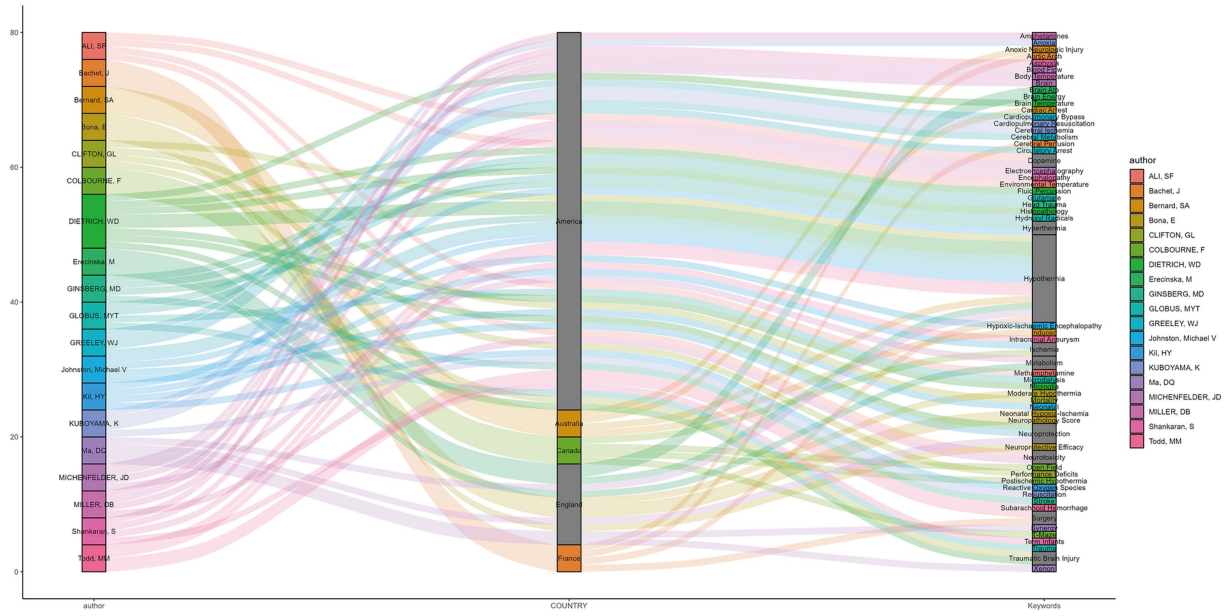

FIGURE 7
Sankey plot showing the relationships among authors, countries, and research keywords of the 20 most-cited articles. The left column represents the authors' name, the middle column represents the authors' country, and the right column represents the articles' keywords. These columns are connected with corresponding lines on a one-to-one basis.

University cooperates closely with the University of California, Emory University, and Duke University (42).

The most-cited research in this field is more likely to be published in highly-influential neurosurgical journals such as the *Journal of Cerebral Blood Flow and Metabolism and Stroke* (15, 36). In addition, several studies published in these journals, apart from those in the field of neurosurgery, involve the intersection of anesthesia and critical care, as well as pediatrics and neurosurgery, such as anesthesiology, critical care medicine, and pediatric research (16, 22, 30). Interestingly, these results suggest that hypothermic brain protection has aroused great interest not only among neurologists but also among anesthesiologists and pediatricians due to its close connection to their clinical work.

The Sankey plot illustrated the relationships among authors, countries, and agreed-upon keywords. The keywords used were further extended to include "hypothermia," "brain," "neuroprotection," "surgery," "trauma," "ischemia," "metabolism," and others. A relatively novel keyword, "xenon," was used to explore the treatment of neonatal hypoxic-ischemic brain injury (31, 38, 73). The experimental data from these studies showed that low-concentration xenon combined with mild hypothermia may be a safe and effective treatment for perinatal asphyxia. Most articles mentioned keywords such as "hypothermia" and "neuroprotection" in their titles; however, a few articles do not mention them. We recommend that the terms "hypothermia" and "neuroprotection" are included in the title so readers can easily identify the nature of the article and index it in search databases.

Keywords Plus® was used with the Clarivate Analytics[1] algorithm, which is based on repeated words or phrases appearing in the reference lists of indexed articles (133). In the absence of author keywords, Keywords Plus® is considered to have special value. However, compared with keywords, the number of Keywords Plus® was greater, and the concentration of keywords was not strong. The use of Keyword Plus® to construct Sankey plots may have caused data distortion. Therefore, we constructed the Sankey plot using keywords. Seven of the 20 most-cited articles in this field did not provide keywords, and three researchers summarized the keywords after their discussion according to Keywords Plus®.

This study has several limitations. The first limitation is inherent in citation analysis which is based on the absolute number of citations of an article. The number of citations is a substitute for this influence; however many factors can affect the citation rate. Generally the number of citations an article receives reflects its impact and level of recognition by academic and clinical communities. However the number of citations depends on many factors such as factors related to the paper including quality length publication year and literature type; factors related to journals such as journal influence language and publication format; and factors related to the author such as reputation academic ranking and productivity. Second only English versions of the articles were included in the study; however English is the most widely-used language worldwide making it possible for articles published in English to be widely read and cited. Third the search was conducted only on the WOS database which may have resulted in missing several relevant publications from other databases such as Google Scholar Scopus and PubMed. Searching databases from multiple sources can yield more complete citation results because the number of citations varies among databases from different sources (134). However different databases have different reference-counting methods which may be unsuitable for merging data from different databases. Among these databases WOS is one of the most commonly used databases for analyzing highly-cited articles in a particular field

1 https://clarivate.com/

(135–137). The fourth limitation was the time factor because the WOS currently covers only articles published after 1980. We may have missed articles published before 1980 with higher citation frequencies than those included in this study. Additionally recently published articles require time to attract citations. Therefore the citation frequency in early studies should be higher than that in recently published studies and some recently-published representative works may not be included. Quotations may not fully represent the true academic value and the impact of a study should be evaluated from all aspects. Future work can start by updating the time periods searching in and merging multiple databases and establishing algorithms for the influence of new and old articles. Nevertheless the results of this study provide valuable insights for researchers.

Conclusion

This bibliometric study offers a comprehensive overview of the advancements, trends, and current trajectories in both basic research and clinical applications within the domain of hypothermic brain protection. By conducting a bibliometric analysis of the WOS database, this study identified and thoroughly analyzed the 100 most impactful articles that have significantly contributed to advancing this field. Rapid growth has been observed in the field of hypothermic brain protection. The United States emerged as a dominant force in terms of the number of highly influential articles, prominent academic institutions, and leading scientists in this area of research. Predominantly, articles in this field focus on basic research and delve into the underlying mechanisms. Keywords, such as "hypothermia" and "neuroprotection" intersect with other fields, enriching the comprehension of mechanisms and broadening their applicability. Continuous and profound research endeavors in this sphere promise a deeper understanding of the molecular pathophysiological mechanisms underlying various diseases, thereby unveiling potential therapeutic targets.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LH: Writing – original draft, Visualization, Software, Methodology, Investigation, Data curation, Conceptualization. SG: Writing – original draft, Visualization, Software, Methodology, Data curation. FL: Writing – original draft, Resources, Methodology, Formal analysis, Data curation. LN: Writing – review & editing, Visualization, Resources, Methodology, Funding acquisition, Formal analysis. JW: Writing – review & editing, Validation, Supervision, Resources, Funding acquisition. JZ: Funding acquisition, Writing – review & editing, Supervision. MW: Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition. YC: Project administration, Methodology, Writing – review & editing, Validation, Funding acquisition.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1433025/full#supplementary-material

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Prognostic value of thrombocytopenia during hospitalizations in intracerebral hemorrhage patients

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Background: The thrombocytopenia influences prognoses of critically ill patients. There are few studies exploring the prognostic value of thrombocytopenia among ICH patients. We perform this study to explore the correlation between thrombocytopenia at different timepoints of hospitalizations and mortality of ICH.

Methods: ICH patients recorded in the Medical Information Mart for Intensive Care-III were selected for this observational study. The thrombocytopenia, defined as platelet $<150 \times 10^9$/L, was divided into three categories: baseline thrombocytopenia (thrombocytopenia occurred at admission), acquired thrombocytopenia (thrombocytopenia developed since the second day after admission), multiple thrombocytopenia (baseline thrombocytopenia + acquired thrombocytopenia). The main outcome in this study was the 30-day mortality of ICH patients. The univariate and multivariate logistic regression was sequentially performed to discover risk factors of mortality and confirm the correlation between thrombocytopenia groups and mortality of ICH.

Results: 66.5% of 902 ICH patients did not experience the thrombocytopenia since admission. 2.2, 14.5 and 16.7% ICH patients showed the baseline thrombocytopenia, acquired thrombocytopenia initial and multiple thrombocytopenia, respectively. The GCS did not show significant difference between thrombocytopenia groups ($p = 0.118$). The multiple thrombocytopenia group had the highest incidence of mechanical ventilation ($p = 0.041$), mortality ($p < 0.001$), and the longest length of ICU stay ($p < 0.001$), length of hospital stay ($p < 0.001$). The multivariate logistic regression found age ($p < 0.001$), GCS ($p < 0.001$), glucose ($p = 0.013$), mechanical ventilation ($p = 0.002$) was correlated with the mortality of ICH patients. Only the multiple thrombocytopenia group showed significant influence on the mortality of ICH ($p = 0.002$) in the multivariate logistic regression.

Conclusion: Single initial thrombocytopenia at admission dose not influence the mortality of ICH patients. ICH patients experiencing both initial thrombocytopenia and acquired thrombocytopenia have significantly higher mortality risk. The blood platelet level of ICH patients should be monitored continuously during hospitalizations to detect the thrombocytopenia and identify the high risk of poor prognosis.

KEYWORDS

intracerebral hemorrhage, thrombocytopenia, platelet, mortality, hemorrhagic stroke

1 Introduction

Accounting for nearly one third of stroke incidence, the intracerebral hemorrhage (ICH) leads poor prognosis of patients with the mortality more than 50% (1, 2). As the essential component of coagulation and hemostasis, the platelet plays an important role on the pathophysiological process of stroke. Both abnormalities of platelet function and number significantly may influence the bleeding events and prognoses of stroke patients (3, 4). The thrombocytopenia, commonly defined as the platelet level $< 150 \times 10^9$/L, has been confirmed correlated with a serious of bleeding events, transufsion requirements and outcomes of critially ill patients (5, 6). While two studies, respectively, found the thrombocytopenia at admission was not related with the poor outcomes of ICH patients and ichemic stroke patients (7, 8). Another study discovered that only thrombocytopenia developed during ICU stay but not thrombocytopenia at admission was an indepdent risk factor for mortality of patients treated in the neurocritical care unit (9). And one recent study found the risk of hospital mortality in critically ill patients increased significantly with persistent thrombocytopenia but not transient thrombocytopenia (10). These findings lead us to make a hypothesis that thrombocytopenia at different timepoints since admission may exert different effects on prognoses of ICH patients. Therefore, we design this study to explore the prognostici value of thrombocytopenia at admission and thrombocytopenia developed during hospitalizations among ICH patients.

2 Materials and methods

2.1 Enrolled participants

ICH patients (confirmed using ICD-9 code-431) recorded in the Medical Information Mart for Intensive Care-III (MIMIC-III) (an intensive care database enrolling patients from the Beth Israel Deaconess Medical Center between 2001 and 2012) were selected for this observational study. A part of ICH patients were sequentially excluded from this study for four causes: (1) no records of platelet ($n = 14$); (2) no records of platelet at admission ($n = 6$); (3) records of platelet after day $1 \leq 2$ ($n = 435$); (4) no records of Glasgow Coma Scale (GCS) ($n = 9$). Nine hundred and two ICH patients were enrolled after the screening. The MIMIC-III deidentified personal information of patients and received ethical approvements from the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

2.2 Variables collection

Demographic information (age, gale gender), comorbidities (hypertension, hyperlipidemia, diabetes, atrial fibrillation, coronary heart disease, chronic renal disease), vital signs at admission (mean blood pressure, heart rate), pulse oxygen saturation (SpO_2) and GCS at admission were recorded. Laboratory examinations including white blood cell, hemoglobin, hematocrit, platelet, glucose, calcium, phosphate, prothrombin time, activated partial thromboplastin time, international normalized ratio (INR) were analyzed using the first blood sample after admission (within 24 h since admission). The subsequent platelet level after day 1 was also collected with the median frequency of 9 for measurements. The thrombocytopenia, defined as platelet $< 150 \times 10^9$/L, was divided into three categories: baseline thrombocytopenia (thrombocytopenia occurred at admission), acquired thrombocytopenia (thrombocytopenia developed since the second day after admission), multiple thrombocytopenia (baseline thrombocytopenia + acquired thrombocytopenia). The main outcome in this study was the 30-day mortality of ICH patients. The incidence of mechanical ventilation, length of ICU stay, length of hospital stay was also compared between different thrombocytopenia groups.

2.3 Statistical analyses

Variables with normal distribution or non-normal distribution were, respectively presented as mean ± standard or median (interquartile range). Kolmogorov–Smirnov test was used for testing the normal distribution of variables. Patients were divided into different groups according to the occurrence and timepoint of thrombocytopenia. Differences between these groups were compared using one way ANOVA (variables with normal distribution), Kruskal–Wallis (variables with non-normal distribution), or chi-square test (categorical variables). The univariate and multivariate logistic regression was sequentially performed to discover risk factors of mortality and confirm the correlation between thrombocytopenia groups and mortality of ICH. Two sides p-value <0.05 was set as statistically significant. All analyses and figures were performed using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, United States) and SPSS 23.0 (SPSS, Inc., Chicago, IL).

