CRITICAL CARE AFTER STROKE

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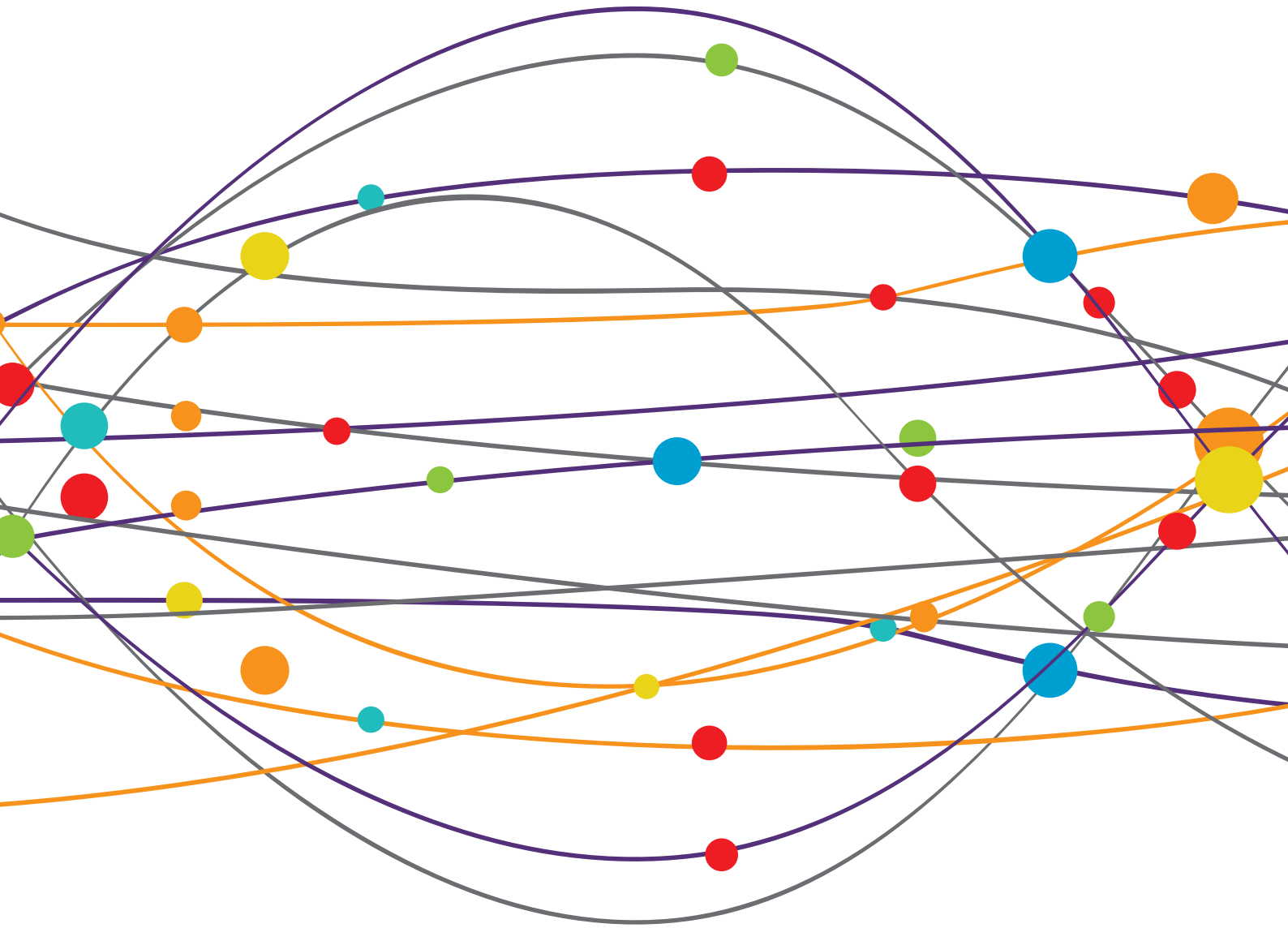

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CRITICAL CARE AFTER STROKE

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EDITORIAL
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Editorial: Critical Care After Stroke

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Keywords: stroke, intracerebral hemorrhage, ischemic stroke, acute medicine, critical care, thrombolysis (tPA), thrombectomy, endovascular therapy (EVT)

Editorial on the Research Topic

Critical Care After Stroke

Stroke, as an entity comprising both acute ischemic stroke (AIS) and Intracerebral Hemorrhage (ICH), is the second leading cause of global mortality (1). Although advances in the management of AIS, in particular endovascular therapy for large vessel occlusion, have led to improved functional outcomes (2), 3-month mortality in those undergoing treatment remains substantial. Despite surgical intervention and changes in recommendations for acute medical management for ICH in recent years (3), 30 day mortality is as high as 46% (4). *Critical Care After Stroke* is therefore of upmost importance to improve functional outcomes and reduce mortality in both the short term and longer term follow up.

Endovascular Therapy (EVT) is now the standard of care for patients presenting with a large vessel occlusion in the anterior circulation (5), blood pressure management thereafter, however, is not standardized. In their mini review, Peng et al. address one of the elephants in the room, namely that, despite successful reperfusion, many patients do not regain functional independence. Their review identifies blood pressure (BP) optimization as an area of focus in those with hemodynamic variability and vast BP fluctuations. Ongoing trials are addressing the role of BP, but *post-hoc* analyses from several thrombectomy trials suggest that high systolic BP trajectories in the first 24 h post procedure are associated with an increased risk of poor outcome. An individual, autoregulation-guided approach to BP, seems to increase the chances of a good clinical outcome.

Hong et al.'s review on hemorrhagic transformation after an AIS highlights the associated risk of poor outcome and increased mortality. The mechanism of hemorrhagic transformation is explained by disruption of the blood-brain barrier and reperfusion injury that leads to leakage of peripheral blood cells. In AIS this transformation may be a natural progression of tissue ischemia that is facilitated, and thus worsened, by reperfusion therapy. There are several strategies that can be considered for management of hemorrhagic transformation in AIS, including neurosurgical intervention and medical management. The medical management is individual and can be summarized as reversal of coagulopathy, management of BP, temperature regulation, and supportive neurocritical care with a focus on reducing hematoma expansion and maintaining the integrity of the blood-brain barrier. Regarding the latter, the authors point out the role of matrix metalloproteinases and the need for more research around these biological and molecular mechanisms.

Kobata et al. review recent updates in neurosurgical interventions for spontaneous ICH. Neurosurgical interventions are a matter of debate and clinical practice varies greatly globally. The minimally invasive surgery plus alteplase for intracerebral hemorrhage evacuation (MISTIE) III trial demonstrated a reduction in mortality compared to medical treatment. Despite the overall reduction in mortality, no improved functional outcome categorized as a modified Rankin Scale

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0–3 was observed. Ongoing randomized controlled trials such as the Early miNimally invasive Removal of Intra-Cerebral Hemorrhage (ENRICH) trial, the Minimally Invasive Endoscopic Surgical Treatment with Apollo/Artemis in Patients with Brain Hemorrhage (INVEST) trial, and the Dutch Intracerebral Hemorrhage Surgery Trial (DIST) are further addressing the optimal treatment for ICH. The authors point out that the outcome of surgical treatment is also dependent on the site and surgeon experience, something that should be taken into consideration when interpreting results for clinical practice.

Gao L. et al. address end-of-life care and the underlying decision-making process and associated prognostic uncertainties as a pivotal part of a stroke physician's challenge in the clinical setting. Patients suffering a stroke, especially those who require critical care, are commonly unable to actively participate in the care decision-making processes, and care decisions rest on the shoulders of surrogate decision-makers. Decision-making around many aspects of critical care can be challenging; surgical interventions, intensive care unit treatment, artificial nutrition, tracheostomy, withdrawal of life-sustaining care to name a few. This mini review highlights the difficulties in outcome prognostication, and provide strategies to address uncertainty and elicit goals of care. The authors conclude that clear communication regarding decision-making, prognostication, and patients' and surrogates' wishes after stroke are pivotal in all care settings, but especially in the critical care unit.

This topic also includes publications on the evaluation of the patient safety climate in acute care (Bohmann et al.), the impact of blood pressure and volume contraction in acute stroke (Bahouth et al.), early initiation of renal replacement therapy in ICH (Schenk et al.), reduction of intracranial pressure mediated through surgical intervention (Al-Kawaz et al.), individual predictors of mortality in ICH (Gao B. et al.; Sun et al.), and Subarachnoidal hemorrhage (Yang et al.; He et al.), the impact of atrial fibrillation Wu et al. and prolonged QT interval Ahn et al. on clinical outcomes in AIS patients, as well as other reports of original research showcasing the diversity in critical care by Mazza et al. and Nguyen et al.

The publications in this fascinating Research Topic have highlighted its multifaceted nature and comprise molecular and biological mechanisms, epidemiology, reviews of current literature of hot topics in the field of stroke care, outcome prediction, and prognostication and communication to name a few. The publications also point out areas for further research. This Research Topic highlights that *Critical Care After Stroke* poses substantial clinical challenges in a rapidly evolving area of stroke research.

AUTHOR CONTRIBUTIONS

RA drafted the manuscript. RF and S-BK contributed with conceptualization and editing of the final version. The final version was approved by all authors.

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BRIEF RESEARCH REPORT
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Early Laboratory Predictors for Necessity of Renal Replacement Therapy in Patients With Spontaneous Deep-Seated Intracerebral Hemorrhage

Lorena M. Schenk[1], Matthias Schneider[1], Christian Bode[2], Erdem Güresir[1], Christoph Junghanns[1], Marcus Müller[3], Christian Putensen[2], Hartmut Vatter[1], Julian Zimmermann[3], Patrick Schuss[1†] and Felix Lehmann[2*†]*

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Objective: The need for continuous renal replacement therapy (CRRT) in patients with deep-seated intracerebral hemorrhage (ICH) requires sustained intensive care and often postpones further rehabilitation therapy. Therefore, an early identification of patients at risk is essential.

Methods: From 2014 to 2019, all patients with deep-seated ICH who were admitted to intensive care for >3 days were included in the further analysis and retrospectively reviewed for the need for CRRT. All patients underwent CRRT with regional citrate anticoagulation for continuous veno-venous hemodialysis (CVVHD). Outcome was evaluated after 3 months using the modified Rankin scale. A multivariate analysis was performed to identify potential predictors for CRRT in patients with deep-seated ICH.

Results: After applying the inclusion criteria, a total of 87 patients with deep-seated spontaneous ICH were identified and further analyzed. During the first 48 h after admission, 21 of these patients developed early acute kidney injury (AKI; 24%). During treatment course, CRRT became necessary in nine patients suffering from deep-seated ICH (10%). The multivariate analysis revealed "development of AKI during the first 48 h" [$p = 0.025$, odds ratio (OR) 6.1, 95% confidence interval (CI) 1.3–29.8] and "admission procalcitonin (PCT) value >0.5 μg/l" ($p = 0.02$, OR 7.7, 95% CI 1.4–43.3) as independent and significant predictors for CRRT in patients with deep-seated ICH.

Conclusions: Elevated serum levels of procalcitonin on admission as well as early development of acute renal injury are independent predictors of the need for renal replacement therapy in patients with deep-seated intracerebral bleeding. Therefore, further research is warranted to identify these vulnerable patients as early as possible to enable adequate treatment.

Keywords: intracerebral hemorrhage, renal replacement therapy, acute kidney injury, procalcitonin, critical care (ICU)

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INTRODUCTION

Acute renal injury (AKI) is a frequent and devastating complication with high morbidity and mortality in patients requiring treatment in an intensive care unit (ICU). Previous studies have reported an incidence of AKI up to 67% depending on the definition of AKI and the underlying cause of ICU admission (1, 2). With regard to neurological diseases, the presence of chronic kidney disease (CKD) in patients with acute stroke (ischemic/hemorrhagic) was identified as a strong independent predictor for both mortality and adverse outcomes (3). Both the increased appearance of atherosclerotic alterations and a less effective dynamic cerebral autoregulation in acute stroke were discussed as potential explanations for this correlation (3, 4). Furthermore, mortality increases dramatically with growing severity of AKI, resulting in patients with the need for continuous renal replacement therapy (CRRT) accounting for the highest mortality (1).

However, much of the data on the kidney–brain interaction focuses on patients with ischemic or undifferentiated stroke (5). Intracerebral hemorrhage (ICH) constitutes a major hemorrhagic manifestation of acute stroke (6). Regarding ICH, further evaluation of the INTERACT2 data has revealed a prognostic value for decreased estimated glomerular filtration rate (eGFR) at admission (5). Initial lowering of systolic blood pressure is an important therapeutic intervention in the treatment of ICH to prevent further hematoma expansion (7). Especially in border-compensated patients, deterioration of renal function in the acute situation (e.g., due to aggressive blood pressure management) might accelerate the development of AKI (8). In addition, the need for CRRT in patients with ICH requires continued intensive care treatment and often results in further postponement of a potential rehabilitation therapy. This highlights the need for early identification and treatment of these particularly endangered patients.

Therefore, the aim of the present study was to investigate both the incidence and the influence of needed CRRT on mortality in a selected cohort of neurocritically ill patients with deep-seated ICH. Furthermore, we attempted to identify risk factors for the necessity of CRRT in this specific subpopulation of critically ill patients with ICH.

MATERIALS AND METHODS

Patients

Medical records of patients treated for deep-seated spontaneous intracerebral hemorrhage between 2014 and 2019 at the Neurosurgical Department of the University Hospital Bonn, Germany, were retrospectively reviewed. Patients were identified using the ICD coding system and verified as eligible for study inclusion by three authors (LMS, PS, and FL). Hemorrhages originating from the area of the basal ganglia and/or thalamus were classified as deep-seated ICH. All patients with supratentorial deep-seated ICH who developed AKI with or without CRRT during the course of treatment were included in the further analysis after approval of the local IRB. Patients with lobar ICH and/or ICH with underlying bleeding source (e.g., aneurysm, arteriovenous malformation, and trauma) were excluded from this study. In addition, all patients in whom no further treatment or treatment for <3 days in intensive care was initiated due to the devastating clinical situation and/or an existing patient wish for withdrawal of life-sustaining treatment were excluded from further analysis. Information collected for each patient included general characteristics, ICH location, ICH volume (9), ICH score (10), parameters of intensive care and laboratory, necessity of surgical intervention, need for hyperosmolar therapy, occurrence of AKI, necessity of CRRT, neurological status at admission, 3-month outcome/mortality, and treatment strategies during hospitalization. Initial systolic blood pressure (SBP) was categorized into mild (<180 mmHg), moderate (180–219 mmHg), and severe (≥220 mmHg), as previously described (11). In addition, all patients with infratentorial localization of ICH were excluded from further analysis. In the case of extensive space-occupying hemorrhage, the affected patients were assigned by two authors (LMS and FL) to either the lobar or deep-seated group, depending on probability and image morphologic findings. If any disagreement occurred regarding the classification between these two authors, it was resolved in a consensus meeting with the senior neurosurgical author (PS).

All patients suffering from deep-seated ICH received the best medical treatment according to the hospital's in-house standard operating procedures, which comply with the guidelines of the American Heart Association/American Stroke Association (12).

Modified Rankin scale (mRS) was applied to assess functional outcome. Patients were dichotomized according to mRS into two groups: (1) favorable outcome (mRS 0–4) versus (vs.) (2) unfavorable outcome (mRS 5–6), as defined in previous studies (13, 14).

In order to assess renal function, the daily serum creatinine (SCr) was assessed over the first 3 days after admission as defined in a previous study (8). Early onset of AKI was defined and graded according to the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines: a minimum increase in SCr of either ≥0.3 mg/dl or >150% of baseline SCr during the first 48 h after admission (15). Urinary output was not considered for definition or staging of the AKI in the present study due to limited data. The decision to initiate CRRT was made by intensive care physician/neurosurgeon according to the current international and national guidelines (16–18). CRRT was performed using regional citrate anticoagulation for continuous veno-venous hemodialysis (CVVHD) in all patients included in the present analysis. All patients were observed for at least 3 months and were divided into two groups according to the presence or absence of CRRT for further analysis.

Statistics

Data analyses were performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY). Mann–Whitney test was used for nonparametric statistics after testing for normal distribution. Categorical variables were analyzed in contingency tables using Fisher's exact test. Results with $p < 0.05$ were considered statistically significant. In addition, in order to determine independent predictors of the necessity of

TABLE 1 | Baseline patient characteristics.