3 Results

3.1 Comparison between thrombocytopenia groups of ICH patients

The occurrence of thrombocytopenia is concentrated in the first 10 days with the peak on the third day since admission (Figures 1A,B). Among 902 ICH patients, 66.5% ($n = 600$) of them did not experience the thrombocytopenia since admission (Table 1). 2.2% ($n = 20$) ICH patients showed the only initial thrombocytopenia at admission and 14.5% ($n = 131$) experienced acquired thrombocytopenia since the second day after admission. 16.7% ($n = 151$) ICH patients experienced both initial thrombocytopenia and acquired thrombocytopenia during hospitalizations (Table 1). Age ($p = 0.002$) and gender ratio ($p = 0.006$) showed significant difference among thrombocytopenia groups. The comorbidity atrial fibrillation was most prevalent in the baseline thrombocytopenia group ($p = 0.029$). The GCS did not show significant difference between thrombocytopenia groups though the multiple thrombocytopenia group had relatively lower GCS [9 (6–14)] ($p = 0.118$). Laboratory examination presented the multiple thrombocytopenia group had the lowest level of hemoglobin ($p = 0.006$), hematocrit ($p = 0.003$), platelet ($p < 0.001$), calcium ($p < 0.001$) and the highest level of prothrombin time ($p < 0.001$), activated partial thromboplastin time ($p < 0.001$), INR ($p < 0.001$). Furthermore, the multiple thrombocytopenia group had the highest incidence of mechanical ventilation ($p = 0.041$), mortality ($p < 0.001$)

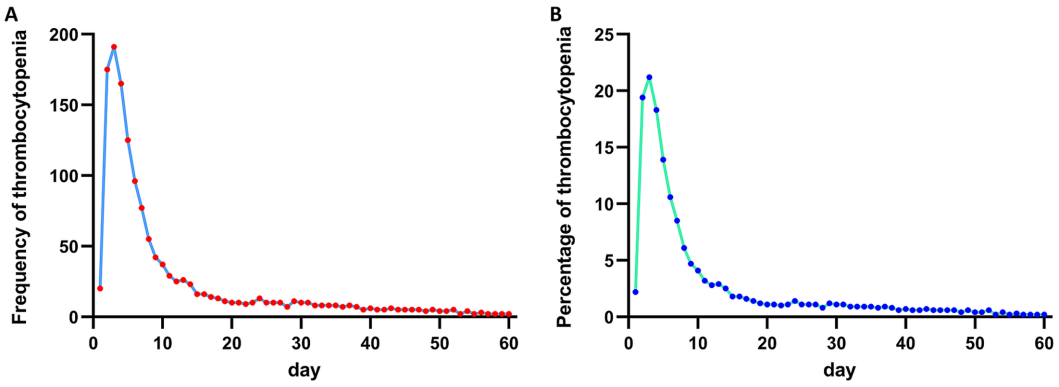

FIGURE 1
(A) Frequency of thrombocytopenia during hospitalizations in ICH patients. (B) Percentage of thrombocytopenia during hospitalizations in ICH patients.

and the longest length of ICU stay ($p < 0.001$), length of hospital stay ($p < 0.001$).

3.2 Correlation between thrombocytopenia and 30-day mortality of ICH patients

The univariate logistic regression presented age ($p < 0.001$), atrial fibrillation ($p = 0.005$), chronic renal disease ($p = 0.016$), mean blood pressure ($p = 0.021$), GCS ($p < 0.001$), hemoglobin ($p = 0.001$), hematocrit ($p = 0.002$), glucose ($p < 0.001$), mechanical ventilation ($p < 0.001$) was correlated with the mortality of ICH patients (Table 2). Only the multiple thrombocytopenia group ($p < 0.001$) showed statistical significance on influencing the mortality of ICH in the univariate logistic regression (Figure 2A). The multivariate logistic regression found age ($p < 0.001$), GCS ($p < 0.001$), glucose ($p = 0.013$), mechanical ventilation ($p = 0.002$) was correlated with the mortality of ICH patients. The multiple thrombocytopenia still showed statistical significance ($p = 0.002$) in the multivariate logistic regression while other thrombocytopenia groups did not correlate with the mortality of ICH patients (Figure 2B).

4 Discussion

As a disorder of coagulative system, the thrombocytopenia is prevalent among hospitalized patients with the incidence ranging from 8.3 to 67.6% (6). Some studies have explored risk factors for the thrombocytopenia including age, gender, sepsis, liver dysfunction, bleeding, disease severity reflected by the sequential organ failure score (6, 11, 12). While the effect of thrombocytopenia on the prognosis of various patients has not been confirmed. Some studies found the thrombocytopenia were related with the mortality risk of various patients including sepsis, COVID-19, seasonal influenza, systemic lupus erythematosus, cancer (12–18). While one study showed the thrombocytopenia at admission was not related with poor outcomes of ichemic stroke patients (8). Another study implied that the thrombocytopenia did not influence rates of hematoma enlargement and functional status of ICH patients, regardless of the prior antiplatelet therapy (7). It is noteworthy that only thrombocytopenia developed during ICU stay but not thrombocytopenia at admission was confirmed an indepdent risk factor for mortality of patients treated in the neurocritical care unit (9). This fact indicated that the thrombocytopenia at different timepoints since admission may exert different effects on prognoses of crtically ill patients. Consistent with the finding, results of our study implied ICH patients complicated with thrombocytopenia both at admission and developed during hospitalizations had significanly higher mortality while the ICH patients with thrombocytopenia only at admission did not show higher mortaliy risk than non-thrombocytopenia ICH patients.

The insignificance of baseline thrombocytopenia indicated that it may just act as a reflection of initial stroke severity or prior use of antiplatelets. The transient effect of low platelet level at admission may not play a critical role on the prognoses of ICH patients. Only our stated multiple thrombocytopenia which meant persistent thrombocytopenia lasting from the admission to subsequent hospitalization significantly influence the mortality of ICH patients. This finding was consistent with one previous study showing that the mortality of critically ill patients begins to significantly increase only when the thrombocytopenia lasts more than 2 days and the mortality is positively associated with the duration of thrombocytopenia (10). The persistent or multiple thrombocytopenia could be caused by many factors including blood dilution, decreased platelet production, increased platelet consumption, and drugs (19, 20). As for ICH patients, the excessive consumption caused by coagulation, intraoperative blood loss and intracranial progressive hemorrhage may both contribute to the persistent state of low platelet level.

Due to the prognostic effect of multiple thrombocytopenia, the platelet level after ICH should be monitored constantly especially during the first 10 days of hospitalizations. And preventive measures for the trend of reduced platelet level including appropriate platelet transfusion should be provided after ICH. Certainly, the detailed schedule and indications of platelet transfusion for ICH patients has not been decided though studies have been performed to validate the efficiency and safety of platelet transfusion in ICH patients especially those with prior antiplatelet use (21–26). Though most of available evidence showed no benefit of platelet transfusion for ICH patients with prior antiplatelet use, the efficacy of platelet transfusion for the general ICH patients receiving surgical intervention has not been

TABLE 1 Comparison between groups of ICH patients divided by the thrombocytopenia.

	All ICH patients (*n* = 902)	Non-thrombocytopenia (*n* = 600, 66.5%)	Baseline thrombocytopenia (*n* = 20, 2.2%)	Acquired thrombocytopenia (*n* = 131, 14.5%)	Multiple thrombocytopenia (*n* = 151, 16.7%)	*p*
Age (year)	69.2 (56.7–80.0)	67.1 (55.3–79.0)	73.1 (67.9–81.7)	71.4 (61.8–80.5)	72.9 (59.5–82.1)	0.002
Male gender (%)	509 (56.4%)	328 (54.7%)	13 (65.0%)	65 (49.6%)	103 (68.2%)	0.006
Comorbidities						
Hypertension (%)	580 (64.3%)	390 (65.0%)	14 (70.0%)	84 (64%)	92 (60.927%)	0.762
Hyperlipidemia (%)	152 (16.9%)	98 (16.3%)	3 (15.0%)	29 (22.1%)	22 (14.6%)	0.342
Diabetes (%)	193 (21.4%)	123 (20.5%)	6 (30.0%)	33 (25.2%)	31 (20.5%)	0.502
Atrial fibrillation (%)	210 (23.3%)	123 (20.5%)	7 (35.0%)	34 (26.0%)	46 (30.5%)	0.029
Coronary heart disease (%)	148 (16.4%)	91 (15.2%)	5 (25.0%)	27 (20.6%)	25 (16.6%)	0.329
Chronic renal disease (%)	72 (8.0%)	41 (6.8%)	2 (10.0%)	10 (7.6%)	19 (12.6%)	0.135
Vital signs on admission						
Mean blood pressure (mmHg)	94.0 (82.7–105.0)	94.3 (82.7–105.7)	97.7 (85.0–107.0)	92.7 (80.3–103.7)	92.3 (84.7–104.3)	0.830
Heart rate (min^{-1})	79 (69–91)	78 (69–90)	78 (65–84)	82 (72–98)	81 (71–93)	0.007
SpO_2 (%)	99 (97–100)	99 (97–100)	99 (96–100)	99 (97–100)	99 (97–100)	0.975
GCS	11 (6–15)	12 (6–15)	11 (6–14)	11 (6–15)	9 (6–14)	0.118
Laboratory tests						
White blood cell (10^9/L)	10.10 (7.90–13.20)	10.60 (8.50–13.50)	7.70 (5.80–12.10)	10.00 (7.80–13.80)	8.40 (5.80–11.10)	<0.001
Hemoglobin (g/dL)	13.0 ± 2.0	13.1 ± 1.9	12.7 ± 1.8	12.9 ± 2.0	12.5 ± 2.1	0.006
Hematocrit (%)	38.0 ± 5.4	38.4 ± 5.2	37.3 ± 4.5	38.0 ± 5.7	36.6 ± 5.9	0.003
Platelet (10^9/L)	229 (178–285)	256 (216–310)	149 (137–159)	197 (175–246)	133 (92–159)	<0.001
Glucose (mg/dL)	136 (114–169)	134 (114–165)	148 (112–175)	141 (114–189)	141 (115–169)	0.615
Calcium	8.9 (8.4–9.3)	8.9 (8.5–9.4)	8.8 (8.5–9.2)	8.8 (8.4–9.2)	8.6 (8.2–9.0)	<0.001
Phosphate	3.2 (2.7–3.7)	3.2 (2.7–3.7)	3.0 (2.8–3.7)	3.3 (2.8–3.8)	3.0 (2.5–3.6)	0.148
Prothrombin time (s)	13.0 (12.4–14.7)	12.9 (12.2–14.1)	13.5 (13.1–16.6)	13.1 (12.3–14.1)	13.9 (12.7–17.0)	<0.001
Activated partial thromboplastin time (s)	26.4 (23.9–30.0)	26.1 (23.8–29.4)	28.3 (25.6–31.1)	25.9 (23.4–28.6)	28.6 (25.0–33.0)	<0.001
INR	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.2 (1.1–1.6)	1.1 (1.0–1.3)	1.2 (1.1–1.7)	<0.001
Antiplatelets (%)	604 (67.0%)	402 (67.0%)	13 (65.0%)	94 (71.8%)	95 (62.9%)	0.070
Anticoagulants (%)	195 (21.6%)	121 (20.0%)	5 (25.0%)	40 (30.5%)	29 (19.2%)	0.470
Mechanical ventilation (%)	448 (49.7%)	280 (46.7%)	9 (45.0%)	70 (53.4%)	89 (58.9%)	0.041

(Continued)

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TABLE 1 (Continued)

	All ICH patients (n = 902)	Non-thrombocytopenia (n = 600, 66.5%)	Baseline thrombocytopenia (n = 20, 2.2%)	Acquired thrombocytopenia (n = 131, 14.5%)	Multiple thrombocytopenia (n = 151, 16.7%)	p
Neurosurgical intervention (%)	285 (31.6%)	200 (33.3%)	2 (10.0%)	37 (28.2%)	(30.5%)	0.075
30-day mortality (%)	187 (20.7%)	102 (17.0%)	4 (20.0%)	29 (22.1%)	52 (34.4%)	<0.001
Length of ICU stay (day)	5 (2–10)	4 (2–8)	4 (2–6)	6 (3–12)	6 (3–12)	<0.001
Length of hospital stay (day)	11 (7–17)	10 (6–16)	12 (8–19)	12 (8–20)	13 (8–19)	<0.001

SpO_2, pulse oxygen saturation; GCS, Glasgow Coma Scale; INR, international normalized ratio.

confirmed. The discovered effect of thrombocytopenia at different timepoints in our study may be helpful for researchers to design clinical trials exploring the indication of platelet transfusion among ICH patients in the future.

Some limitations were not avoidable in this study. First, this observational study collects patients from the single American Medical Center. The selection bias is not avoidable and the finding should be further confirmed by future studies in other medical centers from other countries. Second, some confounding factors influencing the correlation between thrombocytopenia and mortality may not be included such as platelet transfusion, coagulants transfusion. Third, the low number of baseline thrombocytopenia group would influence the reliability of our findings, which should be verified by future studies with larger sample sizes. Fourth, only the occurrence and timepoints of thrombocytopenia were analyzed but not the severity of thrombocytopenia. The severity of low platelet level may also influence the correlation between thrombocytopenia and mortality of ICH. Future studies should be designed to further analyze the comprehensive effect of severity and timepoint of thrombocytopenia on the prognoses of ICH patients. Fifth, prognostic effect of thrombocytopenia on outcome was analyzed while the effect of correcting thrombocytopenia by platelet transfusion was not analyzed due to the inherent limitation of observational study. Randomized controlled studies are worthy to confirm therapeutic effect of platelet transfusion at different timepoints of hospitalizations on platelet level and prognosis. Finally, other outcomes such as functional status and rebleeding events of ICH patients were not analyzed due to the incomplete record of the database. Future studies could be designed to verify relationships between these outcomes and thrombocytopenia. Although these limitations, the strength of our study is exploring the diverse prognostic effect of the thrombocytopenia at different timepoints among ICH patients after admission.

5 Conclusion

Initial thrombocytopenia at admission is not associated with the mortality of ICH patients. ICH patients experiencing both initial thrombocytopenia and acquired thrombocytopenia have significantly higher mortality risk. The platelet level of ICH patients should be monitored constantly during hospitalizations to detect the thrombocytopenia and identify high mortality risk.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: mimic.physionet.org.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

TABLE 2 Univariate and multivariate logistic regression analysis of correlation between thrombocytopenia and 30-day mortality of intracerebral hemorrhage patients.