	Non-CRRT ($n = 78$)	CRRT ($n = 9$)	
Age (mean ± SD, years)	64 ± 14	60 ± 11	$p = 0.41$
Female gender	27 (35%)	3 (33%)	$p = 0.63$
GCS >12 at admission	28 (36%)	2 (22%)	$p = 0.33$
GCS <8 at admission	24 (31%)	4 (44%)	$p = 0.32$
ICH volume (abc/2, mean ± SD)	47.1 ± 42.3	54.5 ± 33.6	$p = 0.61$
Presence of IVH	48 (61%)	7 (78%)	$p = 0.29$
ICH score ≥3 at admission	32 (41%)	6 (67%)	$p = 0.13$
Initial SBP (mmHg)			
Mild (<180)	51 (65%)	6 (67%)	$p = 1.0$
Moderate (180–219)	18 (23%)	2 (22%)	$p = 1.0$
Severe (≥220)	9 (12%)	1 (11%)	$p = 1.0$
Hyperosmolar therapy	9 (12%)	1 (11%)	$p = 0.73$
Early AKI (≤48 h after admission)	15 (19%)	6 (67%)	$p = 0.005$, OR 8.4, 95% CI 1.9–37.5
Surgical treatment through treatment course	18 (23%)	4 (44%)	$p = 0.16$
Baseline SOFA score (mean ± SD)	4 ± 3	6 ± 2	$p = 0.072$
Baseline SAPS score (mean ± SD)	40 ± 17	48 ± 13	$p = 0.15$
Baseline SCr (mean ± SD, mg/dl)	0.99 ± 0.78	1.60 ± 0.77	$p = 0.03$, 95% CI 0.07–1.2
Baseline CRP (mean ± SD, mg/l)	15.7 ± 33.9	31.9 ± 55.2	$p = 0.21$
Baseline PCT (mean ± SD, μg/l)	0.20 ± 0.45	1.11 ± 1.79	$p = 0.0004$, 95% CI 0.4–1.4
Baseline WBC (mean ± SD, g/l)	11.06 ± 4.40	13.26 ± 7.09	$p = 0.19$
Baseline Glc (mean ± SD, mg/dl)	146 ± 69	151 ± 63	$p = 0.84$
Length of hospital stay (days)	20 ± 16	73 ± 79	$p < 0.0001$, 95% CI 33.7–72.3
90-day mortality	30 (39%)	7 (78%)	$p = 0.03$, OR 5.6, 95% CI 1.09–28.8

CRRT, continuous renal replacement therapy; SD, standard deviation; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SBP, systolic blood pressure; AKI, acute kidney injury; SOFA, sepsis-related organ failure; SAPS, simplified acute physiology; SCr, serum creatinine; CRP, c-reactive protein; PCT, procalcitonin; WBC, white blood cells; Glc, glucose; mRS, modified Rankin scale.

CRRT during treatment course in patients with deep-seated ICH, a multivariate analysis using binary logistic regression was performed. Variables with significant *p*-values in the univariate analysis, as well as variables that were considered meaningful in the clinical context, were considered potentially independent variables in a multivariate analysis. A backward stepwise method was used to construct a multivariate logistic regression model in relation to the CRRT as a dependent variable with an inclusion criterion of a p-value <0.05.

RESULTS

Patient Characteristics

Overall, 87 patients suffering from deep-seated spontaneous ICH were identified and further analyzed. Initial SBP was mild (<180 mmHg) in 61 patients (65%), moderate (180–219 mmHg) in 23 patients (25%), and severe (≥220 mmHg) in 10 patients (10%). During the first 48 h after admission, 21 of these patients developed early AKI (24%). Of these patients, 18 patients had early AKI stage 1 (86%), two patients with early AKI stage 2 (10%), and one patient with early AKI stage 3 (4%). During treatment course, CRRT became necessary in nine patients suffering from deep-seated ICH (10%). CRRT was required on median day 9 (range 1–22) after admission. Neither required surgical intervention due to the space-occupying effect of deep-seated ICH nor the administration of hyperosmolar therapy as part of intracranial pressure treatment was found to have a significant effect on the need for CRRT ($p = 0.73$; $p = 0.16$). Further baseline characteristics of the present study cohort are given in **Table 1**.

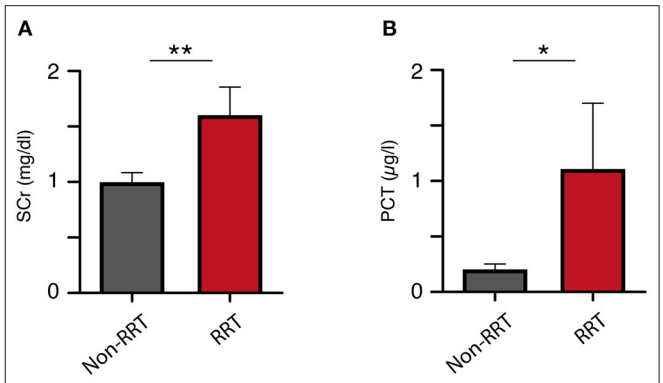

FIGURE 1 | Initial **(A)** serum creatinine and **(B)** procalcitonin levels correlate to the rate of renal replacement therapy. *$p = 0.024$; **$p = 0.009$.

Influence of Admission Laboratory Results

Mean serum concentrations of creatinine as well as procalcitonin (PCT) were significantly higher in the group with subsequent CRRT at the time of ICU admission (**Table 1**). ICH patients without CRRT during treatment course presented with a mean admission SCr concentration of 0.99 ± 0.78 mg/dl compared to 1.60 ± 0.77 in ICH patients with subsequent CRRT ($p = 0.009$; **Figure 1A**). Furthermore, patients with CRRT during treatment course presented with a significantly higher mean PCT concentration (1.11 ± 1.79 μg/l) compared to patients without CRRT [0.20 ± 0.45 μg/l; $p = 0.024$ 95% confidence interval (CI) 0.4–1.4; **Figure 1B**]. Mean CRP laboratory value, mean WBC count, as well as mean glucose concentration at admission did not differ significantly between patients with and without CRRT.

Outcome

Overall, mortality rate after 3 months was 43%. Mortality rates differed significantly between patients with and without CRRT (78 vs. 39%; $p = 0.03$). Patients with deep-seated ICH and subsequent CRRT remained significantly longer hospitalized compared to ICH patients without CRRT ($p < 0.0001$, 95% CI 33.7–72.3). In addition, patients with deep-seated ICH and subsequent CRRT achieved significantly less often favorable

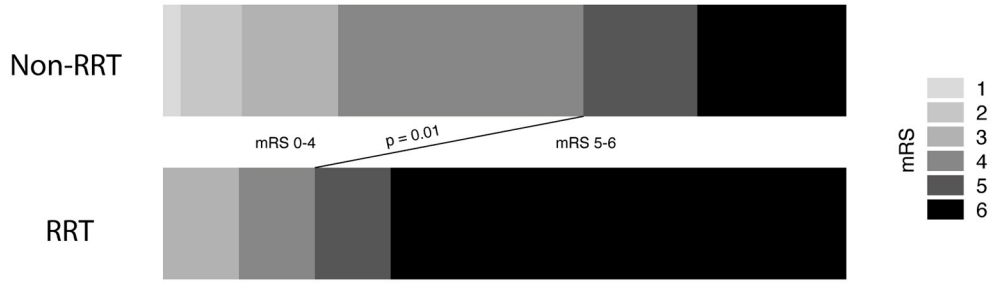

FIGURE 2 | Necessity of renal replacement therapy correlates to unfavorable outcome in intracerebral hemorrhage disease.

outcome assessed at the 3 months follow-up examination compared to patients without the necessity of CRRT [22 vs. 62%; $p = 0.03$, odds ratio (OR) 5.6, 95% CI 1.09–28.8; **Table 1**, **Figure 2**].

Multivariate Analysis

We performed a multivariate regression analysis to identify independent predictors for the necessity of CRRT during the treatment course of patients suffering from deep-seated ICH. Herein, "development of AKI during the first 48 h" ($p = 0.025$, OR 6.1, 95% CI 1.3–29.8) and "admission PCT value >0.5 μg/l" ($p = 0.02$, OR 7.7, 95% CI 1.4–43.3) were identified as the only independent and significant predictors for CRRT in patients with deep-seated ICH (Nagelkerke's $R^2 = 0.295$; **Table 2**).

TABLE 2 | Multivariate logistic regression analysis of independent factors related to necessity of renal replacement therapy in patients with deep-seated ICH.

Factors	Adjusted OR	95% CI	*p*-value
Age ≥65 years	2.3	0.3–20.7	0.4
Presence of IVH	0.7	0.09–4.8	0.7
Hyperosmolar therapy	0.8	0.06–11.9	0.9
Early AKI (within 48 h)	**6.1**	**1.3–29.8**	**0.025**
Baseline CRP >3 mg/l	2.5	0.2–26.6	0.5
Baseline PCT >0.5 μg/l	**7.7**	**1.4–43.3**	**0.02**
Baseline SCr >1.2 mg/dl	0.4	0.04–2.9	0.3
Baseline WBC >12 g/l	0.3	0.05–1.6	0.1

ICH, intracranial hemorrhage; OR, odds ratio; CI, confidence interval; IVH, intraventricular hemorrhage; AKI, acute kidney injury; CRP, C-reactive protein; PCT, procalcitonin; SCr, serum creatinine; WBC, white blood cell. The significant values of the multivariate analysis are shown in bold.

DISCUSSION

In general, AKI occurs in approximately 10–15% of patients admitted to the hospital, whereas its incidence in the ICU has been reported in more than 50% of patients (19). In neurological patients, AKI appears to be somewhat less common. In a *post-hoc* analysis of pooled data from randomized clinical trials of acute ischemic stroke, AKI was diagnosed in 3.5% of patients (20). The present study reveals a considerable prevalence of early AKI in patients with deep-seated ICH, namely, 24%. Furthermore, this single-center series provides descriptive analysis and identifies predictors regarding the need for CRRT, which are easily available at an early stage in the treatment of patients with deep-seated ICH. The present multivariate regression analysis indicates that an increased baseline PCT laboratory value at time of admission and the development of AKI during the first 48 h of hospital treatment are independent and significant predictors of the development of renal failure with subsequent CRRT over the course of treatment in patients with deep-seated ICH.

Acute renal failure often occurs during the treatment of critically ill patients who subsequently require some form of RRT. However, patients with ICH represent a distinct patient population that merits special attention when planning RRT (21). The main focus of treatment is the prevention of secondary brain damage by maintaining adequate cerebral blood flow (CBF) by controlling cerebral perfusion pressure (CPP) and intracranial pressure (ICP). These treatment goals could be seriously affected by RRT. Thus, patients with ICH are extremely sensitive to osmotic gradients/shifts, and even minor changes might lead to exacerbation of brain edema/ICP. In the present study, patients with deep-seated ICH and CRRT achieved significantly worse functional outcome. In addition to the criticism regarding the definition of favorable outcome in studies investigating destructive pathologies in high-eloquent cerebral areas, patients requiring CRRT are considerably longer confined to an appropriate intensive care unit. Furthermore, immobilization is likely to result from intensified apparatus medicine (herein: CRRT) in addition to the initial impairment due to hemorrhage (22).

A previous meta-analysis revealed that AKI is a frequent complication with a prevalence of 19% in patients with ICH, although the nonsignificant influence of AKI on mortality in ICH may be due to lack of studies on this topic (23). The authors included only two studies reporting prevalence and mortality of AKI in patients after ICH. Many clinical studies investigating ICH seem to exclude patients with AKI due to its identification as a potential outcome modifier (23).

In the present study, increased serum procalcitonin at the time of admission was an additional significant predictor of the necessity of CRRT during the course of treatment in patients with deep-seated ICH ($p = 0.02$). PCT is a widely available specific biomarker for bacterial infections and has additional benefits that make it a serially used diagnostic marker in intensive

care medicine (24, 25). While much has been reported on PCT tests for diagnosing infectious diseases, relatively little attention has been paid to its potential role in the diagnosis and treatment of non-infectious diseases (26). Nevertheless, a recent retrospective study found a significant association between increased serum PCT at hospital admission and the subsequent development of AKI in critically ill, non-septic patients (27). This association could be supported by the assumption that a decrease in renal function (whether acute or chronic) might lead to increased serum concentrations of proinflammatory metabolites (28). Thus, the latter would stimulate the immune system, which in turn could result in an aggravated inflammatory response and thus an increased release of PCT into the circulation (28, 29). Regarding ICH, a prospective cohort study in patients with primary ICH indicated an association between serum PCT levels and clinical outcome (30). Another study on the influence of elevated PCT levels in patients with clinically and radiologically severe aneurysmatic subarachnoid hemorrhage assumed that these patients suffered more severely from cerebral circulatory disturbance at the time of bleeding (31). Thus, the PCT values probably reflect an acute systemic stress response to the bleeding (31). Another consideration might be an early depiction of aspiration pneumonia in comatose patients with ICH given the elevated PCT levels at admission (32). An important finding regarding the applicability of PCT beyond the identification of infections is that PCT values are higher in patients with impaired renal function and that hemodialysis values can decrease by up to 80% (26, 29).

Limitations

The present study has several limitations. Statistical analysis and data collection were done retrospectively, of which the available data represent only a single-center experience. Furthermore, only patients with deep-seated ICH as well as patients who were in stationary care for a certain period of time were assessed and further analyzed. This might result in a significant level of selection bias. However, this high level of selection is also considered a strength of the present study, as certain influencing factors (underlying pathologies, therapy limitation due to patient desire/disastrous condition) can therefore be excluded. Nevertheless, future studies should focus even more on developing advanced predictive models for the forecast of these intensive care complications in patients with ICH to enable treating physicians to further optimize/adapt the treatment and counseling of patients/family members.

CONCLUSIONS

The present study identifies elevated serum levels of procalcitonin at admission, as well as an early development of acute kidney injury, as independent predictors of the necessity of renal replacement therapy in patients with deep-seated intracerebral bleeding. Therefore, further research is warranted to identify these critically ill and additionally endangered patients as early as possible in order to provide adequate treatment.

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 human participants were reviewed and approved by Ethics committee, University Hospital Bonn. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PS and FL conceptualized the study. MS, PS, and FL were responsible for the methodology. LS, MS, PS, and FL performed data collection. LS, PS, and FL were responsible for the statistics and wrote the original draft. MS and PS were responsible for the figures. PS and FL supervised the study. All authors contributed to the article and approved the submitted version.

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Admission Dehydration Is Associated With Significantly Lower In-Hospital Mortality After Intracerebral Hemorrhage

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Background and Purpose: Our aim was to investigate the frequency of dehydration at admission and associations with in-hospital mortality in patients with intracerebral hemorrhage (ICH).

Methods: Data of consecutive patients with ICH between August 2015 and July 2019 from the China Stroke Center Alliance (CSCA) registry were analyzed. The patients were stratified based on the blood urea nitrogen (BUN) to creatinine (CR) ratio (BUN/CR) on admission into dehydrated (BUN/CR $\geq$ 15) or non-dehydrated (BUN/CR $<$ 15) groups. Data were analyzed with multivariate logistic regression models to investigate admission dehydration status and the risks of death at hospital.

Results: A total number of 84,043 patients with ICH were included in the study. The median age of patients on admission was 63.0 years, and 37.5% of them were women. Based on the baseline BUN/CR, 59,153 (70.4%) patients were classified into dehydration group. Patients with admission dehydration (BUN/CR $\geq$ 15) had 13% lower risks of in-hospital mortality than those without dehydration (BUN/CR $<$ 15, adjusted OR = 0.87, 95%CI 0.78–0.96). In patients aged $<$ 65 years, admission dehydration was associated with 19% lower risks of in-hospital mortality (adjusted OR = 0.81, 95%CI 0.70–0.94. adjusted $p = 0.0049$) than non-dehydrated patients.

Conclusion: Admission dehydration is associated with significantly lower in-hospital mortality after ICH, in particular, in patients <65 years old.

Keywords: intracranial hemorrhage, dehydration, mortality, blood urea nitrogen, creatinine

INTRODUCTION

Stroke was the second leading cause of deaths and disability globally in 2017, and acute intracerebral hemorrhage (ICH) accounted for 26% of all strokes (1). Dehydration is common and associated with poor outcomes in ischemic stroke (2–4). Correlation between admission dehydration and mortality of ICH during hospitalization remains unclear. The ratio of blood urea nitrogen/creatinine (BUN/CR) $\geq$ 15 was considered as ideal biomarker of dehydration,

especially in patients with normal kidney function (3–5). We aimed to investigate the relationship between admission dehydration and in-hospital mortality in a large ICH cohort from a multicenter prospective registry.

METHODS

Data Availability

Data are available to researchers on request for the purpose of reproducing the results or replicating the procedure by directly contacting the corresponding authors.

China Stroke Center Alliance Registry

This study was approved by the Human Studies Institutional Review Board of Beijing Tiantan hospital. The data of patients were prospectively collected and retrospectively analyzed from the China Stroke Center Alliance (CSCA) registry. The CSCA is a national, multicenter, hospital-based, voluntary, multifaceted intervention and continuous quality improvement (QI) initiative. This multifaceted intervention includes stroke center development, written care protocols, workshops, and a monitoring and feedback system of evidence-based performance measures. The data coordinating center of the CSCA resides at the China National Clinical Research Center for Neurological Diseases and Beijing Tiantan Hospital. The CSCA registry enrolled 1,006,798 patients diagnosed as acute ischemic stroke (AIS), transient ischemic attack (TIA), ICH, or subarachnoid hemorrhage from August 1, 2015, to July 31, 2019. Patients > 18 years of age were enrolled within 7 days of symptom onset. The CSCA registry collects data through an internet-based tool (Medicine Innovation Research Center, Beijing, China). Only in-hospital data were recorded, as follow-up data were not available. All participating hospitals in the CSCA were approved to collect data without requiring individual patient informed consent under the common rule or a waiver of authorization and exemption from their institutional review board (6). The study was performed according to the principles included in the Declaration of Helsinki.

Patient Recruitment and Data Collection

Between August 2015 and July 2019, 85,705 patients with acute ICH were enrolled in the CSCA registry, and 1,662 of them were excluded for the study due to missing BUN or CR data. Therefore, 84,043 patients diagnosed with ICH were included for our study (**Figure 1**). ICH was diagnosed according to the World Health Organization criteria combined with imaging data by doctors in local hospital (7).

The patients were divided into dehydrated and non-dehydrated groups according to the ratio of BUN (mg/dL)/CR (mg/dl). BUN/CR $\geq$ 15 was defined as the dehydrated group, and BUN/CR < 15 was defined as the non-dehydrated group according to previous reports (3–5, 8).

Abbreviations: ICH, intracerebral hemorrhage; BUN, blood urea nitrogen; CR, creatinine; BUN/CR, the ratio of blood urea nitrogen to creatinine; CSCA, China Stroke Center Alliance; eGFR, estimated glomerular filtration rate; OR, odds ratios; CI, confidence interval; IQR, interquartile range.

Demographic data, stroke risk factors, and medical history, including age, sex, previous history of intracranial hemorrhage, hypertension, liver insufficiency or kidney insufficiency, current smoking and drinking, the use of antiplatelet, anticoagulation, antihypertensive, or diabetic medication, were abstracted from the registry. Laboratory test results, including fasting blood glucose, homocysteine, and admission BUN and CR levels were also extracted (**Table 1**).

All laboratory data were the initial test results at admission. Estimated glomerular filtration rate (eGFR) were calculated by a modified four-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula with an adjusted coefficient of 1.1 for the Chinese population to estimate eGFR (9): $eGFR_{CKD-EPI} = 141 \times \min(CR/\kappa,1)^{\alpha} \times \max(CR/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times$ 1.1, where CR was creatinine, κ was 0.7 for females and 0.9 for males, α was -0.329 for females and -0.411 for males, min was the minimum of CR/κ or 1, and max indicated the maximum of CR/κ or 1. In-hospital mortality was collected as primary outcome, which was defined as all-cause death during hospitalization. In the CSCA registry, all variables and data were locally collected or adjudicated by doctors at each site.

Statistical Analysis

Categorical variables were reported as absolute numbers with percentages, and continuous variables were reported as median along with interquartile range (IQR). We analyzed the differences in baseline characteristics between the two groups. An absolute standardized difference (ASD) of >10% indicates significant differences in the variable between two groups (10). We used ASD > 10% in univariate analysis to select out covariables that need to be adjusted for in the multivariable regression model. Covariates associated with outcomes reported in the medical literature, even if ASD < 10%, were also included in the multivariable regression model. For dichotomous outcomes, we used hierarchical binary logistic regression to determine adjusted odds ratios (aORs) and 95% confidence intervals (CIs) after median imputation of missing data (11). Missing data were minimal ($\geq$98% complete) with the exceptions of fast blood glucose (missing in 1.2%) and homocysteine (15%). We performed group analysis for the association of BUN/CR with in-hospital mortality according to age (<65 or $\geq$65 years), sex, medical histories, smoking status, drinking, and renal function based on eGFR ($\leq$60 or >60 mL/min/1.73 m^2). All tests were two-sided, and p-value <0.05 was considered statistically significant. Interaction terms were retained only when the interaction p-value was <0.05. All statistical analyses were performed using SAS Version 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

In this large cohort study, 84,043 patients met the inclusion criteria. The median age of the patients was 63.0 years (53.0–72.0), and 37.5% of the patients were women. Among these patients, 59,153 (70.4%) were classified into the dehydration group (BUN/CR $\geq$ 15) and 24,890 (29.6%) into the non-dehydrated group (BUN/CR < 15) (**Figure 1**). **Table 1** shows

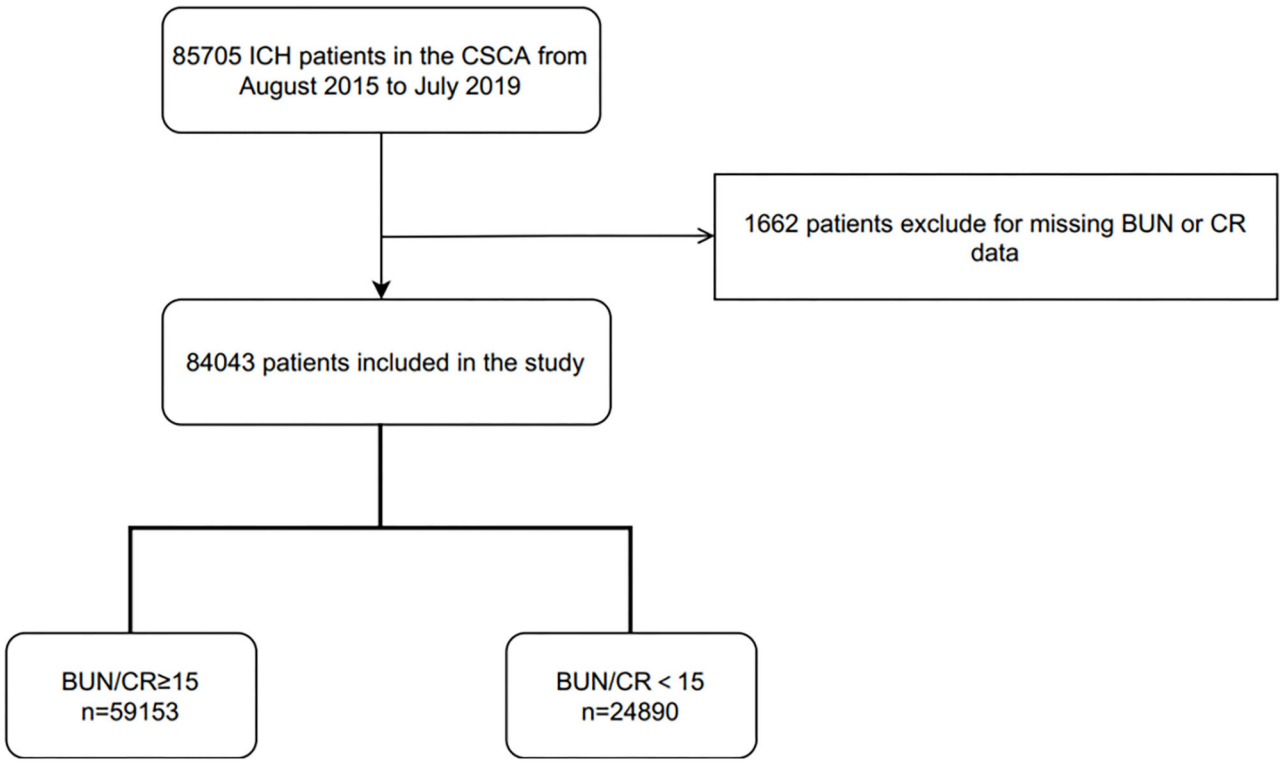

FIGURE 1 | Patient flowchart. CSCA, China Stroke Center Alliance; BUN, blood urea nitrogen; CR, creatinine; BUN/CR, the ratio of blood urea nitrogen to creatinine.

clinical profiles of the two groups according to hydration status at admission. Patients with dehydration at admission were older (median age, 64.0 [IQR, 54.0–73.0] vs. 61.0 [IQR, 51.0–70.0]). They were also more likely to have a history of smoking, alcohol consumption, or liver/renal insufficiency and higher homocysteine level.

The in-hospital mortality of the entire study cohort was 2.3% (1,915/84,043). It was significantly lower in the dehydration group than in the non-dehydration group (2.2% vs. 2.5%, unadjusted OR 0.86, 95%CI 0.78–0.95, $p = 0.0029$) (**Table 2**). Admission dehydration was associated with 13% lower in-hospital mortality after adjusting for confounders (adjusted OR = 0.87, 95%CI 0.78–0.96, $p = 0.0050$).

There was an interaction between age and BUN/CR ratio on the in-hospital mortality ($p = 0.0211$) (**Table 2**). In subgroup analysis, the dehydration group was associated with significantly lower in-hospital mortality than the non-dehydration group only in patients <65 years old (1.61 vs. 2.2%, $p < 0.0001$). There was 19% lower risk of in-hospital mortality in the dehydration group (adjusted OR = 0.81, 95%CI 0.70–0.94, $p = 0.0049$). Of note, there was no difference in in-hospital mortality between the two groups in patients aged 65 or older (2.79 vs. 2.98%, $p < 0.3094$).

Further analyses of the interaction effects of sex, hypertension, diabetes, current smoking, drinking, and renal function on the association between dehydration and in-hospital mortality of patients with ICH showed that none of those interaction factors had a significant effect on the association (all of them $p > 0.05$), although the OR values for some subgroups were significant (**Table 2**).

DISCUSSION

Our study provided evidence that admission dehydration was associated with 13% lower risk of in-hospital mortality in ICH patients (adjusted OR = 0.87, 95%CI 0.78–0.96, $p = 0.0050$). Most importantly, subgroup analysis showed that admission dehydration was associated with 19% lower risk of all-cause death in hospital in patients <65 years old (adjusted OR = 0.81, 95%CI 0.70–0.94, $p = 0.0049$).

Although dehydration is a risk factor of early neurological deterioration (END) after AIS (12–14), the effect of dehydration on outcome after ICH remains unclear.

To the best of our knowledge, only one previous study focused on the relationship between admission dehydration based on the ratio of BUN/CR ≥ 15 and the prognosis of hemorrhagic stroke, and there was no difference on discharge outcomes including modified Rankin scale (mRS) and Barthel index (BI) between dehydrated (BUN/CR ≥ 15) and non-dehydrated (BUN/CR < 15) groups (3).

Different from AIS, ICH may cause immediate elevation of intracranial pressure, mass effect, and impending herniation at initial presentation. Admission dehydration might be associated with lower mass effect and herniation following ICH than the non-dehydrated cohort. We analyzed data from a large

TABLE 1 | Baseline characteristics of stroke patients according to dehydration status based on the ratio of BUN/CR.

Variables*	BUN/CR ≥ 15 (*n* = 59,153 [70.4%])	BUN/CR < 15 (*n* = 24,890 [29.6%])	ASD, %,†
Age, years, median (IQR)	64.0 (54.0–73.0)	61.0 (51.0–70.0)	23.9
Men, *n* (%)	34,065 (57.6)	18,426 (74.0)	35.1
BMI, kg/m^2, median (IQR)	23.5 (21.6–25.4)	23.6 (21.8–25.4)	2.1
Medical history, *n* (%)			
TIA	330 (0.6)	167 (0.7)	1.2
Cerebral infarction	7,875 (13.3)	3,080 (12.4)	2.7
SAH	339 (0.6)	117 (0.5)	1.4
ICH	10,101 (17.1)	4,575 (18.4)	3.4
Current smokers	10,638 (18.0)	5,905 (23.7)	14.1
Alcohol Consuming	13,112 (22.2)	7,446 (29.9)	17.6
Liver/renal insufficiency	478 (0.8)	768 (3.1)	16.7
Hypertension	42,081 (71.1)	17,843 (71.7)	1.3
Dyslipidemia	2,440 (4.1)	1,156 (4.6)	2.5
Atrial fibrillation	941 (1.6)	357 (1.4)	1.6
Peripheral vascular disorder	533 (0.9)	277 (1.1)	2.0
Carotid artery stenosis	213 (0.4)	93 (0.4)	0.0
Dementia	257 (0.4)	80 (0.3)	1.7
Mental disorder	251 (0.4)	70 (0.3)	1.7
Medication history, *n* (%)			
Antihypertensive	27,868 (47.1)	11,731 (47.1)	0.0
Diabetic medication	4,252 (7.2)	1,596 (6.4)	3.2
Antiplatelet	4,130 (7.0)	1,678 (6.7)	1.2
Anticoagulation	1,018 (1.7)	531 (2.1)	2.9
Cholesterol-lowering medication	3,373 (5.7)	1,517 (6.1)	1.7
Lab test results			
Homocysteine, mmol/L, median (IQR)	12.8 (9.5–17.8)	13.7 (10.0–19.4)	12.3
Fasting blood glucose, μmol/L, median (IQR)	5.9 (5.2–7.2)	5.7 (5.0–6.9)	7.0
Glycated hemoglobin, %, median (IQR)	5.6 (5.2–6.0)	5.6 (5.1–6.0)	0.0
Platelets, *10^9/L, median (IQR)	199.0 (155.0–244.0)	200.0 (156.0–245.0)	0.6

ICH, intracranial hemorrhage; IQR, interquartile range; BMI, body mass index; TIA, transient ischemic attacks; SAH, subarachnoid hemorrhage.

**Continuous variables were presented as median (interquartile range), and category variables were presented as counts (percentages).*

†An absolute standardized difference (ASD) of >10% indicates significant differences in the variable between two groups.

multicenter prospective registry to investigate admission dehydration and in-hospital mortality after ICH. We found that admission dehydration was associated with significantly lower in-hospital mortality, in particular, in patients <65 years old. The mechanisms of the effect are unclear. There are a few possibilities: (1) dehydration is known to increase blood viscosity and to decrease blood pressure and cerebral perfusion (4, 15), leading to reduced hematoma growth and good in-hospital outcome (16, 17). (2) Dehydration-related hypovolemia and hypernatremia may increase intravascular osmolality and reduce perihematomal edema and intracranial pressure (18–22).

This large cohort study has provided sufficient statistical power to ensure the robustness of the findings. However, our study has a few limitations. First, BUN/CR ratio is not a reliable biomarker of dehydration, in particular, in patients with congestive heart failure, gastrointestinal bleeding, or urinary tract obstruction. We were unable to exclude patients with these confounding conditions. Second, imaging data were unavailable, so it was uncertain whether the effect of BUN/CR on mortality is related to the size or location of the hematoma. Third, ICH severity on admission was not collected in our study. Last, the management of dehydration after admission was unknown. The relative benefit of admission dehydration vs. persistent dehydration remains unclear.

CONCLUSIONS

This multicenter, large-scale prospective cohort study demonstrates the predictive value of initial hydration status on in-hospital mortality after ICH. An additional study combined with more biomarkers of dehydration, imaging data,

TABLE 2 | Associations between dehydration status and in-hospital mortality and subgroup analysis.

Group	No. of patients	No. of death/total patients (%)		Unadjusted			Adjusted **		
		BUN/CR < 15* $n = 24,890$	BUN/CR ≥ 15 $n = 59,153$	OR (95%CI)	*p*-value	Interaction *p*	OR (95%CI)	*p*-value	Interaction *p*
Overall	84,043	626/24,890 (2.5)	1,289/59,153 (2.2)	0.86 (0.78–0.95)	0.0029, †	/	0.87 (0.78–0.96)	0.0050, †	/
Age									
≥65 years	38,630	296/9,922 (2.98)	800/28,708 (2.7)	0.93 0.81–1.07)	0.3094	0.011	0.97 (0.84–1.12)	0.6758	0.0211
<65 years	45,413	330/14,968 (2.20)	489/30,445 (1.61)	0.72 (0.63–0.83)	<0.0001, †		0.81 (0.7–0.94)	0.0049, †	
Sex									
Male	52,491	467/18,426 (2.53)	777/34,065 (2.28)	0.90 (0.80–1.01)	0.0685	0.448	0.89 (0.79–1.00)	0.0467, †	0.8855
Female	31,552	159/6,464 (2.46)	512/25,088 (2.04)	0.83 (0.69–0.99)	0.0376, †		0.83 (0.69–1.01)	0.0580	
Hypertension									
Yes	59,924	454/17,843 (2.54)	911/42,081 (2.16)	0.85 (0.76–0.95)	0.0044, †	0.55	0.85 (0.76–0.96)	0.009, †	0.4475
No	24,119	172/7,047 (2.44)	378/17,072 (2.21)	0.91 (0.75–1.09)	0.2838		0.89 (0.73–1.07)	0.2175	
Diabetic									
Yes	8,005	100/2,205 (4.54)	203/5,800 (3.50)	0.76 (0.60–0.97)	0.0305, †	0.312	0.74 (0.57–0.95)	0.0202, †	0.4352
No	76,038	526/22,685 (2.32)	1,086/53,353 (2.04)	0.88 (0.79–0.97)	0.0132, †		0.90 (0.81–1.01)	0.0618	
Current smoker									
Yes	16,543	125/5,905 (2.12)	211/10,638 (1.98)	0.94 (0.75–1.17)	0.5601	0.385	0.91 (0.73–1.15)	0.4318	0.9158
No	67,500	501/18,985 (2.64)	1,078/48,515 (2.22)	0.84 (0.75–0.93)	0.0139, †		0.86 (0.77–0.96)	0.0077, †	
Alcohol consumption									
Yes	20,558	197/7,446 (2.65)	310/13,112 (2.36)	0.89 (0.74–1.07)	0.2113	0.759	0.90 (0.75–1.08)	0.2559	0.974
No	63,485	429/17,444 (2.46)	979/46,041 (2.13)	0.86 (0.77–0.97)	0.0111, †		0.86 (0.76–0.97)	0.0136, †	
Chronic renal dysfunction, ‡									
Yes	8,792	355/6,001 (5.92)	171/279 (6.13)	1.04 (0.86–1.25)	0.6959	0.013	0.99 (0.81–1.21)	0.9373	0.067
No	75,251	271/18,889 (1.43)	1,118/56,362 (1.98)	1.39 (1.22–1.59)	<0.0001, †		1.22 (1.06–1.40)	0.0049, †	

OR, odds ratio; BUN/CR, the ratio of blood urea nitrogen to creatinine.