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.036	1.024–1.049	<0.001	1.043	1.028–1.059	<0.001
Male gender	0.793	0.574–1.095	0.158			
Hypertension	0.884	0.634–1.233	0.467			
Hyperlipidemia	1.073	0.702–1.641	0.744			
Diabetes	1.082	0.734–1.594	0.691			
Atrial fibrillation	1.665	1.164–2.382	0.005	1.458	0.935–2.273	0.097
Coronary heart disease	1.016	0.658–1.567	0.944			
Chronic renal disease	1.906	1.129–3.219	0.016	1.890	1.030–3.468	0.040
Mean blood pressure	0.989	0.980–0.998	0.021	0.993	0.983–1.004	0.209
Heart rate	1.009	1.000–1.019	0.051			
SpO_2	1.015	0.958–1.075	0.610			
GCS	0.872	0.839–0.907	<0.001	0.899	0.850–0.95	<0.001
White blood cell	1.021	0.996–1.046	0.094			
Hemoglobin	0.868	0.799–0.943	0.001	0.890	0.618–1.281	0.530
Hematocrit	0.954	0.926–0.983	0.002	1.004	0.882–1.143	0.951
Glucose	1.005	1.002–1.008	<0.001	1.004	1.001–1.007	0.014
Calcium	0.833	0.681–1.017	0.073			
Phosphate	1.067	0.919–1.240	0.394			
Thrombocytopenia group						0.041
Non-thrombocytopenia	1.000	Reference		1.000	Reference	
Baseline thrombocytopenia	1.221	0.400–3.727	0.726	0.876	0.257–2.991	0.833
Acquired thrombocytopenia	1.388	0.873–2.208	0.166	1.142	0.677–1.926	0.620
Multiple thrombocytopenia	2.564	1.723–3.816	<0.001	1.890	1.215–2.939	0.005
Prothrombin time	1.022	0.999–1.046	0.057			
Activated partial thromboplastin time	1.017	1.000–1.034	0.056			
INR	1.115	0.990–1.256	0.074			
Antiplatelets	0.637	0.415–0.977	0.039	0.520	0.315–0.859	0.011
Anticoagulants	0.639	0.459–0.890	0.008	0.427	0.284–0.643	<0.001
Mechanical ventilation	3.128	2.206–4.434	<0.001	2.545	1.580–4.101	<0.001
Neurosurgical intervention	0.997	0.705–1.410	0.988	1.029	0.677–1.566	0.892

OR, odds ratio; CI, confidence interval; SpO_2, pulse oxygen saturation; GCS, Glasgow Coma Scale; INR, international normalized ratio.

Author contributions

HF: Conceptualization, Writing – original draft. XL: Data curation, Formal analysis, Writing – original draft. AF: Writing – review & editing. RW: Data curation, Formal analysis, Methodology, Resources, Software, Writing – original draft. FQ: Supervision, Validation, Writing – review & editing.

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Conflict of interest

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

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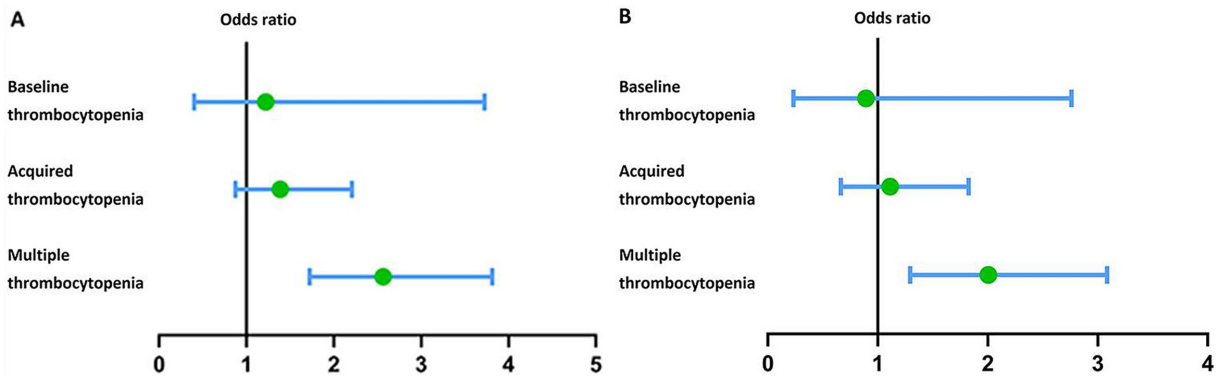

FIGURE 2
(A) Forest plot showing the correlation between different types of thrombocytopenia and mortality of ICH patients analyzed by the univariate logistic regression. (B) Forest plot showing the correlation between different types of thrombocytopenia and mortality of ICH patients analyzed by the multivariate logistic regression.

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Emamectin·chlorfenapyr-induced fatal leukoencephalomyelopathy with delayed hyperthermia: insecticide endanger public safety

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Background: Emamectin·chlorfenapyr is a compound comprising chlorfenapyr and emamectin benzoate that is widely used in agriculture. Chlorfenapyr toxicity has been verified in animals; however, its true mechanism and progression in humans remain to be elucidated. Cases of emamectin·chlorfenapyr poisoning are seldom.

Case presentation: We present a case of a 65-year-old female who attempted suicide by consuming 30 g of 9.5% chlorfenapyr and 0.5% emamectin benzoate 14 days before admission to our hospital. Laboratory tests revealed extremely high creatinine kinase levels upon admission. Magnetic resonance imaging revealed diffuse and symmetric T2 hyperintensities in the entire white matter tract of the brain and spinal cord, and cytological smears of the cerebrospinal fluid showed abnormal lymphocyte aggregation. The patient died 19.5 h after admission owing to cardiopulmonary arrest and hyperthermia.

Conclusion: Further research is needed on how to perform flow cytometry in patients with emamectin·chlorfenapyr intoxication, and to elucidate the immunological mechanism underlying the inflammatory response caused by emamectin·chlorfenapyr and provide new insights into antidote development.

KEYWORDS

emamectin·chlorfenapyr, leukoencephalomyelopathy, hyperthermia, lymphocyte, fatal outcome

Introduction

Emamectin·chlorfenapyr is a formulation that contains 9.5% chlorfenapyr and 0.5% emamectin benzoate (EB). EB (C104H154N2O28) is employed extensively as a broad-spectrum insecticide and pesticide in agriculture (1). It serves as a GABA receptor agonist and modifies the permeability of chloride ions in membranes (2). Chlorfenapyr (C15H11BrClF3N2O), a pyrrole insecticide, is widely used in the cultivation of vegetables and fruits (3). It inhibits the normal oxidative phosphorylation in mitochondria, leading to a decrease in adenosine triphosphate (ATP) and impairing the function of organs that require oxygen (4).

Agriculture serves as a crucial industry pillar in the Asia-Pacific region. The prevalent use of pesticides enhances the accessibility of these toxic substances, which may be ingested either accidentally or intentionally in suicide attempts. Initial clinical symptoms of poisoning are often not immediately apparent. Approximately 7 days post-exposure, toxicity can manifest

with delayed onset. Both EB and chlorfenapyr are associated with depression of the nervous system (2). Additionally, common manifestations of chlorfenapyr poisoning include hyperthermia and rhabdomyolysis (5).

Chlorfenapyr exposure, though not necessarily lethal, has resulted in significant mortality in the Asia-Pacific region (4–6) and the United States (7). While the toxicity of chlorfenapyr has been established in animal studies, its exact mechanism and progression in humans remain elusive. This paper describes a fatal incident involving a 65-year-old female who ingested a bottle of emamectin·chlorfenapyr in an attempt to commit suicide. Unlike previous reports on chlorfenapyr and EB poisoning, this case study includes results from cerebrospinal fluid tests and cytological smears.

Case report

A 65-year-old female patient was admitted to our emergency department presenting with urinary incontinence and a 5-day history of progressive weakness and hypoesthesia in the lower extremities. She had a medical history of hypertension, type 2 diabetes mellitus, and depression. 14 days prior to admission, the patient had attempted suicide by ingesting 30 g of 9.5% chlorfenapyr and 0.5% EB.

Electrocardiogram monitoring indicated the following vital signs: body temperature at 37.6°C, heart rate at 73 beats per minute, respiratory rate at 22 breaths per minute, and blood pressure at 140/69 mmHg. Neurological examination revealed motor weakness in both legs (grade 0/grade 0) and diminished response to acupuncture pain below the T8 dermatome. The patient was fully conscious with a Glasgow Coma Scale (GCS) score of E4, V5, M6.

Toxicity screening revealed trace amounts of chlorfenapyr and emamectin benzoate; cholinesterase inhibitors, illicit drugs, and benzodiazepines were not detected. Prior computed tomography of the chest and abdomen conducted in our emergency room showed no significant abnormalities. Laboratory results indicated a markedly elevated creatine kinase level of 2,406 IU/L (normal range: 40–200 IU/L) and mild liver dysfunction, evidenced by an aspartate aminotransferase level of 85 IU/L (normal range: 13–35 IU/L) and an alanine transaminase level of 47 IU/L (normal range: 7–40 IU/L). Routine blood tests disclosed a white blood cell count of 9.93*10^9/L (normal range: 3.5–9.5*10^9/L) and a neutrophil percentage (NEU%) of 82.7% (normal range: 40–75%). The procalcitonin level was slightly abnormal at 0.081 ng/mL (normal range: 0–0.046 ng/mL).

Magnetic resonance imaging (MRI) of the patient's brain and spine was performed using a 3.0 T unit (MAGNETOM Skyra; Siemens Healthcare GmbH, Erlangen, Germany). The brain MRI exhibited diffuse, bilaterally symmetrical leukoencephalopathy affecting the dentate nucleus of the cerebellum, ventral medulla, bilateral inferior cerebellar peduncles, pons, midbrain, bilateral cerebral peduncles, bilateral corticospinal tracts, corpus callosum, and bilateral parieto-occipital white matter (Figure 1). T2-weighted imaging (T2WI) showed lesions with increased signal intensity (Figure 1A). Diffusion-weighted imaging and an apparent diffusion coefficient map indicated cytotoxic edema and diminished Brownian movement (Figure 1B). The spinal cord was characterized by swollen, hyperintense lesions on T2WI, particularly noted in the cervical spinal cord and conus medullaris (Figure 1C). A lumbar puncture conducted in the emergency room revealed that the cerebrospinal fluid pressure was 240 mmH2O, and the fluid appeared as a yellowish, cloudy liquid containing flocculent material. The total cell count in the cerebrospinal fluid was 6000*10^6/L, with a white blood cell count of 5200*10^6/L and NEU% at 94%. Cerebrospinal fluid analysis yielded the following results: chloride at 114 mmol/L (normal range: 120–132 mmol/L); glucose at 2.37 mmol/L (normal range: 2.5–4.5 mmol/L); lactate at 7.7 mmol/L (normal range: 0.6–2.2 mmol/L); and protein at 1.57 g/L (normal range: 0.15–0.45 g/L). Next-generation sequencing of the cerebrospinal fluid detected no pathogens. Tests for autoimmune encephalitis-related antibodies, demyelinating disease-related antibodies, paraneoplastic nerve syndrome antibodies, cerebrospinal fluid oligoclonal bands, and serum oligoclonal bands were negative. A cytological smear of the cerebrospinal fluid unveiled some lymphocytes clustered around proteinaceous material in a wreath-like configuration (Figures 1D,E).

Based on the imaging and laboratory findings, toxic leukoencephalomyelopathy was suspected. The patient's condition deteriorated on the second day, and hyperthermia ensued 16 h post-admission, with body temperatures rising to 39–40°C. Antipyretic medications proved ineffective. The Glasgow Coma Scale (GCS) was assessed at E3, V3, M5, indicating a progressive deterioration in consciousness. 18 h after admission, the patient developed tachycardia (heart rate of 110 beats/min) and tachypnea (respiratory rate of 30 breaths/min) with shallow breathing. Consequently, steroid pulse therapy was initiated. The patient's percutaneous oxygen saturation fluctuated between 80 and 90%, and a Venturi mask delivering 10 L/min was employed to enhance oxygenation. 19 h post-admission, arterial blood gas analysis revealed hypoxemia (pH 7.31; partial pressure of CO2 50 mmHg; partial pressure of O2 44 mmHg; HCO3 26.5 mmol/L). The patient then entered a deep coma, reflected by a GCS score of E1, V1, M1. Immediate transfer to the intensive care unit was arranged, where tracheal intubation was performed. Unfortunately, the patient succumbed to cardiopulmonary arrest 19.5 h after admission, following the family's issuance of do-not-resuscitate orders.

Discussion

Reports on the full spectrum of manifestations of emamectin-chlorfenapyr poisoning in humans are scarce. A review of the literature was conducted to identify characteristics of such poisoning, yielding a total of 17 reported cases of emamectin-chlorfenapyr poisoning. The details are presented in Table 1. Among these cases, the mean age of the patients was 46.11 ± 15.82 years, and the average hyperthermal temperature was 40.08 ± 1.46°C. Only three cases in which the patient survived have been documented, resulting in a mortality rate of 84.21%. More than half of the patients died in hospital within 1 day of admission.

Mammalian species exhibit low sensitivity to EB due to the chemical's minimal affinity for gamma-aminobutyric acid and the relative impermeability of the blood–brain barrier (2). Chlorfenapyr, classified as moderately hazardous, disrupts the conversion of adenosine diphosphate to ATP by targeting mitochondria, thereby halting ATP production and leading to energy depletion, cellular dysfunction, and death (5). Emamectin·chlorfenapyr, a pesticide combination, is formulated to delay resistance development in insect pests and enhance synergistic effects. EB synergistically contributes to

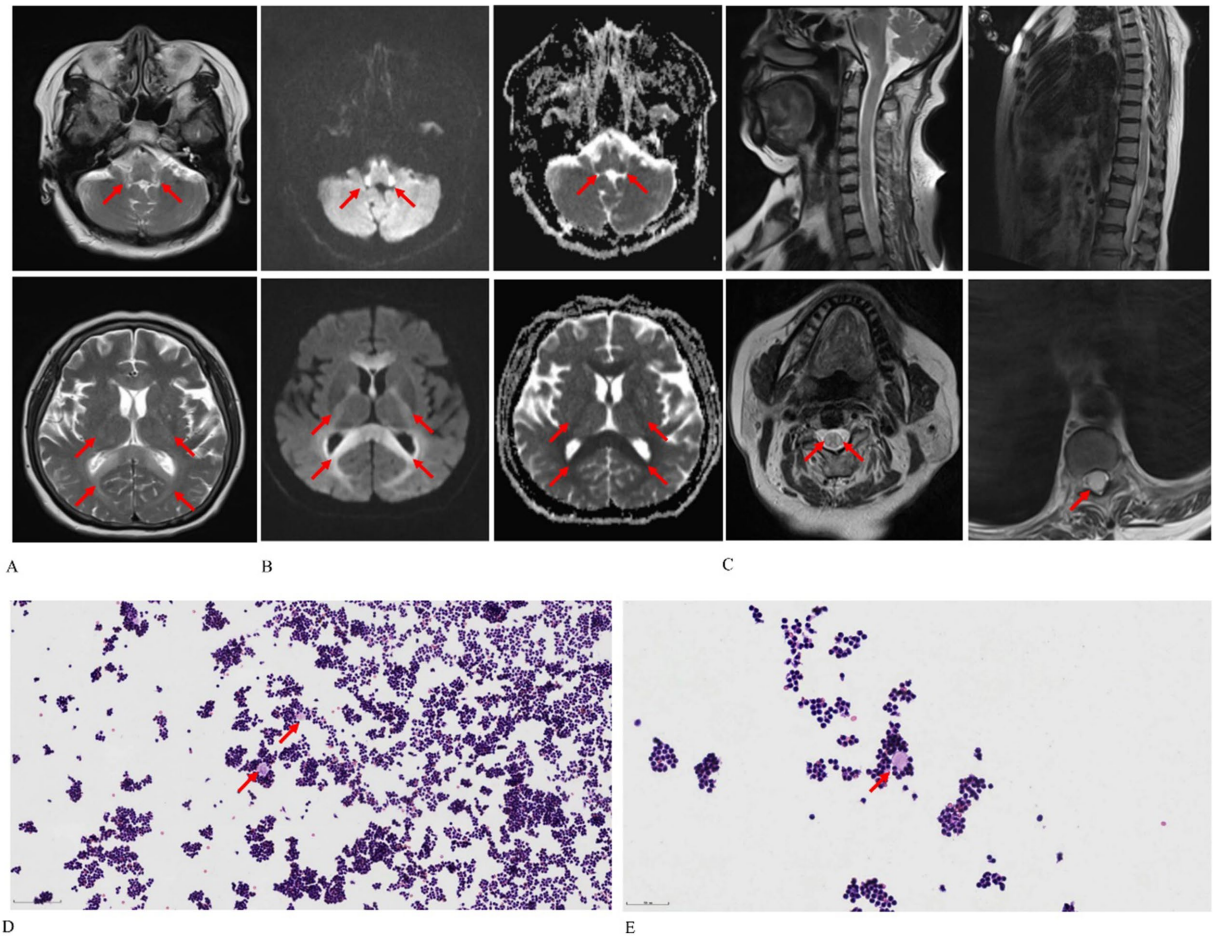

FIGURE 1
Chlorfenapyr and emamectin benzoate-induced leukoencephalomyelopathy in a 65-year-old female patient. **(A)** Axial T2-weighted images reveal diffuse and bilaterally symmetrical leukoencephalopathy affecting the dentate nucleus of the cerebellum, ventral medulla, bilateral inferior cerebellar peduncles, pons, midbrain, bilateral cerebral peduncles, bilateral corticospinal tracts, corpus callosum, and bilateral parieto-occipital white matter. **(B)** Axial diffusion-weighted imaging and apparent diffusion coefficient maps demonstrate cytotoxic edema and reduced Brownian motion. **(C)** Sagittal T2-weighted spine images display swelling and hyperintensity throughout the spinal cord, particularly in the cervical region and conus medullaris. **(D,E)** Cytological smears of cerebrospinal fluid [optical microscope: Hematoxylin–eosin stain, 100× **(D)**, 200× **(E)**] show lymphocytes clustering around protein-like material in a wreath-like formation, as indicated by the red arrow.

oxidative phosphorylation decoupling induced by chlorfenapyr, leading to cell death (8). This mechanism likely underlies the predominant features of emamectin·chlorfenapyr toxicity, which include decreased consciousness, respiratory failure, rhabdomyolysis, and demyelination of the brain and spinal cord, targeting organs with high energy demands.

In previous studies on chlorfenapyr poisoning, the clinical trajectory typically exhibits a latent period of up to 14 days, succeeded by a rapid progression to death (4, 9, 10). Kang et al. (10) postulated that the incubation period for chlorfenapyr toxicity correlates with the time needed for the pro-insecticide to convert into the active toxicant. Similarly, our patient underwent a latent phase of approximately 9 days, during which she displayed no discernible symptoms until the onset of paraplegia. Furthermore, the exact lethal dosage of chlorfenapyr or emamectin·chlorfenapyr remains undetermined, owing to variations in medical settings and individual biochemical characteristics. In a documented survival case (11) following chlorfenapyr ingestion, the patient, who ingested about 10 mL, did not show hyperintensity in the central nervous system and received immediate treatment through early gastrointestinal decontamination, including gastric lavage and whole-bowel irrigation. Conversely, our patient experienced a concealed progression of the condition, with severe damage to her brain and spinal cord upon hospital admission, thus missing the critical window for effective treatment. EB may also contribute synergistically to the lethality of this process.

Other typical clinical manifestations of chlorfenapyr poisoning observed in our patient include rhabdomyolysis and hyperthermia. Delayed hyperthermia, a common observation in cases of chlorfenapyr intoxication, was also noted. In a case report from China, similar to ours, tracheal intubation appeared to hasten clinical decline (12), This deterioration may be associated with pulmonary infections and respiratory muscle failure following tracheal intubation, although the exact mechanisms are yet to be elucidated. Rhabdomyolysis and hyperthermia are also indicative of malignant hyperthermia, a rare condition triggered by certain anesthetics. In this patient, no anesthetics or medications known to induce malignant hyperthermia were administered. It is hypothesized that the lipophilic nature of chlorfenapyr leads to its accumulation in

TABLE 1 List of reports documenting toxicity due to emamectin·chlorfenapyr.

Reference	Year	Country	Age (years)	Sex	Route	Amount of poisoning	Highest BT (°C)	AMS	Elevated CK (IU/L)	AKI	Management	LOS (days)	Outcome
(4)	2010	Korea	55	Male	Oral	250 mL of 10% chlorfenapyr	40.9	Yes	Yes (10507) Yes		Gastric lavage and activated charcoal, and intubation	5	Mortality
(18)	2012	Korea	49	Male	Oral	200 mL	40	Yes	Yes (14336)	Unknown	Intubation and mechanical ventilation	7	Mortality
(9)	2013	India	28	Female	Oral	Unknown	Unknown	Yes	Unknown	Unknown	Gastric lavage and supportive treatment, intubation	1	Mortality
(19)	2013	Korea	74	Male	Intra-abdominal injection	20 mL	Unknown	Unknown	Unknown	Unknown	Emergency surgery and fluid drainage	Unknown	Mortality
(10)	2014	Korea	41	Female	Oral	20 mL	40.7	Yes	Yes (3081)	No	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	0.83	Mortaliy
(11)	2015	Korea	61	Female	Oral	10 mL	38.3	Unknown	Yes (859)	Unknown	Gastric lavage and activated charcoal	19	Survival
(6)	2016	Korea	44	Female	Oral	Unknown	Unknown	Unknown	Unknown	Unknown	Steroid pulse therapy	Unknown	Survival
(7)	2017	United States	42	Male	Oral	Approximately 300 mL of 21% chlorfenapyr and 500 mL vodka	Unknown	Yes	Unknown	Unknown	Gastric lavage and activated charcoal	Unknown	Mortality
(20)	2018	Korea	44	Female	Oral	10-20 mL	Unknown	Unknown	Unknown	Unknown	Gastric lavage and high-dose intravenous corticosteroid pulse therapy	Unknown	Survival
(21)	2019	Korea	49	Male	Dermal	Unknown	41.5	Yes	Yes (4484)	Unknown	Intubation, sedation and analgesia, intravenous administration of paracetamol and tepid sponging	0.46	Mortality
(22)	2020	China	66	Male	Oral	20 mL	38.5	Yes	Yes (8174)	Yes	Gastric lavage and supportive treatment, intubation	5	Mortality

(Continued)

10.3389/fneur.2024.1449728

TABLE 1 (Continued)

Reference	Year	Country	Age (years)	Sex	Route	Amount of poisoning	Highest BT (°C)	AMS	Elevated CK (IU/L)	AKI	Management	LOS (days)	Outcome
(12)	2021	China	50	Female	Oral	60 mL	40	Yes	Yes (1960)	Unknown	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	<1	Mortality
(12)	2021	China	50	Male	Transnasal	Unknown	41	Yes	Yes (1590)	Unknown	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	<1	Mortality
(12)	2021	China	38	Male	Transnasal	Unknown	40	Yes	Yes (5945)	Unknown	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	<1	Mortality
(12)	2021	China	32	Female	Oral	5 mL	41.8	Yes	Yes (3762)	Unknown	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	1	Mortality
(8)	2022	China	21	Male	Oral	Unknown	39	Yes	Yes (933.74)	No	Intravenous fluid hydration and urine alkalinization, intubation and mechanical ventilation	1	Mortality
(8)	2022	China	55	Male	Oral	60 mL	37.3	Yes	Yes (820.48)	No	Emergency surgery and fluid drainage, intubation	<1	Mortality

CK, creatinine kinase; normal range, 40–200 IU/L; LOS, length of stay; BT, body temperature; AMS, altered mental status; AKI, acute kidney injury.

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striated muscles, uncoupling oxidative phosphorylation in mitochondria, disrupting ATP synthesis, and inducing cell death, which elevates creatine kinase levels. Consequently, this triggers non-shivering thermogenesis in brown adipose tissue, culminating in hyperthermia (10).

Few cases of chlorfenapyr intoxication in humans that include integrated radiological data have been reported. Tharaknath et al. (9) reported a case of chlorfenapyr poisoning with diffuse and bilateral hyperintensity in the white matter of the brain and spinal cord on T2WI MRI; their case was very similar to ours. Baek et al. (6) reported a case of survival after chlorfenapyr intoxication and found reversible signal changes in the white matter tracts throughout the brain, brainstem, and spinal cord after 75 days of follow-up visits. Other similar radiological features reported by Kang et al. (10) also indicated a low white matter density in the whole brain tissue on computed tomography scans. In a previous animal experiment involving rats with chlorfenapyr poisoning, vacuolar myelopathy and mild myelin sheath swelling were found in a variety of structures ranging from the subcortical areas to the brainstem and spinal cord in neurohistopathological examinations (13); this is consistent with MRI findings in clinical case reports. However, the pathophysiology of the susceptibility of the white matter tracts alone is unknown. We presume that chlorfenapyr tends to invade and accumulate in the myelin sheath owing to its weak lipophilic acid features, and causes myelin disintegration, the presence of which is shown on MRI. In addition, heat-regulating centers in the hypothalamus are believed to be involved in chlorfenapyr cases, causing hyperthermia (13).

A detailed interpretation of why the cerebrospinal fluid had a count of a white blood cell count of 5200*10^6/L and NEU% of 94% could be assumed that toxicant destroyed blood–brain barrier and raised immunologic derangement, which recruiting inflammatory cells. Decidedly few case reports that present cerebrospinal fluid consequences have been published. Baek et al. (6) reported that the cerebrospinal fluid test results of a patient with diffuse abnormal signals in the brain and spinal cord were normal. However, using next-generation sequencing and cytometric bead array, we confirmed that the cerebrospinal fluid of our patient showed a secondary inflammatory process with no pathogenic microorganisms or related antibodies. In the cytological smear of the cerebrospinal fluid, we observed that some lymphocytes surrounded the protein-like material and lined up in a wreath-like pattern. We speculated that the protein-like material may be a type of myelin tissue that has been shed and that contains abundant tralopyril, which is a metabolized form from chlorfenapyr (14). In addition, chlorfenapyr could activate some lymphocyte subsets, which, in turn, could gather around the exogenous substance. Only one case report of methadone intoxication may provide some evidential support of our speculations. Repple et al. (15) performed flow cytometry on the cerebrospinal fluid of methadone-intoxicated patients and found cell composition alterations that were characterized by the transformation of monocytes from the classical ($CD14^+CD16^-$) to the nonclassical ($CD14^+CD16^+$) and a switch from $CD56^{bright}$ nonkilling cells to $CD56^{dim}$ nonkilling cells. Notably, $CD14^+CD16^+$ monocytes and $CD56^{dim}$ nonkilling cells are pro-inflammatory cells that may be involved in delayed encephalopathy (16). These findings from Repple et al. may explain the lymphocyte aggregation observed in the current case, which provides the first reported cerebrospinal fluid findings of chlorfenapyr intoxication.

Pesticide poisoning is a significant global public health issue, resulting in approximately 110,000–168,000 deaths annually, predominantly in Asia. The World Health Organization (WHO) reported that accidental poisonings led to around 350,000 deaths in 2000. A further estimate indicates that in 2012, unintentional poisoning claimed the lives of 193,000 people globally, with 84 percent of these fatalities occurring in low- and middle-income countries (17). Developing nations experience higher rates of suicide via poisoning, notably through pesticides. Conversely, in high-income countries, substances used in suicide attempts include psychotropic drugs, painkillers, antihistamines, antidepressants, psychoactive medications, and sedative hypnotics. It raises concerns that suicide remains an increasingly prevalent "illness." Pesticide poisoning represents merely one method of suicide; thus, focusing on prevention is substantially more critical than merely addressing the effects. Health systems must continue to provide special attention to the mental health of their citizens.

Limitations in this case reports include that: (1) The precise dosage of emamectin·chlorfenapyr is still unclear as described with 30 g. The reason goes that the pesticide were produced by unqualified manufacturer in Chinese mainland, and the manufacturer did not have production permit, so we could not know the specific dosage form. (2) Chlorfenapyr is metabolized to tralopyril in the body and persists for a prolonged period, but the blood concentration levels observed for tralopyril is unreviewable for the interpretation that blood concentration levels were very low at the time when testing, there is no idea about the accurate information. Although there are deficiencies on clinical observations, the diagnosis is still can be done by comprehensive assessment.

Conclusion

We present a fatal case of leukoencephalomyelopathy induced by emamectin·chlorfenapyr with delayed hyperthermia and rapid deterioration. The latent period from emamectin·chlorfenapyr exposure to paraplegia onset was less than 9 days, and MRI revealed bilateral, symmetric, and diffuse T2 hyperintensity of the entire white matter tract in the brain and spinal cord. In the cytological smear of the cerebrospinal fluid, we observed that some of the lymphocytes gathered in a wreath-like pattern surrounding a protein-like material; this is the first report of cerebrospinal fluid microscopic characteristics in emamectin·chlorfenapyr intoxication. Further research is needed to clarify how to perform flow cytometry on patients with emamectin·chlorfenapyr intoxication, to elucidate the immunological mechanism underlying the inflammatory process caused by emamectin·chlorfenapyr, and to provide new insights into antidote development.