**As reference group.*

***Adjusted for age, male, current smokers, alcohol consuming, liver/renal insufficiency, medical history of intracranial hemorrhage (ICH), hypertension, antihypertensive, diabetic medication, antiplatelet, anticoagulation, homocysteine, and fasting blood glucose.*

†p-value < 0.05.

‡ Chronic renal dysfunction defined by estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2.

and long-term outcomes is warranted to investigate the effect of admission dehydration on survival after ICH, in particular, in young patient population.

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 human participants were reviewed and approved by Human Studies Institutional Review Board of Beijing Tiantan hospital. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

BG: designed the study and drafted the manuscript. HG, KK, JZ, QZ, and SL: major role in data acquisition and revised the manuscript for intellectual content. ZL and WY revised the manuscript for intellectual content. YW and XZ: designed and conceptualized the study, analyzed the data, and drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Recent Updates in Neurosurgical Interventions for Spontaneous Intracerebral Hemorrhage: Minimally Invasive Surgery to Improve Surgical Performance

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The efficacy and safety of surgical treatment for intracerebral hemorrhage (ICH) have long been subjects of investigation and debate. The recent results of the minimally invasive surgery plus alteplase for intracerebral hemorrhage evacuation (MISTIE) III trial demonstrated the safety of the procedure and a reduction in mortality compared to medical treatment. Although no improvement in functional outcomes was shown, the trial elucidated that benefits of intervention depend on surgical performance: a greater ICH reduction, defined as $\leq$15 mL end of treatment ICH volume or $\geq$70% volume reduction, correlated with significant functional improvement. Recent meta-analyses suggested the benefits of neurosurgical hematoma evacuation, especially when performed earlier and done using minimally invasive procedures. In MISTIE III, to confirm hemostasis and reduce the risk of rebleeding, the mean time from onset to surgery and treatment completion took 47 and 123 h, respectively. Theoretically, the earlier the hematoma is removed, the better the outcome. Therefore, a higher rate of hematoma reduction within an earlier time course may be beneficial. Neuroendoscopic surgery enables less invasive removal of ICH under direct visualization. Minimally invasive procedures have continued to evolve with the support of advanced guidance systems and devices in favor of better surgical performance. Ongoing randomized controlled trials utilizing emerging minimally invasive techniques, such as the Early Minimally Invasive Removal of Intra Cerebral Hemorrhage (ENRICH) trial, Minimally Invasive Endoscopic Surgical Treatment with Apollo/Artemis in Patients with Brain Hemorrhage (INVEST) trial, and the Dutch Intracerebral Hemorrhage Surgery Trial (DIST), may provide significant information on the optimal treatment for ICH.

Keywords: intracerebral hemorrhage, minimally invasive surgery, endoscopic surgery, stereotactic surgery, thrombolysis, surgical performance

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is the second most common but most devastating type of stroke (1). Although medical and surgical interventions have been developed for the condition, ICH remains a significant cause of death and mortality worldwide (2).

ICH leads to time-dependent progression of brain injury. The initial bleeding causes physical disruption of the cellular architecture of the brain. The hematoma mass can induce intracranial pressure elevation, leading to ischemia and brain herniation. Secondary injury after ICH could be caused by a cascade of events initiated by the primary injury; by the physiological response to the hematoma, such as inflammation; and by the release of clot components such as hemoglobin and iron (3). Theoretically, timely surgical intervention can be effective if a surgery-related brain injury is less severe than that caused by hematoma *per se*.

Consequently, surgery to reduce hematoma volume has been repeatedly evaluated in single-center studies and multicenter randomized controlled trials (RCTs). The International Surgical Trial in Intracerebral Hemorrhage (STICH) was designed to compare early surgery with initial conservative treatment for supratentorial ICH. In this study, 1,033 patients from 83 centers in 27 countries were randomized to receive either early surgery or initial conservative treatment. No significant difference was found in good outcomes between the surgical arm (26%) and the medical arm (24%). However, subgroup analysis suggested that surgery might benefit in patients with lobar hemorrhages within 1 cm of the cortical surface (4). Based on these findings, the STICH II trial was undertaken to assess the effectiveness of early surgery vs. medical management for patients with superficial lobar ICH of 10–100 mL without intraventricular hemorrhage. The rates of favorable outcomes were 41% and 38% in the surgical and medical arms, respectively, with no significant difference (5). However, the results of the STICH trials may not be generalizable because of the high rate of patients' crossover from the medical arm to the surgical arm. Additionally, comatose patients and patients at risk of cerebral herniation were excluded.

To date, surgery did not demonstrate a clear benefit compared to conservative treatment. According to the current guidelines, supratentorial hematoma evacuation might be considered as a life-saving measure, and decompression with or without evacuation might reduce mortality in comatose supratentorial ICH patients with large hematomas. Outcomes with performing minimally invasive clot evacuation using stereotactic or endoscopic aspiration with or without thrombolytic usage were deemed uncertain (6).

Minimally invasive surgery (MIS) with thrombolysis in ICH evacuation (MISTIE) was designed to minimize craniotomy-related secondary brain injury associated with conventional surgical procedures. The procedure was rigorously standardized and electrocautery and mechanical manipulations of brain tissue were eliminated. The recent results of MISTIE III trial have raised a great deal of interest regarding the indications for ICH surgery. Although MISTIE III did not demonstrate a positive effect on functional outcomes compared with standard medical care for ICH patients, it presented an essential insight into surgery for ICH (7).

LESSONS LEARNED FROM THE MISTIE TRIAL

The MISTIE procedure involves stereotactic hematoma evacuation followed by residual clot lysis with alteplase. After manual aspiration of the clot with a syringe, the surgeons insert a soft drainage catheter to facilitate up to nine injections of alteplase and passive clot drainage. The goals of the intervention were to decrease the clot size to <15 mL at the end of treatment (EOT) or stop when a maximum of nine doses of alteplase (1 mg every 8 h) was administered. This procedure seemed safe in the phase 2 study, with a possible advantage of having better functional outcomes compared to medical treatment (8). MISTIE III was a randomized, controlled, open-label, blinded endpoint, phase 3 explanatory trial of image-guided, catheter-based removal of an ICH of 30 mL or more. Seventy-eight hospitals in the USA, Canada, Europe, Australia, and Asia participated in the trial, including 499 patients (250 in the MISTIE group and 249 in the standard care group).

The mean reduction in hematoma size was 69% (SD 20), and the mean end-of-treatment (EOT) volume was 16 mL (SD 13) in the MISTIE group. The trial failed to reach the primary endpoint of improved functional outcomes; 110 (44%) of 249 patients in the MISTIE group and 100 (42%) of 240 patients in the standard medical care group had a modified Rankin Scale (mRS) score of 0–3 at 365 days (adjusted risk difference, 4%; 95% CI: −4–12; $P = 0.33$). However, the secondary endpoints indicate acceptable safety and a slight decrease in mortality in the MISTIE group, with a hazard ratio of 0.67 (95% CI: 0.45–0.98; $p = 0.037$) (7).

Most importantly, MISTIE III was the first to examine surgical performance in association with outcomes. The as-treated analysis demonstrated that a more significant ICH reduction has a higher likelihood of achieving an mRS of 0–3 with a minimum evacuation threshold of ≤15 mL EOT ICH volume or ≥70% volume reduction when controlling for disease severity factors. Mortality benefit was achieved at ≤30 mL EOT ICH volume or >53% volume reduction. Moreover, each additional milliliter removed beyond 70% led to a 6% improvement in the chance of achieving a good outcome of mRS 0–3 (OR = 1.06, 95% CI: 1.02–1.10, $P = 0.002$). In addition, surgeon and site case experiences were related to ICH evacuation efficacy. There was a threshold of four prior MISTIE trial cases by the surgeon and seven prior cases by the site, above which there were no cases with poor (>30 mL) EOT ICH (9). In an aim to improve surgical performance and maximize its benefits, a guide to the surgical protocols for MISTIE and CLEAR (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage) (10) has been recently published, and this also includes tutorial videos (11).

These findings led to a re-evaluation of the STICH trials (4, 5). In the analysis of lobar hemorrhages in MISTIE III and STICH II, EOT ICH volume ≤28.8 mL in MISTIE III and ≤30.0 mL in STICH II showed increased probability of an mRS of 0–3

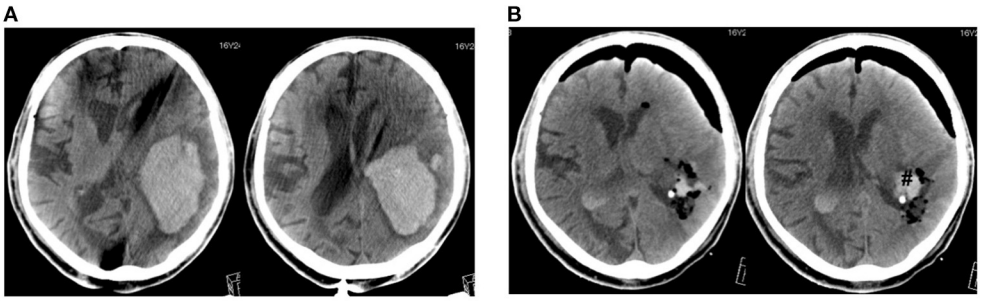

FIGURE 1 | A case of large lobar hemorrhage (110 ml). CT scans before **(A)** and after operation **(B)**. #Hematoma remnant.

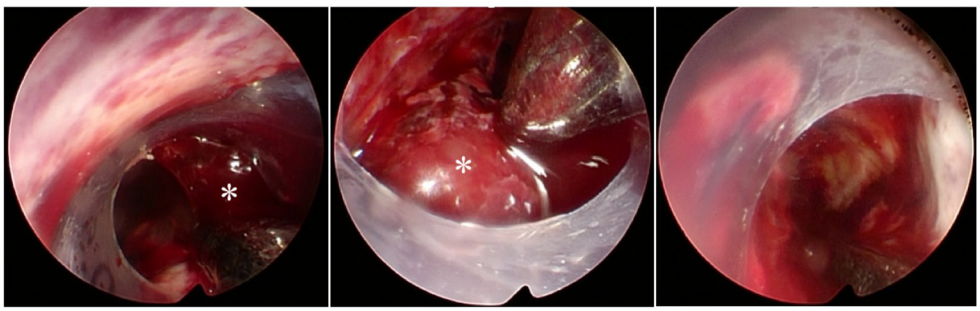

FIGURE 2 | Endoscopic view through a transparent sheath inserting to the hematoma cavity. *Hard clot difficult to suction.

at 180 days ($P = 0.01$ and 0.003, respectively). Two different interventions for ICH evacuation showed similar threshold EOT volumes for good outcomes (12).

In MISTIE III, several issues must be considered. Patients were randomized when active bleeding was stopped. Consequently, the mean time from onset to enrollment, to surgery, to the first dose of alteplase, and to the end of treatment was delayed for 47.0, 58.3, 72.6, and 123 h, respectively. This time course seems suboptimal for the management of ICH, because studies in animal models suggest that the time window for hematoma evacuation is 6–12 h (13). Irregularly shaped hematomas were significantly associated with less efficient ICH removal. The thalamic ICH ("Trajectory B" per trial protocol) was most likely associated with catheter malposition and poor evacuation efficacy (9, 14). Clot lysis may be insufficient in such cases. Life-threatening ICHs were excluded (7). Urokinase-type plasminogen activator may be more beneficial than alteplase (15). Fibrinolysis may be enhanced by Doppler sonography (16).

ENDOSCOPIC SURGERY

Neuroendoscopic surgery enables the removal of ICH under direct visualization in a less invasive manner than conventional craniotomy. In contrast to the stereotactic procedure, hemostasis at the bleeding point is also possible. ICES (Intraoperative Stereotactic Computed Tomography-Guided Endoscopic Surgery), a multicenter RCT, showed considerable safety and efficacy (17). Advantages of neuroendoscopic surgery over conventional craniotomy include a higher hematoma evacuation rate, shorter operation time, less intraoperative blood loss, better neurological outcomes, and shorter hospital stay (18). Its hematoma evacuation rate has been reported to reach around 90% (18, 19). Tips for safe and effective endoscopic clot evacuation are presented in schematic drawings (19). Endoscopic hematoma evacuation without decompression was safe and effective, even in patients with large putaminal ICH (20). The effectiveness of endoscopic surgery for large, life-threatening ICH has also been reported (21). It is unlikely that a large decompressive craniectomy would be required when the endoscopic procedure was successfully and timely achieved. With the development of endoscope technology and the accumulation of therapeutic experience, endoscopic evacuation will become more widely employed.

Although endoscopic ICH evacuation seems promising, there are some concerns. In conventional craniotomy, the CT angiography spot sign is associated with increased intraoperative bleeding, more postoperative rebleeding, and larger residual ICH volumes (22). Likewise, in endoscopic surgery, multivariate analysis revealed that the spot sign was the only independent predictor of postoperative recurrent hemorrhage and a significant risk factor for intraoperative bleeding (23). Thus, extra effort and treatment are needed to manage ICH patients with the spot sign (23). The bleeding point should be identified under the guidance of the navigation system and coagulated for hemostasis. To avoid intraoperative and postoperative bleeding, intentional preservation of hard clots may be safer (**Figures 1**, **2**). It is important to recognize

TABLE 1 | Summary of recent meta-analyses on minimally invasive surgery for intracerebral hemorrhage.

Study (search period)	Patients number	Trials included	Treatment compared	Outcomes	Risk/Odds Ratio (95% CI)	
Sun et al. (25) (up to June 2019)	1,506	8	NE vs. CT	Good functional outcome	OR	3.27 (1.73, 6.21)
	1,859	15		Mortality		0.43 (0.32, 0.58)
	883	10		Hematoma evacuation rate		8.14 (3.46, 12.83)
	781	7		Blood loss volume		−294.77 (−494.61, −94.93)
	1,060	13		Operation time		−99.03 (−119.56, −78.50)
	287	3		Hospital stay		−2.32 (−3.96, −0.68)
	157	3		ICU stay		−4.35 (−6.45, −2.26)
Zhou et al. (26) (up to March 2019)	1,955	11	MIS vs. conservative	Significant neurological debilitation or death	RR	0.82 (0.72, 0.94)
	1,955	11		Death		0.74 (0.62, 0.88)
Sontag et al. (27) (up to February 21, 2019)	3,886	20	Any surgery vs. medical	Good functional outcome	RR	1.40 (1.22, 1.60)
	2,045	20	MIS vs. medical			1.47 (1.26, 1.72)
	2,133	4	Any surgery vs. medical*			1.10 (0.98, 1.25)
Xia, et al. (28) (up to April 2018)	2,466	14	MIS vs. CT	Mortality	RR	0.76 (0.60, 0.97)
	1,273	10		Rebleeding		0.42 (0.19, 0.95)
	1,858	6		Good recovery		2.27 (1.34, 3.83)
Nam and Kim (29) (up to December 2017)	295	3	NE vs. CT	Death	OR	0.56 (0.24, 1.31)
	295	3		Complication		0.11 (0.03, 0.20)
Zhao et al. (30) (up to December 2017)	295	3	NE vs. CT	Death	RR	0.58 (0.26, 1.29)
	295	3		Complication		0.11 (0.06, 0.20)
Tang et al. (31) (up to November 2017)	258	4	MIS vs. conservative	GOS score	RR	1.55 (1.21, 1.97)
	352	5	MIS vs. CT			1.69 (1.10, 2.59)
	282	4	MIS vs. conservative	Pulmonary infection		1.26 (1.13, 1.40)
	486	3	MIS vs. CT			0.47 (0.26, 0.83)
	600	6	MIS vs. conservative	Mortality		0.26 (0.17, 0.40)
	1,127	8	MIS vs. CT			0.84 (0.65, 1.09)
	696	4	MIS vs. CT	ADL score		1.26 (1.13, 1.40)
	745	6	MIS vs. CT	Rebleeding		0.47 (0.26, 0.83)
Scaggiante et al. (32) (up to October 2017)	2,152	15	MIS vs. other treatment	Significant neurological debilitation or death	OR	0.46 (0.36, 0.57)
	863	5	MIS vs. CT			0.44 (0.29, 0.67)
	384	5	NE vs. other treatment			0.40 (0.25, 0.66)
	1,526	8	SE vs. other treatment			0.47 (0.34, 0.65)
	2,086	14	MIS vs. other treatment	Death		0.59 (0.45, 0.76)
	797	5	MIS vs.CT			0.56 (0.37, 0.84)
	384	5	NE vs. other treatment			0.37 (0.20, 0.67)
	1,404	7	SE vs. other treatment			0.76 (0.56, 1.04)
Yao et al. (33) (up to October 2017)	1,213	18	NE vs. other treatment	Mortality	RR	0.61 (0.48, 0.78)
	721	10		GOS 1–3, mRS 4–6		0.78 (0.70, 0.87)
	881	13		Rebleeding		0.40 (0.23, 0.69)
	641	8		Pneumonia		0.42 (0.28, 0.61)
	364	4		Meningitis		0.52 (0.16, 1.70)
	395	3		Epilepsy		0.58 (0.32, 1.05)
	451	4		Digestive disease		1.27 (0.75, 2.15)

**High quality studies only.*

NS, neuroendoscopy; MIS, minimally invasive surgery; SE, stereotactic evacuation; CT, craniotomy; GOS, Glasgow Outcome Scale; mRS, modified Rankin Scale; OR, Odds ratio; RR, Risk ratio.