Author contributions

XL: Software, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Resources. YY: Conceptualization, Investigation, Writing – review & editing. YZ: Investigation, Supervision, Writing – review & editing. XZ: Validation, Visualization, Writing – review & editing. NZ: Conceptualization,

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Conflict of interest

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

Publisher's note

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Clinical management and nursing care for patients with tracheostomy following traumatic brain injury

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Tracheostomy is a routine surgical procedure in patients with severe traumatic brain injury, which requires mechanical ventilation to maintain gas exchange and avoid hypoxemia. Inadequate tracheostomy timing, nursing care, and decannulation would lead to a series of complications, such as aggravated pneumonia and prolonged intubation. The effects of early tracheostomy versus late tracheostomy have been explored. And early tracheostomy is more likely associated with shorter hospital stays and fewer complications. But the relevant reports are controversial. A safe and fast tracheostomy decannulation would facilitate the recovery. However, there was a broad variability in the indications and timing of tracheostomy and decannulation. High-quality evidence is subsequently lacking. We conducted this review to address gaps in knowledge regarding the management strategy and nursing protocol in patients with tracheostomy and decannulation following traumatic brain injury. A multidisciplinary tracheostomy team containing nursing care was also discussed to provide the best service to these patients.

KEYWORDS

tracheostomy, traumatic brain injury, decannulation, multidisciplinary team, nursing

Introduction

Patients suffered from severe traumatic brain injury (sTBI, the list of abbreviations was shown in Table 1) usually require mechanical ventilation in the neurosurgical intensive care unit (ICU). Approximately 31.8% of patients in the TBI cohort have experienced tracheostomy, which is more frequent than patients in general ICU cohorts with rates of about 10% (1). As the state of unconsciousness is persistent, tracheostomy is commonly performed to maintain gas exchange to avoid hypoxemia and accelerate liberation from mechanical ventilation. With the stable airway access provided, the tracheostomy tube could also be convenient for suctioning (2). The main indications for tracheostomy in patients with sTBI include absence of protective airway reflexes, impairment of respiratory drive, prolonged mechanical ventilation, reduction of dead space to facilitate ventilatory weaning, and difficulties in managing secretions (1, 3). However, optimal timing for tracheostomy is still controversial.

A safe and fast decannulation in tracheostomized patients with sTBI is considered as a main rehabilitative goal. However, there was substantial heterogeneity in tracheostomy care and decannulation practices among the different centers (4). In this study, we reviewed the effects of tracheostomy, tracheostomy timing, and decannulation timing to provide valuable information for clinicians. We further discussed the role of a multidisciplinary tracheostomy team, especially the nursing care protocol, in the clinical management of tracheostomized patients with sTBI.

TABLE 1 List of abbreviations.

ABI	Acute brain injury
CRS-R	Coma recovery scale-revised
ET	Early tracheostomy
GCS	Glasgow Coma Scale
ICU	Intensive care unit
LT	Late tracheostomy
LOS	Length of stay
mPATH	Multiprofessional acute trauma health care
sTBI	Severe traumatic brain injury

The effects of tracheostomy on patients with sTBI

It has been reported that tracheostomy has advantages in improving outcomes of patients with sTBI compared with prolonged endotracheal intubation. Villemure-Poliquin N et al. (5) conducted a retrospective multicenter cohort study and examined the potential benefits of tracheostomy versus prolonged endotracheal intubation. Tracheostomy was shown to be associated with decreased 30-day mortality. The increased survival owing to tracheostomy was also confirmed by Stephen S et al. (6). Specifically, tracheostomy could comfort the patients by reducing oropharyngeal irritation, reducing sedative administration, and achieving more autonomy earlier (7). Besides, tracheostomy could decrease the risk of ventilator-associated pneumonia and ventilator-induced lung injury (8). Patients with long-term mechanical ventilation could also get positive weaning and shorter duration by tracheostomy. As an invasive procedure, tracheostomy would inevitably have risks for the airway, including tracheomalacia, hemorrhage, and tracheal stenosis (9). However, tracheostomy would still be recommended for sTBI patients when weighing the benefits and risks (10).

The timing of tracheostomy for patients with sTBI

Conventionally, tracheostomy is commonly used for patients with sTBI under the condition of Glasgow Coma Scale (GCS) score ≤ 8 and these who rely on a mechanical ventilator for more than 7 days (11, 12). According to the recommendations of the European Society of Intensive Care Medicine consensus (13), tracheostomy is strongly recommended in mechanically ventilated patients with acute brain injury (ABI) who have failed one or several trials of extubation. It should also be considered in mechanically ventilated patients with ABI who have persistently reduced consciousness levels (weak recommendation).

Although tracheostomy is generally indicated for patients with sTBI, the timing of tracheostomy for patients with sTBI is unclear (14). Tracheostomy is usually defined as early tracheostomy (ET, performed within 7 days of admission) or late tracheostomy (LT, performed more than 7 days after admission). A previous study classified ET and LT as tracheostomy performed ≤10 days and > 10 days after tracheal intubation, respectively (15). Another study defined ET and LT as tracheostomy performed ≤3 days and > 3 days after admission, respectively (16). The effects of early tracheostomy versus late tracheostomy have been explored. But the results are controversial. According to a retrospective, 15-year observational cohort study from January 1990 to December 2005, 3,277 patients with TBI were found to have a tracheostomy (17). The investigation indicated a relationship between tracheostomy timing and prognosis, and suggested that ET may lead to a better overall clinical outcome than LT. Similarly, Shibahashi K et al. (18) explored the performance of earlier tracheostomy (within 72 h of admission) and found a decrease in the duration of mechanical ventilation and length of stay (LOS) in patients with TBI, with acceptable mortality. Besides, a propensity-matched analysis on children's patients with sTBI and a retrospective cohort study on adult patients both showed that ET was related with shorter hospital LOS and fewer complications (8, 19). Along with a decreased risk of pneumonia, a lower risk of deep venous thrombosis, and decubitus ulcer, a decreasing trend of pulmonary embolism was observed in ET. A lower incidence of gram-negative microorganism-related nosocomial pneumonia and shorter antibiotic duration use were also identified in ET (20). In a meta-analysis comparing ET and LT in sTBI or stroke, the mean time to tracheostomy in the ET cohort was 7.1 ± 0.00 days and 15.3 ± 0.01 days in the LT cohort. ET was shown to reduce the risk for ventilator-associated pneumonia and decrease mechanical ventilation duration in ICU and hospital LOS (21). Another meta-analysis comparing ET and LT in sTBI displayed similar results (10). However, a recent US national analysis showed that mortality was slightly higher in ET than in LT, while other benefits from ET notably existed (22). Villemure-Poliquin N et al. (5) revealed no effect on mortality was observed when comparing ET and LT. Relevant studies on time to tracheostomy in patients with severe TBI in Table 2.

In general, priority seems to be given to ET for patients with sTBI rather than delayed tracheostomy or LT. However, high-quality evidence is lacking. In 2020, an international consensus panel attempted to provide a recommendation regarding the optimal timing of tracheostomy in patients with ABI. But they failed due to contradictory and low-quality evidence (13). Following that, results from CENTER-TBI as a prospective observational longitudinal cohort study on patients with TBI were reported (1). The study demonstrated that LT was more likely to have a worse neurological outcome, poor neurological sequels, and longer LOS. Due to various tracheostomy timing, different brain injury severity, and a mix of isolated brain injury versus multiple injury, there was a broad variability in current studies. Standardized comparisons are needed in future research. Given the variable indications for mechanical ventilation and the different underlying lung mechanics in patient subgroups, more detailed information is needed to implement guidelines (23).

The timing of decannulation for patients with sTBI

The majority of patients with tracheostomy who survive to hospital discharge could be successfully decannulated (24). An early decannulation could avoid secondary complications, such as respiratory infections and airway obstructions, to improve clinical outcomes and facilitate the recovery (25). However, the indications and optimal time for decannulation remain unclear. According to a systematic scoping review on critically ill patients in mixed ICU, the

TABLE 2 Studies on time to tracheostomy in patients with severe TBI.

Authors/published year/journal	Aims	Study design	*N*	Primary results
Amirhossein et al. (22)/2023/Neurocrit Care	To compare the effect of ET versus LT in patients with TBI.	A retrospective cohort of inpatient study.	2,397 patients with ET (<7 days from admission) and 4,041 with LT (≥7 days from admission).	The patients with ET had a shorter length of stay as compared LT ($p < 0.001$) and had a lower hospital charge ($p < 0.001$). The mortality was higher within the ET group compared with the LT group ($p < 0.001$). Patients in the LT had higher odds of developing any infection ($p < 0.001$), emerging sepsis ($p < 0.001$), pneumonia ($p < 0.001$), and respiratory failure ($p = 0.004$)
Villemure-Poliquin N et al. (5)/2023/Can J Anaesth	To compare the effect of tracheostomy and prolonged intubation on patients' outcomes, and to evaluate the tracheostomy timing on outcomes.	A retrospective multicentre cohort study.	374 with a tracheostomy and 609 with intubated remained;144 with an ET and 233 with a LT.	Tracheostomy was associated with a reduction in 30-day mortality (HR, 0.33; 95% CI, 0.21 to 0.53) compared with prolonged intubation. No effect on mortality was observed when comparing ET vs. LT procedures.
CENTER-TBI ICU Participants and Investigators (1)/2020/ Intensive Care Med	To assess the effect of tracheostomy and its timing on patients' outcomes.	A prospective observational longitudinal cohort study from CENTER-TBI.	1,358 included TBI patients and 433 with a tracheostomy. 180 with ET (≤7 days) and 253 with LT (>7 days).	Patients with a LT were more likely to have a worse mortality and poor neurological sequels ($p = 0.018$), and LOS (38.5 vs. 49.4 days, $p = 0.003$).
Cory et al. (19)/2019/J Trauma Acute Care Surg	To determine if ET is associated with decreased length of stay and fewer complications in children with sTBI.	A retrospective propensity score matching study.	168 with ET and 190 with LT.	ET was associated with fewer ventilator days (RR [95% CI] 0.55 [0.46, 0.65]), and a shorter hospital length of stay (0.62 [0.53, 0.72]). ET was also associated with less frequent pneumonia (OR 0.44 [0.26, 0.76]), and venous thromboembolism (0.20 [0.07, 0.57]). No significant differences in mortality (1.26 [0.46, 3.49]) were observed
Lu W et al. (16)/2019/J Craniofac Surg	To find the optimal time for tracheostomy in sTBI.	A retrospective study.	51 with ET (<3d) and 47 with LT (>3d).	The NICU stay, hospitalization stay, and antibiotic use time of patients in the ET group were shorter than those in the LT group ($p < 0.05$). The pneumonia rates and the cost in the ET group were lower than those in the LT group ($p < 0.05$). The complications and mortality were not statistically significant ($p > 0.05$).
Shibahashi K et al. (18)/2017/Br J Neurosurg	To examine the effects of tracheostomy performed within 72 h after admission in TBI patients.	A retrospective cohort study.	40 were in the ET group (≤72 h) and 51 were in the control group (>72 h).	The duration of mechanical ventilation and LOS in ICU were significantly less in the ET group than in the control group. The 30-day mortality rates were 3 and 8% for the ET and control groups, respectively.
Khalili H et al. (11)/2017/ World Neurosurg	To compare the effects of ET versus LT on TBI-related outcomes and prognosis	A retrospective study.	53 with ET (≤6 d) and 99 with LT (>7 d).	Patients with ET had a significantly lower hospital stay (46.4 vs. 38.6 days; $p = 0.048$) and intensive care unit stay (34.9 vs. 26.7 days; $p = 0.003$). Mortality rates were not significantly different between the 2 groups ($p > 0.99$).
Aziz S et al. (8)/2014/J Trauma Acute Care Surg	To define the optimal timing of tracheostomy in patients with sTBI.	A retrospective observational cohort study.	873 with ET (≤8 days) and 938 with LT (>8 days).	ET was associated with fewer mechanical ventilation days (RR, 0.70; 95% CI, 0.66, 0.75), shorter intensive care unit stay (RR, 0.70; 95% CI, 0.66, 0.75), shorter LOS (RR, 0.80; 95% CI, 0.74, 0.86), and lower odds of pneumonia (OR, 0.64; 95% CI, 0.51, 0.80), deep venous thrombosis (OR, 0.53; 95% CI, 0.37, 0.78), and decubitus ulcer (OR, 0.43; 95% CI, 0.26, 0.71). No significant difference in pulmonary embolism (OR, 0.52; 95% CI, 0.24, 1.10). Hospital mortality was similar between both groups (OR, 1.25; 95% CI, 0.80, 1.96).

(Continued)

TABLE 2 (Continued)

Authors/published year/journal	Aims	Study design	*N*	Primary results
Wang HK et al. (20)/2012/ Injury	To examine the impact of the tracheostomy timing in patients with sTBI.	A retrospective analysis.	16 were in the ET group (≤10 d) and 50 were in the LT group (>10 d).	ET a shorter duration of ICU LOS ($p < 0.001$), lower incidence of gram-negative microorganism-related nosocomial pneumonia ($p = 0.001$), and shorter duration of antibiotic use ($p < 0.001$).
Rizk EB et al. (17)/2011/ Neurocrit Care	To determine the impact of tracheostomy timing on outcomes in sTBI.	A retrospective observational cohort study.	1,577 with ET (<7d) and 1,527 with LT (>7 d).	ET was more likely to be functionally independent at discharge ($p = 0.001$) and have a shorter LOS ($p < 0.0001$). However, LT were approximately twice as likely to be discharged alive ($p < 0.0001$).
Ahmed N et al. (14)/2007/ Surg Infect (Larchmt)	To determine the impact of ET and LT in patients with sTBI.	A retrospective cohort study.	27 with ET and 28 with LT.	ET group had a significantly shorter stay in the ICU than late group (19.0 +/− 7.7 vs. 25.8 +/− 11.8 days; $p = 0.008$). There was no difference between the groups in ventilator days (15.7 +/− 6.0 vs. 20.0 +/− 16.0 days; $p = 0.57$). There were no significant differences between the groups regarding overall mortality (15% vs. 4%; $p = 0.19$).

ET, early tracheostomy; LOS, longer length of stay; LT, late tracheostomy; sTBI, severe traumatic brain injury.

assessment criterion differed as informed consent, clinical stability, airway patency, physiological decannulation, swallowing assessment, consciousness level, effectiveness of cough, and clearance of secretions (26). However, it would not be adequate for patients with sTBI. Because patients with sTBI are usually in a coma, and the ability of self-body control and executing simple voluntary tasks are lost.

Weaning protocols are difficult for decision-making. There are numerous and confounding factors to judge. For example, common comorbidities such as diabetes and acute kidney injury would influence the chances for decannulation in patients with sTBI (27). Despite that, identifying efficient factors for time to decannulation is essential for safe weaning. It is reported that the predictive factors for safe removal of the tracheal tube in patients with ABI including high neurological status, TBI rather than stroke or anoxic brain lesions, younger age, effective swallowing, an effective cough, and the absence of pulmonary infections (28). Independent breathing and airway protection may indicate successful decannulation in patients with sTBI. Perin C et al. (29) found that mean expiratory pressure, spontaneous cough, and cough strength were positive predictors of tracheostomy tube removal. However, in a decannulation study on 74 patients with ABI, airway patency, cough reflex test, SpO2, and GCS ≥ 8 showed high specificity but low sensitivity (30). Shrestha KK et al. also proposed that consciousness level based on GCS score was not significant in successful decannulation (31). Meanwhile, a higher coma recovery scale-revised (CRS-R) score was suggested to accurately evaluate the state of consciousness, which was demonstrated to be associated with a higher probability of decannulation (32). Thus, accurate parameters for accessing consciousness need to be used for studies on decannulation indications in depth.

Several methods have been observed to contribute to successful decannulation. Lanini B et al. (33) emphasized the roles of flexible bronchoscopy and thought it would guide successful tracheostomy weaning. Zanata Ide L et al. (34) thought that phonation and coughing were helpful for early tracheal decannulation in 20 patients with TBI. Moreover, the swallowing ability was verified in a retrospective study with a Danish population of 324 participants. Eskildsen SJ et al. (35) found that an improvement in swallowing ability during the initial 4 weeks of rehabilitation was associated with an 8.2-day reduction in time to decannulation. This study concluded that swallowing ability is a potentially significant factor with reduced time to decannulation. Relevant studies on time to decannulation in patients with severe TBI in Table 3. In general, the clinical criteria for tracheostomy decannulation in patients with sTBI included: (1) toleration of tracheostomy tube capping for 72 h (36); (2) Absence of severe dysphagia, defined as the ability to manage secretions (37); (3) endoscopic patency of airways (lumen diameter > 50%) (38); (4) swallowing instrumental assessment (penetration assessment scale 5, no aspiration events); and (5) blue dye test (absence of blue traces) (30).

Multidisciplinary tracheostomy team

Inadequate tracheostomy timing, nursing care, and unsafe decannulation would lead to complications, such as aggravated pneumonia, prolonged intubation, or induced paroxysmal sympathetic hyperactivity (39). Therefore, a multidisciplinary team trained and qualified is essential. Patients would benefit from a specialized multidisciplinary tracheostomy team. LeBlanc J et al. (40) retrospectively compared the effect of a multidisciplinary tracheostomy team from 27 patients before implementation of the tracheostomy team approach and 34 patients followed by the team. The team comprised trauma surgeons and residents, respiratory therapists, speech-language pathologists, and clinical nurse specialists. The results suggested that patients in the multidisciplinary group had a significantly shorter LOS and decreased time to decannulation. Based on research in the Level I trauma center of Carolinas Medical Center of America, Alvin et al. (41) investigated whether the multidisciplinary team would decrease LOS. The team was called a dedicated multiprofessional acute trauma health care (mPATH) team, consisting of a physical, occupational, speech, and respiratory therapist, nurse navigator, social worker, advanced care provider, and physician. They retrospectively compared the patients in the year before the mPATH team was established ($n = 60$) to those in the first

TABLE 3 Studies on time to decannulation in patients with severe TBI.

Authors/published year/journal	Aims	Study design	*N*	Evaluation for decannulation	Outcomes
Eskildsen SJ et al. (35)/2024/Respir Care	To identify significant factors for time to decannulation in subjects with tracheostomy after TBI.	A retrospective register-based cohort study.	324 patients	Associations between selected explanatory variables representing demographic and clinical characteristics and time to decannulation were analyzed using linear regression models.	An improvement in swallowing ability during the initial 4 weeks of rehabilitation was associated with an 8.2 d reduction in time to decannulation (95% CI −12.3 to −4.2, $p < 0.001$).
Jenkins R et al. (27)/2020/ Brain Inj	To assess variables associated with decannulation in patients with TBI.	A retrospective study.	79 patients	Patients decannulated prior to 90 days were compared with patients who remained cannulated. Variables prior to tracheostomy and throughout hospitalization were used.	Variables prior to tracheostomy associated with decannulation included diabetes (HR, 0.15; 95% CI, 0.03–0.84; $p = 0.03$), craniotomy (HR, 0.25; 95% CI, 0.06–1.02; $p = 0.05$) and acute kidney injury (AKI) (HR, 0.06; 95% CI, 0.01–0.48; $p = 0.01$).
Hakiki B et al. (32)/2020/ Arch Phys Med Rehabil	To identify the effect of some clinical characteristics on decannulation success in severe ABI.	A retrospective study.	351 patients with severe ABI.	Variables collected at admission during clinical examination, conducted by trained and experienced examiners were collected for analysis.	Absence of pulmonary infections ($p < 0.001$), sepsis ($p = 0.001$), tracheal alteration at the fibrobronchoscopy examination ($p = 0.004$) and a better state of consciousness at admission ($p = 0.001$) were associated with a higher probability of decannulation.
Enrichi C et al. (30)/2017/ Respir Care	To find the most sensitive and specific clinical criteria for decannulation in ABI.	A cross-sectional experimental study.	74 patients	Control group: tracheostomy tube (TT) capping 72 h, no severe dysphagia, ability to manage secretions. Experimental group: TT capping ≥72 h, endoscopic patency of airways (lumen diameter > 50%), swallowing instrumental assessment, blue dye test, voluntary cough (PCF > 160 L/min), cough reflex, number of tracheal suctions, oxygen saturation > 95% ambient air, LOC (insufficient when the GCS was consistently ≤8)	Parameters showing the highest values of sensitivity and specificity, respectively, were tracheostomy tube capping (80, 100%), endoscopy assessment of airway patency (100, 30%), swallowing instrumental assessment (85, 96%), and the blue dye test (65, 85%). All these were combined in a clinical cluster parameter, which had higher sensitivity (100%) and specificity (82%).
Perin C et al. (29)/2017/Int Arch Otorhinolaryngol	To identify the factors associated with the outcome of tube removal in severe ABI patients.	A retrospective study	45 patients	Variables including demographic characteristics, GCS, cause of hospitalization, duration of Neurorehabilitation Ward hospitalization, comorbidities, kind of tracheostomy tube used, SpO2, pulmonary secretion, respiratory pressure, respiratory frequency and presence of spontaneous cough, cough strength, and blood gas analysis.	Mean expiratory pressure, presence of spontaneous cough, and cough strength. Provoked cough and GCS were not predictive of weaning success.

(Continued)

TABLE 3 (Continued)

Authors/published year/journal	Aims	Study design	*N*	Evaluation for decannulation	Outcomes
Zanata et al. (34)/2014/Int Arch Otorhinolaryngol	To accesses the applicability of a protocol for tracheal decannulation	A prospective observational study	20 patients	Informed consent, adequate LOC ≥ 8, phonation (orally responsive or nonresponsive), swallowing, secretions (amount, aspect and color), coughing, toleration of capping/cuff deflation	The protocol was relevant to establish the beginning of the decannulation process.
Matesz et al. (38)/2014/Orv Hetil	To describe the safe tracheostomy decannulation method of patients with brain injury during rehabilitation.	A prospective, descriptive study	20 patients	Consent, clinical stability (BP, pulse and peripheral oxygen saturation), bronchoscopy-aerogastric reflexes, state of vocal cords and possible stenosis were observed before decannulation, swallowing and speech assessment.	During the procedure successful decannulation was performed in 13 patients. Decannulation occurred 62 days after tracheostomy on average. The involvement bronchoscopy was feasible.
Shrestha et al. (31)/2012/Nepal Med Coll J	To evaluate gradual vs. abrupt techniques for successful decannulation in tracheostomised patients with sTBI.	A prospective case–Control study.	118 patients	Time since tracheostomy, timing of decannulation, Glasgow Coma Scale, amount of secretions, breath holding time, CXR and STN radiographs and cough reflex were all assessed.	Sixty-eight patients were decannulated gradually and 50 abruptly. Of the various factors assessed, only cough reflex, number of suctioning required per day, radiograph STN and use of antibiotics for more than 7 days were found to be statistically significant.

ABI, acquired brain injury; ET, early tracheostomy; LT, late tracheostomy; LOC, level of consciousness; sTBI, severe traumatic brain injury.

full year following the team implementation ($n = 70$). As the primary endpoint, LOS obviously decreased due to the successful team. Meanwhile, a cost savings of US $11,238 per index hospitalization was observed. Thirty-day readmission and mortality rates had no significant change. Hence, the involvement of a multidisciplinary team is feasible during the entire hospitalization from tracheostomy to decannulation. However, it should be noted that the population sample size of the above study is limited, and more prospective research evidence is needed.

Nursing care

In a recent methodological study conducted in a public hospital in the city of Belém in Brazil (42), 34 nursing professionals participated in this survey. Developed through two phases: (I) target audience characterization and (II) technology development, and guided by the 5W2H management tool: 1 – What; 2 – Who; 3 – When; 4 – Where; 5 – Why; 1 – How; 2 – How Much, investigators thought the educational demands and continuing health education, with an emphasis on standardizing care through a protocol, were important for critical patients with tracheostomy. Although the study was limited by the lack of content validity by expert judges, appearance validity by design judges, semantic validity by the target audience, and usability assessment, clinical significance may truly exist. Because they appealed that care protocols and educational technologies were effective tools to address inconsistent topics in assisting patients with tracheostomy in NICU. A cross-sectional descriptive study involving a self-administered questionnaire conducted in a tertiary medical center in Saudi Arabia also recommended continuous training and competency evaluation for delivering optimal nursing care (43).

Tracheostomy is an invasive procedure and requires the participation of specialized multidisciplinary tracheostomy team collaboration (44). Among those, if the nursing work is not in place, various complications could arise, and the clinical prognosis would be affected. Hence, evidence-based nursing for patients with tracheostomy is beneficial to form standardized practices and prevent complications (45).

According to our experience, an individualized and feasible respiratory care plan should be developed by the supervising nurse based on the patient's condition. Firstly, different body postures should be used for patients with different disease conditions. For example, patients with irritating cough should be given a semi-recumbent position. Secondly, the suction method should be adjusted based on coughing and changes in airway pressure. The appropriate suction tube should be selected, and airway patency should be ensured. Each suction time should be approximately 15 s to prevent situations such as hypoxia and suffocation caused by prolonged suction. Thirdly, attention should be paid to airway humidification. After tracheostomy, the patient's respiratory tract is in direct contact with air. Therefore, sodium chloride solution should be used for humidification. Simultaneously, a tracheostomy mask could be used to achieve a humidification effect. The gas could be humidified and filtered to protect the tracheal mucosa. Finally, complication care for stoma is important. Nurses should strengthen nursing patrols, check the incision, and prevent infection. The incision needs to be kept

clean, the tracheal cuff should be replaced promptly, and disinfected with alcohol or iodine solution. Observe the incision for secretions, collect and culture bacteria, and use sensitive antibiotics to prevent infection.

Discussion

Tracheostomy and its decannulation are common procedures for patients with sTBI. Although ET is mostly reported to be associated with decreased LOS and fewer complications, mortality remains controversial. The different outcomes reported in different studies are likely associated with the various patient models used. Evaluations for ET or LT are more effective when considering 7 days as a cut-off point. Further investigation into standardized patient models could provide more precise insights into the optimal timing for tracheostomy and improve patient outcomes across diverse clinical settings. In addition, the current evidence on protocols for the assessment of tracheostomy decannulation is inadequate. Most recommendations are insufficient due to time bias, population bias, or the small sample size owing to the nature of the study. With the results from CENTER-TBI proving that ET can improve patient outcomes, more prospective randomized controlled trials exploring the timing of tracheostomy and decannulation are warranted to provide clinical guidelines.

The multidisciplinary tracheostomy care is important and its scope is expanding in order to manage the complex needs and expectations of tracheostomy patients. Initiatives such as the Global Tracheostomy (Quality Improvement) Collaborative[1] have the potential to collect meaningful patient-level data around the quality of care delivered (46). Quality improvement programs such as this can deliver data that are relevant to patients and their families, multidisciplinary health care professionals and also hospital administrators that can comprehensively benchmark the effectiveness of multidisciplinary tracheostomy care in the future (47). Even when overlapping with other roles from the multidisciplinary team, specialist nursing programs including continuous training and competency evaluation have been shown to be a cost-effective method of improving hospital-wide tracheostomy care.

There are some limitations in this review. Firstly, the included literatures were relatively insufficient. Several researches published before 2000 years were ruled out. And only English literature has been adopted. Articles in other languages such as Chinese, German, and French were not available. Secondly, we only focused on the results and conclusions of the existing research, and did not further analyze the data of the study comprehensively. In addition, the evidence of the multidisciplinary tracheostomy team and nursing care were not powerful. Therefore, some insights may be controversial.

Conclusion

An ET performed within 7 days of admission in TBI patients could increase the opportunity of patient's early rehabilitation. The toleration of tracheostomy tube capping, the ability to manage secretions, the endoscopic patency of airways, the swallowing ability, and the blue dye test may be potentially factors for early decannulation decision-making. A multidisciplinary tracheostomy team with specialist nursing care is crucial to improve clinical outcomes and prevent complications.

Author contributions

XM: Writing – original draft, Writing – review & editing. YuZ: Writing – original draft, Writing – review & editing. QC: Investigation, Writing – original draft, Writing – review & editing. YeZ: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Risk factors for failing endotracheal extubation in neurocritical patients: a retrospective cohort study

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Objective: To identify risk factors of failing endotracheal extubation among neurocritical care patients with endotracheal intubation for more than 48 h and passing the autonomous breathing test (SBT) and establish a prediction model accordingly.

Methods: This study included the clinical data of patients who received standardized monitoring and treatment in the neurocritical care unit of the First Affiliated Hospital of Anhui Medical University from April 2020 to August 2024. Based on the outcomes of extubation after 5 days, data were divided into the success group and the failure group. Clinical features of two groups were compared and accordingly taken into multivariate logistic regression analysis, eventually generating a scoring model with its receiver operating characteristic curve (ROC). The area under the curves (AUC) of other previous scores was compared by Z-test.