TABLE 2 | Ongoing studies of minimally invasive surgery for intracerebral hemorrhage.

Study*	Study type	Intervention	Primary endpoint	Patients number	Time window	Study start point	Estimated study completion point
ENRICH	Randomized	NICO BrainPath and Myriad	Functional improvement (mRS)	300	<24 h	December 2016	December 2021
INVEST	Single arm	Apollo System	Rate of recruitment/successful follow up obtainment	50	<72h	June 30, 2017	June 2021
MIND	Randomized	Artemis Neuro Evacuation Devices	Global disability (mRS)/Mortality	500	<72 h	February 7, 2018	July 2025
DIST	Non-randomized	Artemis Neuro Evacuation Devices	Death/Neurological deterioration/Proportion of volume reduction	400	<8 h	December 3, 2018	February 2021
EVACUATE	Randomized	Aurora Surgiscope System	mRS	240	<8 h	September, 2020	December, 2026
MIRROR	Observational	Aurora Surgiscope System	Rate of Surgical Success (reduction to <15 ml)	500	<12 h	October, 2020	October, 2029

**Official title of the study.*
ENRICH, A Multi-center, Randomized, Clinical Trial Comparing Standard Medical Management to Early Surgical Hematoma Evacuation Using Minimally Invasive Parafascicular Surgery (MIPS) in the Treatment of Intracerebral Hemorrhage (ICH).
INVEST, A Single Arm, Feasibility Study of Minimally Invasive Endoscopic Surgical Treatment with Apollo for Supratentorial Intracerebral Hemorrhage (ICH).
MIND, A Prospective, Multicenter Study of Artemis: A Minimally Invasive Neuro Evacuation Device in the Removal of Intracerebral Hemorrhage.
DIST, The Dutch Intracerebral Hemorrhage Surgery Trial Pilot Study: Minimally-invasive Endoscopy-guided Surgery for Spontaneous Intracerebral Hemorrhage.
EVACUATE, Ultra-Early, Minimally inVAsive intraCerebral Hemorrhage evacUATion vs. Standard treatment.
MIRROR, Minimally Invasive IntRaceRebral HemORrhage Evacuation.
mRS, modified Rankin Scale.

the patient factors against endoscopic surgery. Poor evacuation rate was seen in patients with chronic renal failure who were treated with hemodialysis, as well as patients with liver cirrhosis (24). Hematologic diseases and the use of antithrombotics also adversely affect the surgical outcomes (22).

RECENT META-ANALYSES

The optimal treatment of ICH is of great concern in the field of neurosurgery/neurointensive care. Earlier studies comparing conventional craniotomy with the best medical management failed to show a clear benefit (4, 5). More recent experiences with MIS have shown greater promise. **Table 1** summarizes recent meta-analyses on MIS for ICH (25–33). Two latest studies (26, 27) include the results of MISTIE III. Surgical treatment of ICH, particularly with MIS, is beneficial compared to medical treatment. Compared with craniotomy, MIS is associated with fewer deaths (28, 31, 32), rebleeding (28, 31) and complications (29–31), and more favorable outcomes (28, 31, 32). The latest meta-analysis and trial sequential analysis confirmed the benefits of MIS over conservative treatment (26). Moreover, neuroendoscopic surgery is superior to craniotomy or other treatments in terms of good functional outcomes (25, 32, 33), mortality (25, 32, 33), hematoma evacuation rate (25), blood loss (25), complications (29, 30, 33), operation time (25), hospital stay (25), and ICU stay (25).

EMERGING MINIMALLY INVASIVE TECHNIQUES FOR ICH EVACUATION AND ONGOING STUDIES

MIS procedures have continued to evolve with the support of advanced guidance systems and devices in favor of the better surgical performance of ICH removal. In summary, the hematoma is removed by newly developed aspirators through a narrow tubular retractor to mitigate brain injury. New devices can immediately evacuate the hematoma at the time of the procedure without the need for prolonged thrombolytic irrigation (34–36). Several RCTs are underway using newly developed instruments and techniques for MIS (**Table 2**). These studies include protocols aimed at active clot removal at an earlier phase (<8 h).

Endoport-mediated evacuation is an active evacuation technique that utilizes the BrainPath endoport (NICO Corp., Indianapolis, IN, USA). BrainPath consists of an access sheath of 11.0 or 13.5 mm in diameter and multiple lengths (50, 60, 75, and 95 mm) and an internal obturator (**Figure 3A**). The BrainPath is placed through a small craniotomy (2–3 cm). The opening may be planned with magnetic resonance tractography to facilitate the least traumatic trans-sulcal access to the lesion. Once the sheath is placed stereotactically, the obturator is removed, the clot is evacuated using standard microsurgical techniques. Active bleeding could be identified and controlled. A Myriad handpiece, which is an automated and nonablative resection device (NICO Corp, Indianapolis, IN, USA), can

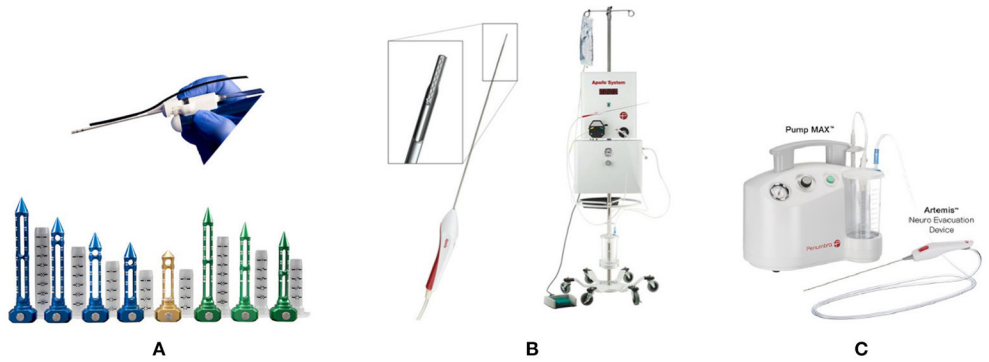

FIGURE 3 | Emerging minimally invasive instruments. **(A)** NICO BrainPath system and myriad handpiece (NICO Corp, Indianapolis, IN, USA). **(B)** The Apollo system. The Wand and aspiration–irrigation system (Penumbra Inc, Alameda, CA, USA). **(C)** The Artemis Neuro Evacuation Device and Pump MAX™ aspiration system (Penumbra, Alameda, CA, USA).

be used when necessary, as in cases of high-density clots. In 39 consecutive patients treated with the NICO device, a clot reduction rate of ≥90% was achieved in 72% of the patients (37). The Early MiNimally-invasive Removal of IntraCerebral Hemorrhage (**ENRICH**) trial, which makes use of Brain Path and Myriad, is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT02880878).

The Apollo system (Penumbra Inc., Alameda, CA, USA) is composed of an aspiration–irrigation system that allows the removal of hematoma through a low-profile wand for the controlled aspiration of soft tissue and fluid (**Figure 3B**). A vibrational element housed within the wand vibrates at a high frequency to break down the clot inside the wand and prevent clogging. No energy is transferred to the tissue outside the device (38). Early experiences with the Apollo system indicate the effectiveness of this device (39). The Minimally Invasive Endoscopic Surgical Treatment with Apollo vs. Medical Management for Supratentorial ICH (**INVEST**) trial is currently underway as a phase II study (https://clinicaltrials.gov/ct2/show/NCT02654015).

The Artemis System (Penumbra, Alameda, CA, USA) is intended for the controlled aspiration of tissue and/or fluid from the ventricular system and/or cerebrum. The device works in conjunction with a neuroendoscope through a 19 F (6 mm) sheath. Together with the Pump MAX™ aspiration system, Artemis offers powerful and controlled evacuation (**Figure 3C**). Stereotactic ICH Underwater Blood Aspiration (**SCUBA**) is an endoscopic evacuation technique that uses Apollo/Artemis devices (40). This procedure could be safely indicated for patients with ICH who showed spot signs or hematoma. Two studies utilizing the Artemis System, namely the Dutch Intracerebral Hemorrhage Surgery Trial (**DIST**) (https://clinicaltrials.gov/ct2/show/NCT03608423) and Artemis in the removal of intracerebral hemorrhage (**MIND**), are currently ongoing (https://clinicaltrials.gov/ct2/show/NCT03342664).

The Aurora Surgiscope System designed by Rebound Therapeutics is the first disposable, single-use endoscope with an outer diameter of 11.5 mm. The first clinical trials of this device, namely the Ultra-Early, Minimally inVAsive intracerebral hemorrhage evacUATion vs. Standard Treatment (**EVACUATE**) (https://www.clinicaltrials.gov/ct2/show/NCT04434807) and Minimally Invasive IntRaceRebral HemORrhage Evacuation (**MIRROR**) (https://clinicaltrials.gov/ct2/show/NCT04494295), began enrolling patients in 2020.

SIGNIFICANCE OF CONVENTIONAL CRANIOTOMY

The role of early ICH evacuation remains a topic of debate. Craniotomy for ICH evacuation remains a life-saving measure in critical situations, although it is difficult to standardize. Craniotomy allows secure hemostasis, multidirectional trajectories for evacuation, and external decompression to control intracranial pressure when necessary. Herein, we also present a case of a 49-year-old woman who arrived at the emergency room 1 h after ictus. Her Glasgow Coma Scale score was 7 (E1V1M5), and head CT scans showed an irregular, lobulated ICH of 66 mL in the right temporal lobe (**Figure 4A**). She was transferred to the operating room 1 h after arrival. A craniotomy of 4.5 cm in diameter was made, and a 1.5 cm corticotomy was performed. Hematoma evacuation was completed 3.5 h after ictus. Postoperative CT images showed >90% removal of the hematoma (**Figure 4B**), and diffusion-weighted MR images taken the next day demonstrated limited high-intensity lesions around the hematoma (**Figure 4C**). She had a remarkable recovery, showing no apparent paresis or disturbed consciousness, but presented with left homonymous hemianopia. Two weeks later, her mRS score was 2, and she was transferred to a rehabilitation hospital. In this case, MIS may carry a higher risk of rebleeding and appeared to be disadvantageous because of the shape and location of the ICH. Open craniotomy allowed meticulous microsurgical manipulation *via* multidirectional trajectories with freely changeable directions for this complex-shaped hematoma. Of note, it is essential to minimize

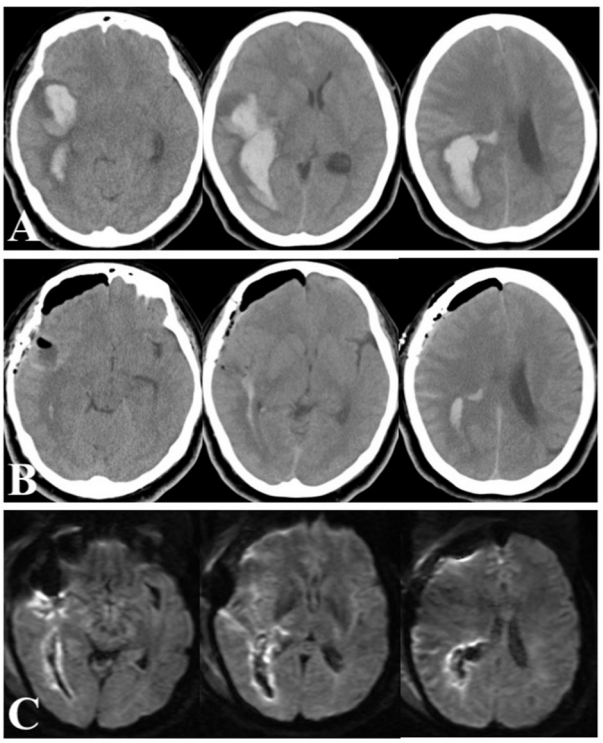

FIGURE 4 | Head CT scans on arrival **(A)**, immediately after ICH removal **(B)**, and diffusion-weighted MRI images next day **(C)**.

the use of electrocautery and brain compression during the procedure.

A meta-analysis indicated improved outcomes with surgery if undertaken within 8 h of ictus (41), whereas ultra-early craniotomy within 4 h from ictus was associated with an increased risk of rebleeding (42). The optimal timing for surgery depends on the balance between the initial hematoma size, the risk of rebleeding, and secondary injury such as peripheral edema caused by the hematoma. In animal experiments, the pathophysiological time window of minimally invasive procedures for hematoma evacuation might be 6–12 h after hemorrhage (13). A systemic review reported the optimal time window for ICH evacuation to be 7–24 h after ictus (43). Since individual patients have different pathological conditions, it may be difficult to generalize the optimal timing of surgical procedures. Craniotomy should further be maintained as an option.

The potential benefits of craniotomy have been reported (44). Decompressive hemicraniectomy associated with ultrasound-guided minimally invasive puncture and drainage showed a significantly higher survival rate and better functional outcome for deteriorating ICH in the basal ganglia (45). Thus, an individual-based tailored surgical approach may be beneficial.

FUTURE PERSPECTIVES

Advances in therapeutic devices and techniques, especially endovascular thrombectomy, have made a significant contribution to the treatment of acute cerebral ischemia. Likewise, recent advances in therapeutic devices are making great strides in the treatment of ICH. Early and optimal treatment for ICH is warranted, by experienced neurosurgeons/neurointensivists, in high-volume centers. It is time to discard the therapeutic nihilism of past days. Although the way forward is still far away, we have every reason to be optimistic for the future of ICH treatment.

AUTHOR CONTRIBUTIONS

HK and NI contributed conception of the article. HK wrote the first draft of the article. All authors approved the submitted version.

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ORIGINAL RESEARCH
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Intracranial Pressure and Cerebral Perfusion Pressure in Large Spontaneous Intracranial Hemorrhage and Impact of Minimally Invasive Surgery

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Introduction: We investigated the effect of hematoma volume reduction with minimally invasive surgery (MIS) on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in patients with large spontaneous intracerebral hemorrhage (ICH).

Methods: *Post-hoc* analysis of the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation (MISTIE III) study, a clinical trial with blinded outcome assessments. The primary outcome was the proportion of ICP readings ≥20 and 30 mmHg, and CPP readings <70 and 60 mm Hg. Secondary outcomes included major disability (modified Rankin scale >3) and mortality at 30 and 365 days. We assessed the relationship between proportion of high ICP and low CPP events and MIS using binomial generalized linear models, and outcomes using multiple logistic regression.

Results: Of 499 patients enrolled in MISTIE III, 72 patients had guideline based ICP monitors placed, 34 in the MIS group and 38 in control (no surgery) group. Threshold ICP and CPP events ≥20/<70 mmHg occurred in 31 (43.1%) and 52 (72.2%) patients respectively. On adjusted analyses, proportion of ICP readings ≥20 and 30 mmHg were significantly lower in the MIS group vs. control group [Odds Ratio (OR) 0.27, 95% Confidence Interval [CI] 0.11–0.63 ($p = 0.002$); OR = 0.18, 0.04–0.75, $p = 0.02$], respectively. Proportion of CPP readings <70 and 60 mm Hg were also significantly lower in MIS patients [OR 0.31, 95% CI 0.15–0.63 ($p = 0.001$); OR 0.30, 95% CI 0.11–0.83 ($p = 0.02$)], respectively. Higher proportions of CPP readings <70 and 60 mm were significantly associated with short term mortality ($p = 0.04$), and ($p = 0.006$), respectively. Long term mortality was significantly associated with higher proportion of time with ICP ≥ 20 ($p = 0.04$), ICP ≥ 30 ($p = 0.04$), and CPP < 70 mmHg ($p = 0.01$).

Conclusion: Our results are consistent with the hypothesis that surgical reduction of ICH volume decreases proportion of high ICP and low CPP events and that these variables are associated with short- and long-term mortality.

Keywords: intracerebral hemorrage, intracranial pressure, cerebral perfusion pressure, minimally invasive surgeries, intracranial pressure monitoring

INTRODUCTION

Intracerebral hemorrhage (ICH) represents 10–15% of all strokes worldwide but imposes significant morbidity and mortality. Approximately, 10–30 patients per 100,000 are affected annually with a case fatality as high as 40% at 1 month and 54% at 1 year (1). Deleterious outcomes in ICH are a result of primary and secondary pathologic insults. Primary ICH insult is inflicted mostly by mechanical mass effect secondary to clot formation (2). Further neurologic deterioration in ICH patients can occur due to delayed insult secondary to hematoma growth, intraventricular expansion, and perihematomal edema (2). Hematomal mass effect, evolving perihematomal edema, and perihematomal growth can result in decreased cerebral perfusion pressure (CPP), increased intracranial pressure (ICP), and herniation (2). In a systematic review and meta-analysis, about two-thirds of ICH patients who underwent ICP monitoring demonstrated at least one episode of elevated ICP (3). Despite this common occurrence, little evidence exists to support specific ICP and CPP thresholds in ICH patients and their impact on long term outcomes (4–7). A systematic review and several retrospective studies do suggest, however, that increased ICP level, duration, and variability are associated with worse outcomes and mortality (5, 7–9).