Results: Of 116 recorded cases, 92 (79.3%) were successfully extubated, while 24 (20.7%) required re-intubation within 5 days. Univariate analysis revealed significant differences between two groups in state of consciousness, Glasgow Coma Scale (GCS) total score, GCS motor score (GCS-M), muscle strength, swallowing ability, coughing response, body temperature, oxygenation index, Apache II score, and APS score (all $p < 0.05$). Multivariate analysis was further carried out, and a scoring model was established accordingly (including GCS-M, coughing ability, and oxygenation index) with a total score of 4 points. The model demonstrated good predictive value, with a cut-off ≥1 distinguishing extubation success with 79.2% sensitivity and 69.6% specificity according to ROC (AUC = 0.79; 95% CI, 0.68–0.90).

Conclusion: This clinical predictive scoring model could provide guidance for extubation decisions in neurocritical care units but requires further external validation.

KEYWORDS

neurocritical care, endotracheal extubation, airway control, Glasgow Coma Scale, risk factors

1 Introduction

Failed extubation, generally defined as the need for re-intubation or tracheotomy within 48 h of planned extubation, can lead to Mechanical injury and hypoxia, prolonged hospitalization, worse prognosis, and even increased mortality. Therefore, the assessment of risk factors for failed extubation and strategies for optimizing extubation success are essential for the clinical management of intensive care unit (ICU) patients (1). Passing the spontaneous breathing trial (SBT) is an important prerequisite for extubation (2). Conversely, unnecessary delays in extubation can also result in deleterious outcomes such as increased risk of ventilator-associated pneumonia, prolonged hospitalization, and higher mortality even among patients passing the SBT and successfully extricated from the ventilator (3). The overall extubation failure rate following SBT is reported to be about 10–20% (4), but can be as high as 38% in brain injury patients (5), so tracheotomy is frequently required within 48 h for many intubated neurocritical patients. This decision is often based on the "Stroke-Related Early Tracheotomy (SET) Score" (6). However, a recent multicenter study found that patients who underwent early tracheostomy according to the SET score did not have a better prognosis at 6 months than those who had to undergo tracheostomy after 10 days of intubation (7). Moreover, earlier tracheotomy deprived some patients of the benefits of direct extubation. Therefore, a major current concern in critical care medicine is how best to predict which neurocritical patients will benefit from extubation at a given time.

Previous studies have identified coma, poor airway protection, severe lung infection, advanced age, and combined underlying chronic cardiopulmonary diseases as predictive factors for unsuccessful extubation (8), but most of these studies enrolled comprehensive ICU patients. Alternatively, the primary pathologies of neurocritical patients, such as traumatic brain injury (TBI), cerebrovascular disease, encephalitis, hypoxic–ischemic encephalopathy, and central demyelinating disorders, and the secondary sequela such as decreased level of consciousness, poor airway protection, and potential damage to the respiratory drive or respiratory motor conduction pathway, may differentially influence extubation failure risk among this clinical group. In addition, the rates of extubation failure, delayed extubation, and tracheotomy are generally higher among neurocritical patients even if respiratory parameters are satisfactory during mechanical ventilation (9). Therefore, the risk factors for extubation failure among neurocritical patients may be distinct and potentially missed in studies of the general ICU population.

For these reasons, the investigation of risk factors for extubation failure requires neurological assessment in addition to evaluation of respiratory parameters (10). Godet and colleagues reported that lower Glasgow Coma Score (GCS) is associated with greater risk of extubation failure (11), but McCredie and associates reported that some patients with impaired consciousness can be successfully extubated, and that age, choking reflex function, and fluid balance are more strongly predictive of extubation success (12). There are several clinically relevant scores available for predicting the risk of failed extubation, including the simplified Clinical Utility Score developed by Godet and colleagues based on assessment of coughing, swallowing, gag reflexes, and neurologic status (11), the VISAGE score is based on visual pursuit, swallowing, age, and GCS (13), the Respiratory Insufficiency Syndrome Intubation Scale-intubated (RIS-i) score based on level of sedation, oxygenation, cough reflex, and swallowing (14), and the Extubation Strategies in Neuro-Intensive Care Unit Patients and Associations With Outcome (ENIO) scale (9). However, most previous studies have used 48 h after extubation as the cut-off for distinguishing success from failure. Moreover, patient group sizes were relatively small with the exception of the ENIO score study.

In clinical practice, many neurocritical patients require re-intubation several days after extubation, and these patients should be counted as extubation failures. Therefore, set 5 days after extubation as the observation cut-off and found that this longer duration encompassed >90% of total failure cases (15). In the present study, we compared demographic characteristics, neurological status indices, airway protection capacity, circulatory function, and respiratory function between extubation success and failure subgroups of neurocritical patients to develop a predictive scoring scheme for extubation. Further, we provide external validation of several other scoring systems.

2 Materials and methods

2.1 Study population and setting

The study was conducted at the ICU of the Department of Neurology (Neurocritical Intensive Care Unit, NICU), the First Affiliated Hospital of Anhui Medical University. Neurocritical patients ≥18 years old requiring endotracheal intubation for over 24 h were screened as study candidates between April 2020 and August 2024 (Figure 1).

Inclusion criteria were as follows: (1) patients diagnosed with TBI, subarachnoid aneurysmal hemorrhage (SAH), intracranial hemorrhage (ICH), ischemic stroke, hypoxic–ischemic encephalopathy (HIE), metabolic encephalopathy, central nervous system infection, encephalitis, or brain tumor; (2) receiving endotracheal intubation for more than 24 h; (3) successfully passing the SBT without any significant deterioration in mental status (16). The SBT requirements were maintenance on intubated oxygen for >2 h with stable blood pressure (systolic <180 mm Hg or > 90 mm Hg), stable heart rate (<120/min or variance <20%), and stable respiration (RR < 35/min, SpO^2 > 90%). Exclusion criteria included (1) unplanned extubation or autoextubation, (2) tracheotomy, (3) withdrawal of care or automatic discharge within 5 days after extubation.

This study meets the standards of medical ethics and is approved by ethics committee of the First Affiliated Hospital of Anhui Medical University (PJ20231136).

2.2 Extubation protocol

After the patient passed the SBT, the physician in charge assessed the level and content of consciousness, airway protection ability, and choking risk. Airway protection ability was evaluated by observing the degree of oral salivary accumulation and the presence of spontaneous thyroid cartilage displacement indicative of swallowing. Further, the risk of choking was assessed by monitoring the frequency and intensity of cough produced during sputum suctioning and the amount, thickness, and blood content of airway secretions.

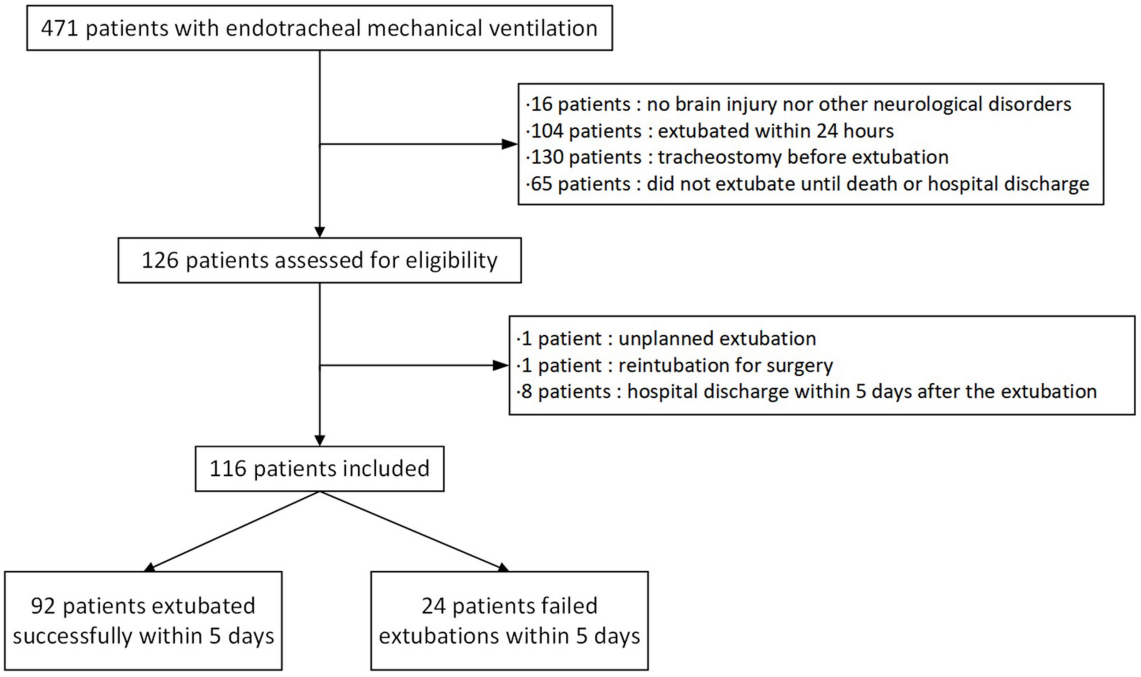

FIGURE 1
Flowchart of data collection.

Once extubation is decided, 5 mg of dexamethasone was administered routinely through intravenous injection half an hour in advance, then the nurse suctioned the oral cavity and nasal catheter secretions, and provided inhaled oxygen via the nasal catheter for 2–3 min. The gas in the air sac was emptied while maintaining negative pressure of the sputum suction tube, and the tracheal tube pulled out. The patient then received aerosol inhalation, ordinary nasal catheter oxygen inhalation, or hyperthermia and humidification high-flow oxygen therapy according to lung function. Some patients were irritable due to primary disease and intubation discomfort, so low-dose sedatives were administered before extubation (dextromethorphan about 0.3 mg/kg/h or midazolam about 0.5 mg/kg/min) to maintain a Ramsay score of 2 or 3 points (17).

2.3 Data collection

At a practical level, documentations as much detail as possible of demographic and clinical data was collected by two experienced neurologists and a nurse through the hospital's electronic record system and actual clinical observations. It is difficult to assess language function during tracheal intubation, so the verbal score of the GCS was set to 1 point (18). When assessing limb movements in people with impaired consciousness, stimulation is performed by pressing on the patient's supraorbital foramen, and muscle strength grading was based on the highest muscle strength of the upper limb on the left or right side. Airway protection ability was classified from strong to weak according to the following criteria: Grade I, strong swallowing action with no saliva accumulation; II, weak swallowing action with a small amount of saliva outflow; III, no swallowing action and a large amount of saliva outflow. Coughing ability was similarly categorized as follows: I, strong coughing, more than 4 consecutive sounds, and sputum choking out of the catheter; II, medium coughing, 2–4 sounds, and sputum not choked out of the catheter; III, weak coughing, less than 2 sounds; IV, no response to sputum suction. Physiological parameters recorded included vital signs, oxygenation index, arterial blood gas concentrations, hemoglobin content, hematocrit, platelet count, white blood cell count, percentage of neutrophils, liver and kidney function variables, and electrolyte concentrations. We also collected the data required to calculate Godet's, VISAGE and RIS-i scores according to the methods detailed here and in previous studies. For original RIS-i score calculation, mental status is assessed using the Richmond Agitation Sedation Score (RASS), the scale is divided into 10 levels of sedation, from +4 points to −5 points represent the degree of the patient from "aggressive" to "coma," and each score corresponds to a state of consciousness. However, it is not usually used for neurological consciousness assessment. Therefore, we replaced the RASS score for RIS-i score calculation with a simple grade of consciousness as follows: awake = 3, drowsiness = 2, lethargy = 1, coma = 0. We then screened the potential risk factors of failing extubation for further analysis from both the perspective of the diseases' pathophysiology included in this study and other previous studies mentioned in Introduction.

2.4 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics 27.0. Dichotomous variables were compared by chi-square test or Fisher's exact test as indicated; independent samples t-test is used when the continuous variable conforms to a normal distribution. The remaining variables including the hierarchical data and skewed distribution data are tested by the Mann–Whitney U-test. Based on

the results of this univariate analysis ($p < 0.05$) and clinical correlation, multivariate analysis was performed using a logistic regression model, and the results expressed as the odds ratio (OR) and 95% confidence interval (95%CI). According to the logistic regression results, the scoring system of this study was established. The corresponding receiver operating curve (ROC) and area under the curve (AUC) were obtained as well. Then the optimal cut-off value was determined by maximizing the Youden index (Youden's J = sensitivity + specificity −1). Z-test was used to compare the AUCs of other previous models mentions in Introduction. A post-hoc power analysis was conducted using G*Power 3.1.

3 Results

3.1 Patient characteristics

A total of 116 patients (Figure 1) were included in the statistical analysis (ranged 18–92 years, 72 males [62.0%]). The most frequent etiology was stroke ($n = 81$, 69.83%), followed by traumatic brain injury ($n = 14$, 12.07%), central nerve system infection and secondary epilepsy ($n = 9$, 7.76%), spinal cord injury ($n = 2$, 1.72%), Parkinson's disease ($n = 2$, 1.72%),acute and chronic inflammatory demyelinating polyradiculoneuropathy ($n = 2$, 1.72%), myasthenia gravis ($n = 2$, 1.72%), ischemic–hypoxic encephalopathy ($n = 1$, 0.86%), brain tumor ($n = 1$, 0.86%) and disorders of consciousness due to other causes ($n = 2$, 1.72%). The duration of intubation ranged from 2 to 18 days. 92 patients in this cohort were successfully extubated while 24 patients were not (failure rate of 20.69%). Median duration of intubation did not differ significantly between the extubation success and failure groups (112 h vs. 90 h, $p = 0.23$). Of these failures, 12 (50%) occurred <24 h after extubation, 4 (16.67%) between 24 and 48 h, 4 (16.67%) between 48 and 72 h, and 4 (16.67%) between 72 and 120 h. The reasons for re-intubation in the failure group were mainly weak cough and unmanageable endotracheal secretion ($n = 14$, 58.33%) and hypoxemia ($n = 10$, 41.67%). Airway narrowing due to edema or spasticity of the airway was found on re-intubation in 4 patients (16.67%), while glossoptosis was found in 3 patients (12.5%), cardiovascular failure in 1 (4.17%), and respiratory muscle weakness in one (4.17%). After extubation failure and re-intubation, 20 patients required tracheostomy (83.33%), while 4 (16.67%) were successfully re-extubated again. Based on the information collected, we additionally calculated acute physiology and chronic health evaluation (Apache II) with its acute physiology score (APS) component, and sequential organ failure assessment (SOFA) score ahead of extubation to represent the patient's overall physiology at that time (19, 20) (Table 1).