Minimally invasive surgery for ICH can reduce mass effect and may mitigate high ICP and low CPP events. However, post-operative re-hemorrhage and brain edema may oppose this potential benefit. The impact of surgical hematoma reduction on ICP and CPP levels and whether these impact patient outcomes has not been systematically studied.

We hypothesized that patients who had ICP monitors placed who underwent minimally invasive surgery (MIS) using stereotactic aspiration with alteplase would have a lower time burden and incidence of increased ICP and decreased CPP compared to patients with ICP monitors treated with medical management alone.

METHODS

Design and Study Population

We conducted a *post-hoc* exploratory analysis of data collected in the Minimally Invasive Surgery Plus Alteplase for Intracerebral Hemorrhage Evacuation III (MISTIE III) trial. MSTIE III was a multicenter, randomized, open label, blinded endpoint trial that found image guided, minimally invasive surgery followed by gentle thrombolytic irrigation of the catheterized intracerebral hemorrhage clot decreased mortality, but was neutral on the primary endpoint of improved functional outcome in patients with moderate to large ICH, compared to standard medical management (9). The main inclusion criteria in the trial were (1) age 18 years or older, (2) spontaneous non-traumatic supratentorial ICH with hematoma volume >30 ml and without evidence of an underlying macrovascular cause, (3) presentation within 24 hours of symptom onset, (4) presentation Glasgow Coma Scale (GCS) ≤14 or National Institutes of Health Stroke Scale (NIHSS) ≥6, and (5) baseline modified Rankin score (mRS) of <2. Patients randomized to MIS ($n = 250$) received up to nine doses of alteplase every 8 h *via* intrahematomal catheter until hematoma volume was reduced to ≤15 ml. The control group received standard medical care ($n = 249$). Details of the methodology and trial results can be found in the primary publication.

In this study, we included all 72 patients who had an ICP monitor placed. ICP monitors were inserted in a guideline supported manner per the neurosurgeons' discretion (10). The trial protocol supported ICP monitoring for "patients with a GCS of 8 or less with two observations over 8 h." The goals of ICP management were to "sustain ICP below 20 mmHg and to improve the patient's level of consciousness (9)." The protocol specified that placement of an ICP monitor had to be followed by a CT scan of the brain to monitor for ICH stability and any new areas of hemorrhage.

Standard Protocol Approvals, Registrations, and Patient Consents

The MISTIE III trial was performed at 78 hospitals in the US, Canada, Europe, Australia, and Asia following local institutional review board and country ethics approval. Written informed consent for research was obtained from all participants (or legal representatives or surrogates when applicable). The study was also approved by the Johns Hopkins Hospital institutional review board.

Measurements and Outcomes

The primary outcomes included occurrence of and percentage of ICP readings ≥20 and 30 mm Hg, and CPP readings <60 and 70 mm Hg. ICP and CPP were recorded every 6 h for up to 6 days after placement of the ICP monitor, including prior to randomization. This time period was intended to include the full duration of the MIS treatment phase. ICP monitors included external ventricular drains (EVDs) and intraparenchymal monitors (IPMs). Choice of monitor placement ipsilateral or contralateral to the ICH was decided by each site's neurosurgical team. ICP and CPP measurements were performed according to standard of care at each center. For EVDs, drainage level and EVD management were directed

TABLE 1 | Baseline demographic and radiographic characteristics by treatment group.

Demographics/Predictors	Medical group 38/72 (52.8%)	Surgical group 34/72 (47.2%)	*P*-value
Gender			
Female	14 (36.8%)	10 (29.4%)	0.51
Age at consent*	56.5 (48–65)	59.5 (48–65)	0.33
Race			
African American	8 (21.6%)	9 (27.3%)	0.83
Asian	3 (8.1%)	2 (6.1%)	
White	26 (70.3%)	22 (66.7%)	
Hypertension	37 (97.4%)	33 (97.1%)	0.94
Hyperlipidemia	13 (34.2%)	11 (32.4%)	0.87
Prior statin use	3 (7.9%)	1 (2.9%)	0.36
SBP on admission*	181.5 (162.5–215)	164 (152–202)	0.13
DBP on admission*	98 (85–119)	101 (90–120)	0.71
CAD	7 (18.4%)	5 (14.7%)	0.67
Cocaine use	1 (2.6%)	2 (5.9%)	0.49
Alcohol Abuse	6 (15.8%)	2 (5.9%)	0.18
Anticoagulant use	4 (10.5%)	3 (8.8%)	0.81
Antiplatelet use	11 (29.0%)	8 (23.5%)	0.61
Current Smoker	9 (23.7%)	5 (14.7%)	0.34
Diabetes	7 (18.4%)	8 (23.5%)	0.59
GCS at randomization*	8 (7–9)	8 (7–10)	0.84
NIHSS at randomization*	23.5 (19–29)	21.5 (17–26)	0.23
ICP therapies used	26 (68.4%)	25 (73.5%)	0.63
EVD inserted	27 (71.1%)	31 (91.2%)	0.03
IPM inserted	11 (28.9%)	3 (8.8%)	
EVD inserted	27 (71.1%)	31 (91.2%)	0.03
EVD ipsilateral to ICH	3 (11.1%)	3 (10.0%)	0.89
Deep ICH location	29 (76.3%)	27 (79.4%)	0.75
Diagnostic septal shift (mm)	4.7 (2.6–6.6)	5.1 (3.5–7.2)	0.39
EOT septal shift (mm)	7.9 (5.7–11.4)	3.9 (2.0–6.2)	<0.001
Delta septal shift (mm)	3.1 (1.4–7.2)	−0.8 (−2.9–1.3)	<0.001
Diagnostic pineal shift (mm)	3.1 (1.7–4.9)	2.1 (1.2–45.0)	0.53
EOT pineal shift	4.0 (2.5–7.1)	2.8 (0–4.4)	0.01
Delta pineal shift (mm)	1.4 (0.1–3.2)	0 (−1.5–1.4)	0.009
IVH present	21 (55.3%)	22 (64.7%)	0.42
Diagnostic IVH volume	0.3 (0–5.4)	4.3 (0.3–10.9)	0.05
Stability IVH volume	2.8 (0–6.9)	5.3 (1.9–9.4)	0.05
EOT IVH volume	1.1 (0.1–5.1)	0.8 (0.3–4.8)	0.83
Diagnostic hydrocephalus	5 (13.5%)	5 (16.1%)	0.76
EOT hydrocephalus	8 (21.1%)	3 (8.8%)	0.15
Diagnostic ICH volume	44.2 (31.9–57.4)	45.4 (32.9–57.9)	0.61
Stability ICH volume	48.5 (38.4–61.7)	48.4 (35.9–69.8)	0.91
EOT ICH volume	47.1 (35.6–66.5)	15.4 (12.2–32.0)	<0.0001
Delta ICH volume	−42.4 (−29.1–21.8)	−3.7 (−0.6–1.8)	<0.0001
EOT <15 mm	0 (0.00%)	16 (47.1%)	0.00
Diagnostic edema volume	26.0 (16.8–33.7)	21.9 (15.4–30.1)	0.52
Stability edema volume	40.5 (36.1–53.0)	31.4 (24.3–42.2)	0.12

*SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; GCS, Glasgow coma scale; NIHSS, NIH stroke scale; EVD, external ventricular drain; IPM, intraparenchymal monitor; ICP, intracranial pressure; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; EOT, end of treatment. *Denotes a value provided in the format of Median (Interquartile Ranger).*

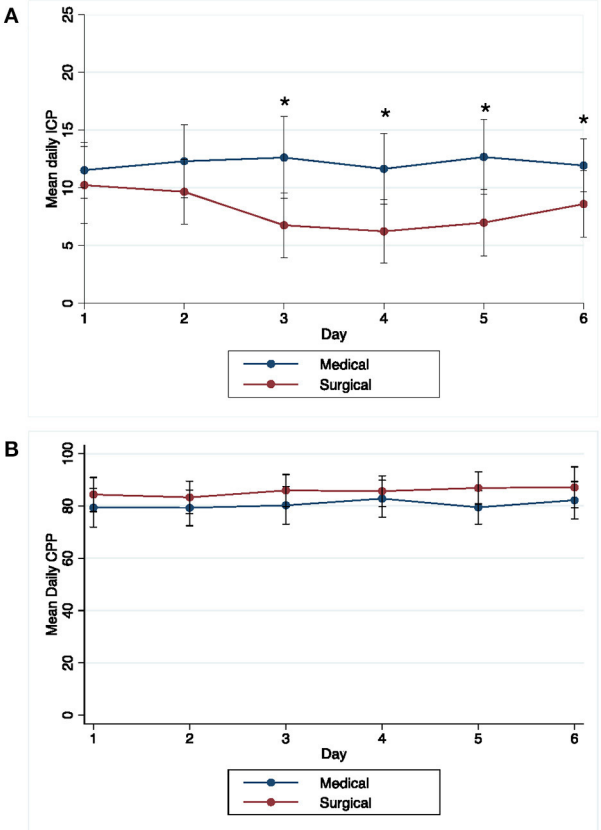

FIGURE 1 | Temporal pattern of daily mean (±1 standard deviation) ICP **(A)** and CPP **(B)** over time in MIS and medical groups. *Days with significant difference in mean ICP between medical and surgical groups ($P < 0.05$).

by site physicians. Validation of q4h measurements with hourly measurements to not miss peak values was previously performed (5). We collected use of any ICP therapy including osmotic therapy, hyperventilation, analgesia, sedation, and where indicated to control ICP, induced coma, but not adherence data to particular thresholds.

Patient demographics and comorbidities were recorded at enrollment. CT scans were evaluated from admission, randomization (termed "stability" when all bleeding had stabilized), and end of treatment (EOT) defined as 24 h after last dose of alteplase or at similar timepoint in the medical group. These were assessed for ICH, IVH, and peri-hematomal edema volumes calculated using semiautomated planimetry, presence of hydrocephalus at diagnosis and EOT, pineal midline shift, and septal midline shift. CT scans were read centrally by trained image readers blinded to treatment and outcomes.

Secondary outcomes were short term and long-term mortality and poor functional outcomes at 30 and 365 days defined by modified Rankin Scale (mRS) score of 4–6. MISTIE III benefited from central blinded adjudication of outcomes using archival video recordings of individual patients.

Statistical Analysis

Demographics, baseline clinical and radiographic characteristics were compared using Wilcoxon rank sum test for non-normally distributed continuous variables, Student's *t*-test for normally distributed continuous variables, and Pearson Chi Square test for categorical variables. Quantitative data were expressed as median with interquartile range if non-normally distributed, mean with standard deviation for normally distributed data, and as proportions for categorical findings. We tested for intergroup differences for any ICP/CPP threshold event using the chi-squared test for categorical variables, Student's *t*-test for continuous variables, and the Wilcoxon Rank Sum test for ordinal variables. We also graphically compared median daily ICP and CPP levels pre and post-intervention in the MIS group and pre and post-randomization in the medical cohort. Finally, the percentage of ICP readings within each individual subject's record that were above the thresholds of 20 and 30 mmHg (% ICP readings $\geq$ threshold) and percentage of CPP readings below the thresholds of 60 and 70 mmHg (% CPP readings $<$ threshold) were calculated. Univariable and multivariable analyses of factors associated with % ICP readings above threshold ($\geq$ 20 and $\geq$30 mmHg) and with % CPP readings below threshold ($<$70 and $<$60 mmHg) were performed using binomial generalized linear models, with clustering by patient to adjust for within patient correlations.

Given that there were multiple variables and a limited data set, we used stepwise backward regression including only variables with $P < 0.05$ from the univariable analysis for association with either % ICP or % CPP readings above and below threshold. We also created a second model with four variables which were the most commonly selected in the step-wise regression: age, SBP on admission, IVH (presence vs. absence) and treatment group.

We fit logistic regression models for secondary outcomes to evaluate the contribution of proportion of ICP and CPP threshold events. Due to the small number of patients, models were conservatively adjusted a priori for 5 covariates included in the primary outcome analysis for the MISTIE III trial: age, diagnostic ICH volume, severity of impairment as measured by GCS and clinically established severity variables [IVH and ICH clot location (lobar vs. deep)]. Due to sample size limitations, we were not able to evaluate for effect modification of MIS on proportion of ICP/CPP threshold events. A p-value $<$0.05 was considered statistically significant. All analyses were carried out in STATA 15 (College Station, TX, USA).

RESULTS

Study Population

Of 499 randomized patients in MISTIE III, the cohort included 72 patients (14.4%) who had an ICP monitor placed; 58 patients had EVDs inserted (80.6%), while 14 patients (19.4%) had an IPM. ICP monitors were placed ipsilateral to the hematoma in 6 patients (8.3%). **Table 1** compares patients with ICP monitors by treatment group; 34/72 (47.2%) were in the MIS group and 38/72 (52.8%) were in the medical management only group. **Supplementary Table 1** compares patients with and without ICP monitors from

the MISTIE trial. Patients who had ICP monitors placed were younger, had a lower median admission GCS score and higher NIHSS score, were more likely to require mechanical ventilation, had higher ICH and IVH volume, and had hemorrhages in deep as opposed to superficial (lobar) locations.

Primary Outcomes

We recorded 1,588 ICP and CPP readings over a median (IQR) of 3 (1–6) days; temporal ICP and CPP trends are shown in **Figure 1**. The percentage of patients with at least 1 ICP reading above threshold was 43.1 and 16.7% for ≥20 and ≥30 mm Hg, respectively. **Supplementary Table 2** compares patients with and without any ICP and CPP threshold event. Any ICP reading ≥20 mm Hg was more likely in younger patients (p =0.004), without diabetes ($p = 0.01$), with deep ICH location ($p = 0.03$), higher EOT ICH volume ($p = 0.04$), larger EOT septal shift ($p = 0.03$), and in the medical management arm ($p = 0.01$). Any ICP readings ≥30 mm Hg was more frequent in patients with diabetes ($p = 0.05$). The percentage of patients with at least 1 CPP reading below threshold was 72.2 and 34.7% for below 70 and 60 mmHg, respectively. Any CPP reading <70 mmHg was more likely with presence of IVH ($p = 0.03$). Any CPP reading <60 mm Hg was more likely in patients with less antiplatelet use ($p = 0.04$), hydrocephalus on diagnostic CT ($p = 0.01$) lower GCS ($p = 0.03$) and larger increase in septal shift at end of treatment ($p = 0.03$) (**Table 2**).

We used general linear models to assess associations of proportion of ICP and CPP threshold events with MIS, ensuring that the models were not over fitted; first after step-wise backward regression, MIS was significantly associated with decreased proportion of ICP events ≥20 and ≥30 mmHg and with decreased proportion of CPP events <70 and <60 mmHg (**Table 3**). Second, we controlled for age, presence of IVH, and admission SBP and again found that MIS was associated with decreased threshold events for ICP ≥20, and ≥30, and CPP <70 and <60 mmHg.

Figure 2 shows median ICP and CPP by time interval. In the MIS group median ICP was significantly lower post MIS compared to pre-MIS ($p = 0.001$); median CPP was higher post MIS, but this difference was not significant ($p = 0.07$). There were no significant differences in median ICP or CPP in the medical group pre and post randomization (correlating to time of surgery).

Secondary Outcomes

In logistic regression models adjusted for the afore mentioned confounders (**Table 4**), percentage of CPP readings per patient <70 mmHg (OR = 1.71, CI = 1.12–2.59, $p = 0.01$), ICP readings ≥20 mmHg (OR = 1.58, CI = 1.01–2.48, $p = 0.04$), and ICP readings ≥30 mmHg (OR = 1.84, CI = 1.01–3.33, $p = 0.04$) were significantly associated with mortality at 1 year (**Figure 3**). Percentage of CPP readings <70 and <60 mmHg were also significantly associated with day 30 mortality. Percentage of ICP and CPP readings above/below thresholds were not associated with functional outcomes at 1 year.

Logistic regression models for short term functional outcomes could not be defined due to all except 1 patient having a poor mRS 4-6 at day 30.

DISCUSSION

In this secondary analysis of the MISTIE III trial, we found that critical thresholds of ICP ≥20 and 30 and CPP <60 and <70 mmHg are not infrequent in patients with ICP monitors and large ICH. This study is the first to demonstrate lower percentage of monitoring time at high ICP and low CPP values in patients undergoing clot evacuation compared to patients with ICP monitors, but without clot removal. Spending less monitoring time with high ICP and low CPP thresholds was significantly associated with lower mortality at 30 and 365 days. but not with functional outcomes at 1 year.

Prevalence of ICP and CPP Threshold Events

Elevated intracranial pressure is most likely a common occurrence following moderate to large intracranial hemorrhage where a decision is made to invasively monitor ICP. Godoy et al. reported a pooled prevalence rate of 67% of any episode of intracranial hypertension (ICP >20 mmHg) after ICH in a metanalysis of six studies (3). Factors reported to have a significant association with elevated ICP included GCS at admission, midline shift, age, hemorrhage volume and hydrocephalus. We also found a high rate of occurrence of any ICP ≥20 mmHg which in the medical cohort was 58%, compared to 26% in the surgical cohort. In ICH patients with small parenchymal clots (< 30 ml) and large obstructive IVH, this occurrence is even higher at 73% in patients from the CLEAR III trial (11).