3.2 Univariate analysis of influencing factors for extubation success

Before extubation, GCS ($p = 0.009$), GCS motor response (GCS-M) ($p < 0.001$), muscle strength grade ($p < 0.001$) and level of consciousness ($p = 0.011$) differed significantly between success and failure groups. Uni-variate analysis also proved statistically significant differences in patients' coughing ($p = 0.0034$), swallowing ($p = 0.018$), body temperature ($p = 0.040$), oxygenation index ($p = 0.039$), Apache II score ($p = 0.005$) and APS score ($p = 0.028$). Further, Godet's, VISAGE, and RIS-i scores differed significantly between success and failure groups. While ENIO score had no significant difference ($p = 0.064$) (Table 1).

3.3 Multivariate analysis of factors independently influencing extubation outcomes

In order to make the model more concise and improve its clinical feasibility, statistically significant factors based on the results above were independently classified: pre-extubation GCS-M (≥ 4, 0; <4, 1), coughing ability (≤II, 0; >II,1), body temperature (<37°C, 0; ≥ 37°C, 1) and oxygenation index (>200, 0; ≤200,1). These four factors were subsequently included in binary logistic regression analysis to find independent influencing factors for extubation outcomes.

It should be noted that swallowing ability was omitted from the analysis for two principal reasons: first, oral intubation may interfere with the assessment of saliva accumulation; second, coughing ability serves as an indicator of bulbar muscle functional recovery, like swallowing does. Concurrently, consciousness level was excluded due to the use of sedatives in a subset of patients. Apache II score and APS score were excluded because of their nature as composite scores and containing many sub-items.

The corresponding regression coefficient β was calculated according to the OR of three independent risk factors proved by logistic regression (Table 2), and the factors were assigned scores according to the β (ln(OR)). Then a neurocritical extubation scoring model of this study was established with a summit score of 4 (Table 3). According to the ROC of the model, a score ≥ 1 predicted successful extubation (low risk of failure) with 79.2% sensitivity and 69.6% specificity. At this optimal cut-off, the AUC was 0.79 (95% CI: 0.68–0.90, $p < 0.001$). Further, these same analyses also indicated that the predictive efficacy of the current model exceeded that of the Godet's score (AUC = 0.68; 95%CI: 0.55–0.81), VISAGE score (AUC = 0.67, 95%CI 0.55–0.80) and RIS-i score (AUC = 0.69; 95%CI: 0.57–0.80) (Table 4). Then Z-test was used to compare the AUCs, the results showed that the prediction efficiency of this study was higher than that of Godet's score ($Z = 2.142$, $p = 0.042$) and VISAGE score ($Z = 1.950$, $p = 0.044$), but there was no significant difference compared with RIS-i score ($Z = 1.184$, $p = 0.343$).

Based on the observed extubation failure rate, the sample size of 116 cases, and the OR, the statistical power was calculated. For a two-tailed test with $\alpha = 0.05$, the achieved power exceeded 80% for all significant factors, indicating sufficient sensitivity to detect clinically relevant associations.

4 Discussion

A large proportion of patients admitted to the neurocritical care unit require endotracheal intubation and mechanical ventilation. Neurocritical care patients are also at high risk of extubation failure, so it is vital to develop reliable clinical tools for guiding decisions on extubation, re-intubation, and tracheostomy. Two recent large-scale studies of factors associated with extubation success and failure (SET and ENIO) have yielded predictive scales for evaluating the safety of

10.3389/fneur.2025.1562454

TABLE 1 Univariate analysis between extubation success group and failure group.

	Extubation success (n = 92)	Extubation failure (n = 24)	$\chi^2/t/Z$	p
Age, median (IQR)	63 (51.25–73.0)	67 (57.25–74.75)	−1.37	0.17
Sex (male), n (%)	59 (64.1%)	13 (54.2%)	0.80	0.37
Stroke, n (%)	63 (68.4%)	18 (75.0%)	0.38	0.54
Endotracheal intubation time, hour, median (IQR)	112 (72, 192)	90 (48, 162)	−1.21	0.23
GCS Total Score, median (IQR)	10 (8.25, 11)	7.25 (5.25, 11)	−2.60	0.009
GCS(E), median (IQR)	4 (3, 4)	3 (3, 4)	−0.93	0.36
GCS(M), median (IQR)	6 (5, 6)	4 (1, 6)	−3.58	<0.001
Muscle strength (0–5), median (IQR)	4 (3, 5)	2 (0, 3)	−4.22	<0.001
Level of consciousness, n (%)			−2.54	0.011
Awareness	36 (39.1%)	6 (25%)		
Sleepiness	41 (44.6%)	7 (29.2%)		
Lethargy	5 (5.4%)	1 (4.2%)		
Coma	10 (10.9%)	10 (41.7%)		
Cough, n (%)			−2.11	0.034
I	30 (32.6%)	5 (20.8%)		
II	48 (52.2%)	13 (54.2%)		
III	12 (13.0%)	5 (20.8%)		
IV	2 (2.2%)	1 (4.2%)		
Swallow, n (%)			−1.38	0.018
I	50 (54.3%)	6 (25%)		
II	39 (42.4%)	15 (62.5%)		
III	3 (3.3%)	3 (12.5%)		
Temperature, n (%)			4.418	0.040
<37°C	45 (48.9%)	6 (25%)		
≥37°C	47 (51.1%)	18 (75%)		
Oxygen inhalation after extubation, n (%)			7.80	0.10
Ordinary Nasal Catheter	17 (18.5%)	3 (12.5%)		
Ordinary Mask	22 (23.9%)	2 (8.33%)		
High Flow Inhaled Oxygen	52 (56.5%)	18 (75%)		
Non-invasive ventilator	0	1 (4.17%)		
No oxygen support	1 (1.1%)	0		
c, PaO_2/FiO_2, median (IQR)	266.5 (213.8, 341.9)	239.68 (187.0, 275.3)	−2.06	0.039
Apache II, median (IQR)	8 (10, 13)	13 (10.5, 16.75)	−2.82	0.005
APS, median (IQR)	5 (7, 9)	9 (6.25, 12)	−2.20	0.028
SOFA, median (IQR)	5 (3, 6)	5 (4, 6.75)	−1.48	0.14
Thomas Godet's score, median (IQR)	14 (14, 14)	13 (12, 14)	−3.86	<0.001
VISAGE score, median (IQR)	2 (2, 3)	2 (1, 2.75)	−2.77	0.006
RIS-i score, median (IQR)	3 (2, 4.75)	5 (4, 6)	−3.52	<0.001
ENIO-score, median (IQR)	59 (46.8, 70.5)	61.0 (59.0, 86.0)	1.905	0.064

IQR, Interquartile Range.

extubation (i.e., the risk of extubation failure); however, a recent meta-analysis including more than 17,000 critical stroke patients concluded that the use of the SET score for determining extubation time did not improve neurological outcome (according to the modified Rankin scale [mRS]) or reduce mortality, ICU and hospital stay (LOS), and the duration of mechanical ventilation. Further, the authors suggested

that the necessity for tracheostomy should be based on patient characteristics, neurological state, prognosis, risk–benefit ratio, and patient comfort rather than SET score (21). Therefore, we developed a novel predictive model incorporating multiple demographic and clinical factors, including neurological status, and tested its efficacy for distinguishing extubation success from failure among neurocritical care patients. The scale presented here demonstrated superior accuracy for identifying patients ultimately achieving successful intubation compared to Godet's, VISAGE and RIS-i scales. The scores according to Godet's, VISAGE, and RIS-i scales did differ significantly between successful and failed extubation groups, and notably all include assessment of consciousness and airway protection, factors identified as independent predictors in the current study. Nonetheless, ROC analysis indicated slightly better performance by the current scale compared to Godet's, VISAGE, and RIS-i scales.

TABLE 2 Results of multivariate analysis.

Parameters before extubation	OR	β	95%CI	p
GCS-M	9.45	2.25	2.59–34.56	0.001
Coughing ability	3.61	1.28	1.08–12.03	0.037
Temperature	2.13	-	0.67–6.74	0.200
Oxygenation index	3.28	1.18	1.03–10.50	0.045

β = ln (OR).

TABLE 3 The extubation scoring model of endotracheal neurocritical patients that have passed SBT.

Factors	Points
GCS-M	
≥4	0
<4	2
Coughing ability	
≤II	0
>II	1
Oxygenation index	
>200	0
≤200	1

Coughing ability: I: strong coughing, more than 4 consecutive sounds, and sputum choking out of the catheter; II: medium coughing, 2–4 sounds, and sputum not choked out of the catheter; III: weak coughing, less than 2 sounds; IV: no response to sputum suction.

In VISAGE and Godet's scales, the level of consciousness is reflected by Coma Recovery Scale-Revised (CRS-R) "visual" subitems, especially visual pursuit. The RIS-i scale also includes items on mental status, bulbar function, oxygenation, and BMI, but mental status is reflected by the RASS, which is usually used to assess the depth of sedation. Therefore, we replaced the RASS with a grade of consciousness (awake 3′, drowsiness 2′, lethargy 1′, coma 0′), and found that RIS-i score was still predictive of successful extubation. Many studies have suggested that a lower total GCS score is predictive of a greater risk for extubation failure. According to univariate logistic regression analysis, however, only the GCS-M has significant predictive value. Indeed, 92.6% of subjects with GCS-M > 4 were successfully extubated (sensitivity), while a large fraction of patient with failed extubation (44%) scored ≤4 on the GCS-M (specificity). Eye opening, as a sub-component of the GCS score, did not have a significant effect on extubation outcomes. Although the total GCS score also demonstrated high sensitivity, its specificity was not ideal and the AUC was lower than that of the GCS-M. It is possible that this lower predictive value resulted from setting the GCS-V as 1 (default). We found that it was more appropriate to use a cognitive item when assessing the level of consciousness, such as the CRS-R "visual pursuit," or to use a simple grade of consciousness (awake 3′, drowsiness 2′, lethargy 1′, coma 0′). In the present cohort, 1 patient in a minimally consciousness state with the same grade as the patient with drowsiness. There were also 6 patients in unresponsive awake syndrome (vegetative state) with the same grade as those in lethargy.

For decisions on extubation among general ICU patients, arterial blood oxygenation index is considered crucial and is included in both ENIO and RIS-i scales. Samely, this study also confirmed that there was a significant statistical difference in the oxygenation index before extubation between the successful and failed groups, and was finally included in this scoring model. The RIS-i scale also considers patient BMI, and we found that 3 of 24 patients in the extubation failure group (12.5%) had glossoptosis, of which 2 exhibited a BMI > 28 and comorbid obstructive sleep apnea syndrome (OSAS). Therefore, obesity and a history of OSAS may be important predictors of extubation failure, when the number of cases is sufficient, the analysis of these population should be focused.

This study included 116 neurocritical patients who passed the SBT by weaning from ventilators for >2 h prior to tracheal catheter removal. We defined extubation failure as the need for re-intubation within 5 days after extubation rather than within 2 days, thus maximizing the actual extubation failure rate. This study indicates that patients need to be comprehensively evaluated for neurological function, airway protection ability, and physiological and biochemical indexes before extubation. These evaluations include mental status,

TABLE 4 Logistic regression analysis results and ROC characteristics of different predictive scoring systems.

	OR	95%CI	p	AUC	95%CI	Sensitivity	Specificity	Cutoff value
Thomas Godet's score	1.32	1.05–1.67	0.006	0.68	0.55–0.81	87	50	>13
VISAGE score	2.21	1.28–3.83	0.010	0.67	0.55–0.80	89.1	37.5	>2
RIS-i score	0.61	0.46–0.80	0.005	0.69	0.57–0.80	84.80	41.70	≤5
Our score	3.37	1.97–5.78	<0.001	0.79	0.68–0.90	79.2	69.6	>1

GCS motor score, swallowing attempt frequency, cough frequency, and body temperature. Based on these main factors, we established a neurocritical extubation risk model including GCS-M, coughing ability, and oxygenation index which could reflect the ability of the airway protection in patients with severe neurological diseases. The model's successful extubation ability was higher than several other prediction scales by previous studies (VISAGE, Godet's, and RIS-i score) for neurocritical patients, thus facilitating safer extubation decisions.

This study has several limitations. Due to the small sample size of a single center, many other possible predictive factors, such as sputum properties, BMI, brain lesion size, and primary etiology were not included in this study's analysis. Secondly, this retrospective design had not done *a priori* sample size estimation, and lack of external validation affected the generalizability and practicability of the conclusions as well. Therefore, we will continue to expand the sample size to test additional factors and validate the existing results in further study.

5 Conclusion

We describe a new scoring model consists of 3 factors (GCS-M, coughing ability, and oxygenation index) which can help with decision making of extubation for neurocritical patients. But it still needs further validation.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of the First Affiliated Hospital of Anhui Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/ next of kin because this is a retrospective study that did not interfere with clinical practice and therapy.

Author contributions

XZ: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SZ: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CC: Investigation, Resources, Validation, Writing – review & editing. SW: Investigation, Resources, Validation, Writing – review & editing. YH: Conceptualization, Writing – review & editing.

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Conflict of interest

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

Generative AI statement

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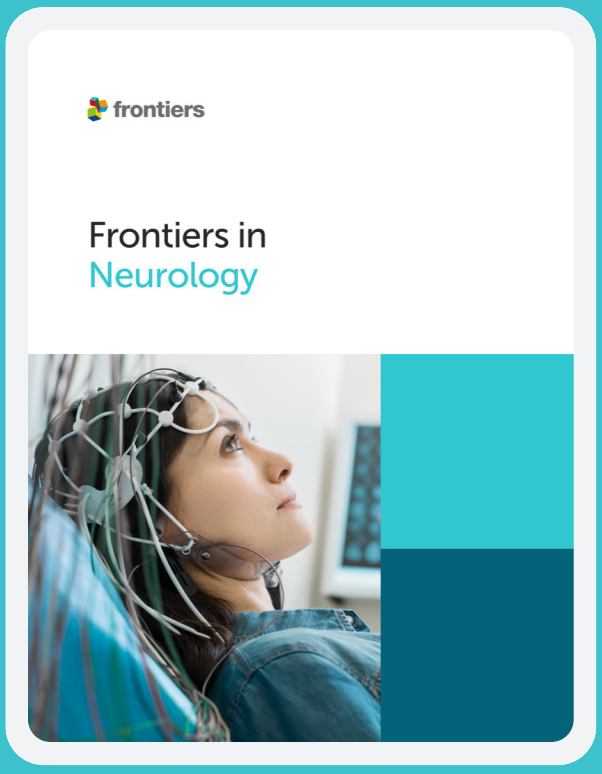

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