ICP and CPP Time Burden and Outcomes

Optimal ICP and CPP treatment thresholds and associations of threshold events with outcomes in ICH patients are less easily defined (7, 10). Recent evidence points toward time burden, rather than occurrence of any ICP or CPP event, as an important marker associated with outcomes in ICH patients (9). In patients with large IVH causing obstructive hydrocephalus requiring EVD, the percentage of monitoring time with ICP single events from >18 mmHg to >30 mmHg predicted higher short-term mortality, and successive events above 20 mmHg predicted long-term mortality as well. The MISTIE III trial excluded patients with massive IVH, but we found similar associations between long-term mortality and proportion of ICP events above common thresholds of 20 and 30 mmHg for parenchymal ICH volumes >30 ml. Although time at high ICP was not associated with short-term mortality, higher percentage of low CPP readings was significantly associated with higher odds of day 30 mortality both for <70 and <60 mmHg thresholds and at day 365 for <70 mmHg. This again is consistent with data from patients with EVD for large IVH where we previously report CPP as an independent predictor of both short- and long-term

TABLE 2 | Baseline demographics and radiographic characteristics for primary outcome measures.

Demographics/Predictors	PC ICP > 20 mm Hg	PC ICP > 20 mm Hg	PC ICP > 30 mm Hg	PC ICP > 30 mm Hg	PC CPP < 70 mm Hg	PC CPP < 70 mm Hg	PC CPP < 60	PC CPP < 60
	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value	OR [95% CI]	*P*-value
Male gender	1.89 (0.61–5.86)	0.27	4.30 (0.48–38.5)	0.19	0.81 (0.39–1.66)	0.56	1.11 (0.43–2.93)	0.82
Age at consent	0.93 (0.89–0.97)	0.002	0.88 (0.81–0.96)	0.002	0.99 (0.96–1.02)	0.54	0.98 (0.94–1.03)	0.41
Race								
African American								
Asian	0.32 (0.03–3.36)	0.34	8.20e-07 (2.89 2e-0.07)	0.98	0.40 (0.05–3.0)	0.38	0.32 (0.03–3.2)	0.33
White	0.36 (0.14–0.92)	0.03	0.13 (0.03–0.53)	0.005	0.73 (0.34–1.56)	0.41	0.39 (0.16–0.95)	0.04
Hypertension	0.46 (0.04–4.96)	0.52	276457.2 (2.89 2e-0.07)	0.99	0.32 (0.07–1.47)	0.14	0.18 (0.04–0.82)	0.03
Hyperlipidemia	0.37 (0.11–1.31)	0.13	0.18 (0.02–2.06)	0.17	0.85 (0.39–1.84)	0.68	0.64 (0.22–1.80)	0.40
Prior statin use	1.09 e-0.06 (2.89 2e-0.07)	0.99	3.89 e-0.6 (2.89 2e-0.07)	0.98	1.44 (0.27–7.55)	0.67	0.48 (0.01–15.93)	0.68
SBP on admission	1.01 (1.00–1.02)	0.12	1.03 (1.01–1.04)	0.004	1.00 (0.99–1.01)	0.57	1.01 (1.00–1.02)	0.04
DBP on admission	1.02 (1.00–1.04)	0.10	1.4 (1.01–1.07)	0.009	1.00 (0.98–1.02)	0.84	1.01 (0.99–1.03)	0.30
CAD	0.62 (0.14–2.75)	0.53	0.32 (0.02–5.72)	0.44	1.20 (0.49–2.96)	0.69	0.91 (0.26–3.18)	0.89
Cocaine use	1.03 (0.12–8.59)	0.98	1.11 (0.05–22.5)	0.95	0.27 (0.01–5.43)	0.39	1.22 e-6 (0-.)	0.98
Alcohol abuse	1.83 (0.57–5.84)	0.31	0.42 (0.02–8.59)	0.57	0.77 (0.23–2.59)	0.68	0.41 (0.05–3.01)	0.38
Anticoagulant use	0.47 (0.04–5.05)	0.53	0.51 (0.02–14.7)	0.70	1.34 (0.42–4.26)	0.62	1.17 (0.25–5.48)	0.84
Antiplatelet use	0.23 (0.04–1.18)	0.08	0.25 (0.03–2.70)	0.25	0.65 (0.27–1.56)	0.34	0.30 (0.07–1.25)	0.10
Current smoker	2.39 (0.93–6.15)	0.07	7.87 (2.09–29.8)	0.002	1.15 (0.49–2.73)	0.75	1.86 (0.71–4.86)	0.21
Diabetes	0.37 (0.97–1.95)	0.24	2.82 2e-0.07 (2.89 2e-0.07)	0.98	1.02 (0.42–2.46)	0.97	0.48 (0.11–2.03)	0.32
GCS at randomization	1.06 (0.86–1.29)	0.59	1.06 (0.79–1.42)	0.71	0.98 (084–1.16)	0.84	0.88 (0.71–1.10)	0.26
NIHSS at randomization	1.04 (0.97–1.11)	0.24	1.12 (1.02–1.23)	0.01	1.02 (0.97–1.07)	0.49	1.04 (0.97–1.11)	0.26
ICP therapies used	1.94 (0.58–6.57)	0.29	15.8 (0.23–1106.2)	0.21	0.85 (0.40–1.81)	0.68	1.46 (0.49–4.30)	0.49
Medical treatment arm	0.22 (0.07–0.69)	0.009	0.09 (0.008–0.96)	0.05	0.30 (0.14–0.65)	0.002	0.30 (0.11–0.82)	0.02
EVD inserted	0.21 (0.08–0.49)	0.00	0.08 (0.02–0.30)	0.00	0.27 (0.14–0.55)	0.00	0.33 (0.13–0.86)	0.03
EVD ipsilateral to ICH	1.02 (0.23–4.45)	0.98	1.42 (0.27–7.58)	0.68	1.28 (0.46–3.55)	0.64	0.98 (0.21–4.63)	0.98
Deep ICH location	3.42 (0.62–19.0)	0.16	9.71 (0.17–543.8)	0.27	1.01 (0.43–2.37)	0.98	1.22 (0.39–3.84)	0.73
Diagnostic septal shift (mm)	0.90 (0.76–1.06)	0.19	0.65 (0.47–0.91)	0.01	0.97 (0.86–1.09)	0.61	0.93 (0.79–1.08)	0.32
EOT septal shift (mm)	1.06 (0.96–1.16)	0.24	1.05 (0.91–1.21)	0.49	1.09 (1.02–1.16)	0.01	1.11 (1.02–1.21)	0.01
Delta septal shift	1.12 (1.01–1.24)	0.03	1.22 (1.04–1.42)	0.01	1.12 (1.04–1.21)	0.002	1.19 (1.08–1.31)	<0.001
Diagnostic pineal shift	1.10 (0.92–1.33)	0.31	1.09 (0.83–1.43)	0.53	1.08 (0.94–1.24)	0.29	1.10 (0.92–1.31)	0.31
EOT pineal shift	1.08 (0.95–1.22)	0.25	1.01 (0.82–1.26)	0.91	1.07 (0.97–1.18)	0.18	1.09 (0.96–1.23)	0.18
Delta pineal shift	1.02 (0.88–1.20)	0.78	0.95 (0.74–1.22)	0.70	1.03 (0.92–1.16)	0.62	1.04 (0.91–1.21)	0.56
Diagnostic hydrocephalus	0.64 (0.15–2.82)	0.56	0.24 (0.01–5.86)	0.38	1.41 (0.60–3.32)	0.44	1.72 (0.62–4.81)	0.31
EOT hydrocephalus	0.58 (0.13–2.59)	0.48	0.40 (0.03–5.14)	0.48	1.18 (0.48–2.87)	0.72	1.39 (0.48–4.06)	0.54
IVH present	0.47 (0.19–1.16)	0.10	0.15 (0.03–0.73)	0.02	0.93 (0.45–1.94)	0.85	0.68 (0.28–1.66)	0.40
Diagnostic IVH volume	0.93 (0.85–1.02)	0.13	0.89 (0.7501.06)	0.18	0.96 (0.91–1.02)	0.18	0.97 (0.91–1.04)	0.38
Stability IVH volume	0.92 (0.83–1.01)	0.09	0.87 (0.72–1.04)	0.13	0.98 (0.93–1.03)	0.34	0.99 (0.93–1.04)	0.63
EOT IVH volume	0.96 (0.86–1.07)	0.43	0.83 (0.62–1.10)	0.20	1.00 (0.95–1.07)	0.75	1.02 (0.94–1.09)	0.70
Diagnostic ICH volume	0.99 (0.97–1.02)	0.49	0.96 (0.92–1.00)	0.04	1.01 (0.99–1.02)	0.84	1.00 (0.97–1.02)	0.64
Stability ICH volume	0.99 (0.96–1.01)	0.33	0.98 (0.94–1.02)	0.34	1.00 (0.99–1.02)	0.60	1.00 (0.98–1.02)	0.91
EOT ICH volume	1.01 (0.99–1.03)	0.22	1.01 (0.99–1.03)	0.42	1.01 (1.00–1.03)	0.02	1.01 (1.00–1.03)	0.16
Delta ICH volume								
EOT ICH <15 mm	0.23 (0.04–1.44)	0.12	0.17 (0.008–3.83)	0.27	0.40 (0.13–1.22)	0.11	0.54 (0.15–1.94)	0.34
Diagnostic edema volume	1.02 (1.00–1.06)	0.12	0.98 (0.94–1.04)	0.57	1.02 (0.99–1.05)	0.26	1.00 (0.97–1.04)	0.88
Stability edema volume	1.00 (0.97–1.04)	0.65	1.01 (0.98–1.04)	0.53	1.01 (0.98–1.03)	0.54	1.01 (0.99–1.03)	0.49

SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; GCS, Glasgow coma scale; NIHSS, NIH stroke scale; EVD, external ventricular drain; IPM, intraparenchymal monitor; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; ICP, intracranial pressure; EOT, end of treatment.

TABLE 3 | Results of multivariable model for percentage of ICP and CPP threshold readings in MIS (vs. medical management only) group patients.

Primary outcomes								
	Percentage ICP > 20 mm Hg	**Percentage ICP > 20 mm Hg**	**Percentage ICP > 30 mm Hg**	**Percentage ICP > 30 mm Hg**	**Percentage CPP < 70 mm Hg**	**Percentage CPP < 70 mm Hg**	**Percentage CPP < 60 mm Hg**	**Percentage CPP < 60 mm Hg**
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
MIS group								
Model 1*	0.27 (0.09–0.83)	0.02	0.04 (0.007–0.21)	<0.001	0.32 (0.14–0.71)	0.005	0.31 (0.11–0.87)	0.03
Model 2†	0.27 (0.09–0.83)	0.02	0.08 (0.01–0.59)	0.01	0.31 (0.14–0.71)	0.005	0.32 (0.11–0.92)	0.03

Model 1: Stepwise backward regression model.*

Model 2† : Multivariable model adjusted for age, presenting systolic blood pressure, IVH, and treatment group.

ICP, intracranial pressure; CPP, cerebral perfusion pressure; MIS, minimally invasive surgery; OR, odds ratio; IVH, intraventricular hemorrhage.

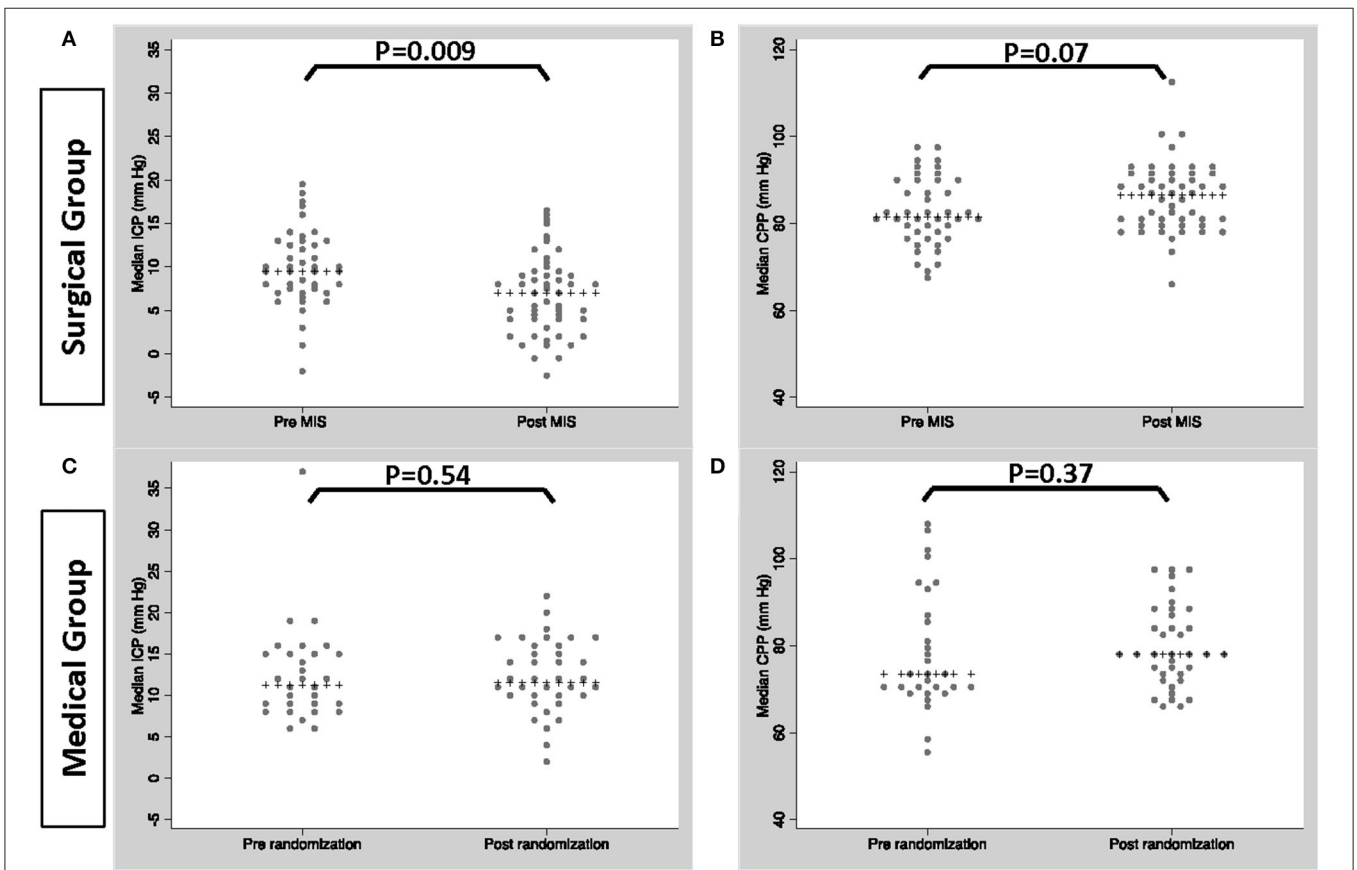

FIGURE 2 | Median ICP/CPP in patients within the MIS group, pre and post MIS **(A,B)** and patients within the medical group pre and post randomization **(C,D)**.

mortality and of short-term poor outcome at all thresholds tested from <65 to <90 mm Hg and of long-term poor outcome at <65 and <75 mm Hg. We did not find significant associations between monitored time above and below ICP/CPP thresholds, respectively, with long-term functional outcomes in this study which might be explained by insufficient power due to small sample size, and relatively infrequent ICP events >30 mmHg and CPP events <60 mmHg. Also, it is possible that parenchymal injury from large ICH volume has a greater impact on functional outcomes compared to the analysis of patients in the CLEAR III trial who had relatively small ICH. One study of 243 patients with predominantly supratentorial ICH (median volume 24 ml) showed no correlation between area under the curve of either ICP or CPP and long-term functional outcomes at 12 months, at CPP thresholds of <60 mmHg or <70 mmHg which is consistent with our findings (4).

TABLE 4 | Results of logistic regression models for short and long-term functional outcome and mortality.

Secondary outcomes at 30 days	Percentage ICP>20 mm Hg*	Percentage ICP>20 mm Hg*	Percentage ICP>30 mm Hg*	Percentage ICP>30 mm Hg*	Percentage CPP<70 mm Hg	Percentage CPP<70 mm Hg	Percentage CPP<60 mm Hg	Percentage CPP<60 mm Hg
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Poor neurologic outcome at 30 days	All ICP and CPP thresholds predict poor neurologic function at 30 days perfectly: unable to model							
Mortality at day 30	1.27 (0.78–2.08)	0.34	3.24 (0.61–17.4)	0.28	1.42 (1.02–1.97)	0.04	3.00 (1.36–6.62)	0.006
Secondary outcomes at 365 days								
Poor neurologic outcome at 365 days	1.09 (0.69–1.71)	0.72	0.91 (0.62–1.34)	0.64	1.22 (0.86–1.73)	0.26	1.52 (0.58–3.97)	0.39
Mortality at day 365	1.58 (1.01–2.48)	0.04	1.84 (1.01–3.33)	0.04	1.71 (1.12–2.59)	0.01	2.17 (0.88–5.36)	0.09

**Multivariable model for neurologic function/mortality at 30 and 365 days adjusted for number of ICP/CPP readings, age, GCS, presence of IVH, ICH volume, and deep ICH location. ICP, intracranial pressure; CPP, cerebral perfusion pressure; MIS, minimally invasive surgery; OR, odds ratio; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale.*

Rationale for ICP Monitoring

Despite the high prevalence of increased ICP after ICH, the impact of ICP monitoring on mortality and functional outcomes is not well-established. A secondary analysis of the MISTIE III trial reported that patients with ICP monitors were more likely to have a poor functional outcome at 1 year (77.1 vs. 53.8%) without a significant influence on mortality at 1 year questioning the benefit of ICP monitoring in patients with ICH (11). Patients with ICP monitors, however, had higher clinical severity including higher ICH volume, higher IVH volume and more frequent hydrocephalus on diagnostic CT. Hydrocephalus may be an important clinical factor requiring EVD placement. EVDs in the MIS group were most commonly placed prior to surgery (67.6%) and less commonly at time of MIS. These are association studies, however, and do not imply causality or any treatment recommendations regarding ICP or CPP control. Although ICP was treated aggressively per protocol, ICP and CPP may be markers of outcome but not necessarily "modifiable" therapeutic targets.

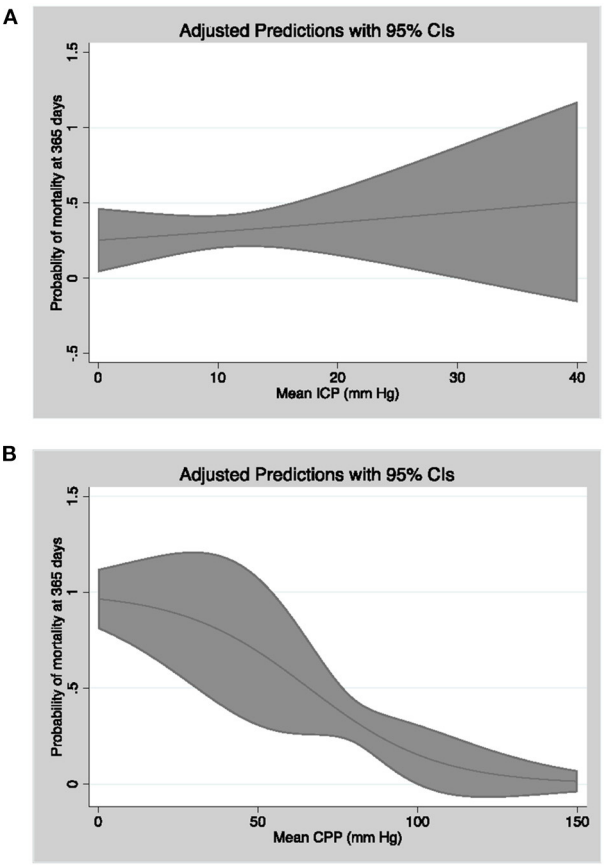

FIGURE 3 | Linear model of probability of mortality at 365 days as a function of mean CPP **(A)** and mean ICP **(B)** with 95% confidence intervals.

Impact of Minimally Invasive Surgery on ICP and CPP

MISTIE III, one of the largest randomized trials of stereotactic aspiration plus thrombolysis for ICH found a mortality benefit in the surgical cohort, but did not show improvement in functional outcomes at 1 year, with the exception of patients who achieved an end of treatment ICH volume <15 ml (12, 13). The mechanism by which surgical evacuation reduces mortality, and with sufficient clot removal, potentially improves outcomes is likely multifactorial; mitigation of secondary injury pathways, edema formation and both suboptimal ICP and CPP likely play a role. After adjusting for confounding variables, patients who underwent clot volume reduction with minimally invasive surgery experienced a lower monitored time burden of ICP $\geq$ 20 and 30 mmHg, and CPP <60 and <70 mmHg. The use of mostly EVDs in both medical and surgical patients suggests that CSF drainage likely contributed to ICP control although ICH volume reduction also played a significant role in improving intracranial hemodynamic measures. Sun et al. investigated intraoperative changes in ICP to calculate intraoperative alterations in the

"brain-hematoma" pressure gradients (14). Patients undergoing large trauma craniotomy had rapid decreases in ICP and a small "brain-hematoma" pressure gradient after the hematoma was removed. For patients undergoing keyhole endoscopy, ICP decreased slowly and the "brain-hematoma" pressure gradient was initially large, and slowly decreased. The latter procedure more closely resembles stereotactic aspiration with thrombolysis used in MISTIE III and is consistent with our finding of a slow reduction in ICP over several days as hematoma volume was gradually reduced.

LIMITATIONS

These data should be considered alongside a number of limitations. The patient sample size was relatively small, and may not be generalizable to all large ICH volume patients, given the stringent inclusion criteria of a clinical trial. We attempted to prevent over-fitting of multivariable models and may have missed important confounders. Most importantly is confounding by indication since ICP monitors were placed at the discretion of the treating physician, and most commonly in higher severity patients. However, the randomized design mitigates this concern with respect to the MIS intervention. We included patients with both intraparenchymal monitors and patients with EVDs which introduces bias into ICP readings, and the effect of CSF drainage. However, a similar number of patients in the medical and surgical treatment groups had ICP monitors placed. Despite these limitations, this dataset was systematically monitored for correctness, has well-defined objective inclusion criteria, blinded assessment of outcome and adds important information about the characteristics and sequelae of elevated ICP and low CPP in patients with ICH treated with surgical evacuation. While the population studied is small, it is important to note that a robust relationship between mitigation of ICP/CPP thresholds and mortality was identified, similar to that of another large trial for IVH (15).

CONCLUSION

This study supports the concept that ICH volume reduction with minimally invasive surgery decreases monitored time spent with high ICP and low CPP in patients with large ICH. Decreasing high ICP and low CPP burden is associated with improved short- and long-term mortality and may represent a mechanism by which mortality outcomes are improved by minimally invasive surgery.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins Hospital institutional review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA-K and WZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. WZ and MA-K: study concept and design. MA-K, DH, and WZ: acquisition, analysis, or interpretation of data. MA-K and WZ: drafting of the manuscript. MA-K, YL, RT, RA, AH, JG, IA, DH, and WZ: critical revision of the manuscript for important intellectual content. MA-K, WZ, and RT: statistical analysis. WZ and DH: administrative, technical, or material support. WZ: study supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Blood Pressure Management After Endovascular Thrombectomy

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Endovascular thrombectomy (EVT) has changed the landscape of acute stroke therapy and has become the standard of care for selected patients presenting with anterior circulation large-vessel occlusion (LVO) stroke. Despite successful reperfusion, many patients with LVO stroke do not regain functional independence. Particularly, patients presenting with extremes of blood pressure (BP) or hemodynamic variability are found to have a worse clinical recovery, suggesting blood pressure optimization as a potential neuroprotective strategy. Current guidelines acknowledge the lack of randomized trials to evaluate the optimal hemodynamic management during the immediate post-stroke period. Following reperfusion, lower blood pressure targets may be warranted to prevent reperfusion injury and promote penumbral recovery, but adequate BP targets adjusted to individual patient factors such as degree of reperfusion, infarct size, and overall hemodynamic status remain undefined. This narrative review outlines the physiological mechanisms of BP control after EVT and summarizes key observational studies and clinical trials evaluating post-EVT BP targets. It also discusses novel treatment strategies and areas of future research that could aid in the determination of the optimal post-EVT blood pressure.

Keywords: blood pressure, thrombectomy, stroke, cerebral autoregulation, neurocritical care

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INTRODUCTION

Large vessel occlusions (LVO) account for approximately one third of ischemic strokes but contribute to more than half of all stroke-related mortality and severe disability (1–3). Over the last several years, LVO strokes are increasingly recognized as unique entities with distinct cerebrovascular pathophysiology and treatment strategies. Acute stroke interventions have traditionally focused on the rapid recanalization of the occluded vessel to restore blood flow to the ischemic tissue. This may be achieved, in a small percentage, by administering intravenous alteplase or, much more effectively, with the use of endovascular thrombectomy (EVT) (4–6). Despite successful reperfusion, LVO stroke patients may continue to have infarct growth, and half do not regain their functional independence, evidencing a need for adjunctive therapies to further improve outcomes (7, 8). Recent evidence suggests that hemodynamic management may play an important role in post-EVT care. While optimal BP targets remain unknown, clinicians must balance the need for sufficient post-thrombectomy blood flow to prevent further infarct growth with the risk of reperfusion injury and hemorrhagic transformation.

This narrative review aims to describe the physiological mechanisms of how BP influences outcome after EVT, provide an overview of observational studies, and discuss completed and ongoing clinical trials of BP management after EVT. We will also discuss recent advances in personalized blood pressure management approaches and suggest potential areas of future research.

CEREBRAL AUTOREGULATION AND PHYSIOLOGIC CONSIDERATIONS OF BP MANAGEMENT AFTER EVT

To understand the importance and relevance of blood pressure in acute ischemic stroke, it is helpful to review normal brain vascular physiology and how it can become impaired during ischemia. In a healthy brain, cerebral blood flow (CBF) depends on the pressure gradient between the cerebral arteries and veins. The cerebral arterial pressure is equivalent to the systemic arterial blood pressure (ABP), while the cerebral venous pressure is equivalent to the intracranial pressure (ICP) (9, 10). Cerebral autoregulation is the process in which the brain is able to maintain a steady CBF despite fluctuations in ABP and ICP (9, 11). The mechanisms of autoregulation are not entirely understood but have been shown to involve changes in arteriolar diameter, which directly affects cerebral vascular resistance (CVR) (11). CBF is directly related to ABP and inversely related to CVR, such that $CBF = ABP/CVR$ (12, 13).

Following vessel occlusion, there is a reduction in CBF to the dependent vascular territory. Below a critical threshold of ∼10 ml/100 g brain tissue/min, disruption of ion homeostasis and membrane depolarization lead to a loss of neuronal electrical activity (14, 15). Unless blood flow is rapidly restored, the damage becomes irreversible, and cell death occurs. Surrounding the infarct core, there is a zone of hypoperfused, functionally impaired but still viable tissue known as the "ischemic penumbra" (14, 16). The low perfusion pressure in the penumbra creates a pressure gradient that promotes retrograde flow to the ischemic territory (17). The rate of ischemic core growth depends on the duration of ischemia and the degree of collateral blood flow (18).

Ischemia-induced vasoparalysis in the penumbra leads to loss of intrinsic autoregulatory function (19, 20). The decrease in downstream perfusion pressure distal to the occluded vessel, with compensatory dilation of brain arterioles, further impairs autoregulation and causes the CBF to become passively dependent on the ABP (21). The loss of autoregulation after LVO can persist even after revascularization is achieved, rendering the brain vulnerable to fluctuations in perfusion pressure (22, 23). Low ABP can exacerbate cerebral hypoperfusion and cause further ischemic core growth, particularly among patients with incomplete reperfusion. In contrast, elevated ABP may cause excessive flow, cerebral edema, and hemorrhagic conversion (22, 23). Advanced age, greater stroke severity, hyperglycemia, large infarct volume, treatment with alteplase, and poor collateral status have been associated with the development of hemorrhagic transformation and may further increase the risk of reperfusion injury with elevated BP (24, 25). After thrombectomy, the optimal BP requires a careful balance of these opposing concerns to provide the ideal environment for penumbral recovery while avoiding secondary injury from hypo- or hyperperfusion.

Targeted BP therapies aim to maintain BP below or above a fixed threshold. However, BP is one of the most dynamic physiologic variables with significant changes during the early phase after LVO stroke. Sustained increases in BP variability (BPV) may reflect alterations in the mechanisms responsible for cardiovascular homeostasis and represent a potentially modifiable contributor to end-organ damage and poor neurological recovery after LVO stroke (26–30). Although the exact mechanism by which BPV may exert a negative influence remains unknown, direct exposure of the vulnerable oligemic brain tissue to perfusion fluctuations created by elevated systemic BPV may play a critical role. Short-term BP fluctuations can occur due to various internal and external factors, including central sympathetic drive, arterial tone, cardiopulmonary reflexes, humeral mechanisms, blood viscosity, volume status, and medications (31).

RELEVANT OBSERVATIONAL STUDIES

Current guidelines by the American Heart Association released in 2019 recommend maintaining a BP goal of ≤180/105 for the first 24 h after mechanical thrombectomy (32). These guidelines are based on limited evidence and do not account for individual patient factors such as reperfusion status or infarct volume. Sustained elevations of systolic blood pressure (SBP) have been associated with higher rates of symptomatic intracerebral hemorrhage (sICH) and poor functional outcomes (33–36). The Blood pressure After Endovascular Stroke Therapy (BEST) multicenter prospective cohort study of 485 patients found that a peak post EVT SBP of >158 mmHg best discriminated between favorable (mRS 0–2) from unfavorable (mRS 3–6) (37), confirming the results of a smaller, previously published study (33). To further characterize BP trajectories during the first 72 h after thrombectomy, Kodali et al. used a person-centered modeling approach to identify subgroups of patients with similar BP patterns (38). Patients with high and high-to-moderate SBP trajectories had significantly greater odds of an unfavorable outcome compared to those with persistently low SBP post-EVT.

Several studies have suggested that the optimal BP target may depend on the degree of recanalization (35, 39, 40). Mistry et al. retrospectively evaluated a group of 228 patients with LVO stroke and found that higher peak values of systolic blood pressure in the first 24 h after EVT independently correlated with worse 90-day outcomes (41). Interestingly, hemorrhagic complications, a marker of reperfusion injury, were observed at lower mean peak SBP levels among recanalized patients compared to non-recanalized patients (41). However, others consistently found that the best outcomes in patients with successful recanalization occurred at lower blood pressures (36, 39, 40, 42, 43). Recanalized patients (TICI 2b-3) demonstrate a significant spontaneous decrease in SBP over 24 h after EVT (36). The relationship between post-EVT BP and functional outcomes becomes linear, with the most favorable outcomes at an SBP of 110 mmHg

(35, 36). In contrast, non-recanalized patients (TICI 0-2a) show a diminished decline in post-EVT BP, and the relationship with functional outcomes is U or J-shaped. Both high and low average post EVT SBP are associated with worse outcomes.

Whether the association between lower post-EVT BP and better functional outcome in patients with successful recanalization is causal or just a reflection of other stroke-related factors, such as better collaterals, remains unclear. However, physiological consideration and the results mentioned above have led many stroke centers to adopt a tiered approach to BP management after thrombectomy stratified by reperfusion status. An online survey regarding BP management post EVT performed across StrokeNet sites in the United States found that most institutions (39%) used a target SBP of 120–139 mmHg on recanalized patients and permissive hypertension on non-recanalized patients (44). However, the complexity of location of vessel occlusion, degree of recanalization, and final infarct volume suggest that a more nuanced approach may be necessary.

Several observational studies have investigated the effect of differing BP treatment protocols after thrombectomy on radiographic and clinical outcomes. Goyal et al. separated patients into three groups based on post-EVT achieved SBPs of <140, <160, and <180 mmHg. Actual BP targets varied and depended on the treating physician's preference and the patient's clinical status. The investigators found that achieving an SBP goal of <160 mmHg during the first 24 h post-EVT was associated with lower odds of mortality than permissive hypertension (34). This study did not find any significant functional outcome differences at 3 months, but results may have been underpowered due to the small sample size. A more recent large multicenter study by Anadani et al. showed that SBP targets of <140 mmHg after successful reperfusion were associated with lower odds of unfavorable outcome and need for hemicraniectomy than SBP targets of <180 mmHg (36, 42).

Besides BP targets, BPV has emerged as an important aspect of post-EVT hemodynamic management. Studies found that BPV is elevated in patients with larger strokes and associated with higher rates of death and disability in stroke patients that did not undergo EVT (30, 45). Furthermore, antihypertensive drug classes have differing effects on interindividual variation in blood pressure. Calcium-channel blockers such as amlodipine (oral) and nicardipine (intravenous) have been shown to reduce BPV, while b-blocker may increase it (46, 47). Several recent studies have focused on the relationship between BPV and outcome in patients receiving EVT. While there was significant heterogeneity in the frequency and duration of measurements as well as BPV parameters, high BPV was consistently associated with a reduced likelihood of neurological recovery (29, 30, 48).

The effect of reperfusion status on the relationship between BPV and outcome is more controversial. After incomplete reperfusion, higher infarct volumes with surrounding ischemic tissue may make patients more vulnerable to BP fluctuations. Conversely, successful recanalization exposes friable brain tissue to changes in perfusion pressure, potentially increasing the risk of reperfusion injury. While one of the early studies showed the association between BPV and unfavorable outcome appeared strongest among patients with incomplete recanalization (29), others found the opposite effect (49–51). In a *post-hoc* analysis of the BEST study, patients were stratified by recanalization status (TICI 0-2a, 2b, and 3), and high BPV was associated with poor outcomes for patients with TICI 3 exclusively (37). Similarly, another study showed that the effects of higher BPV on outcomes were more pronounced among patients with better reperfusion status (52). A link between higher BP variability and an increased risk of reperfusion injury is supported by Kim et al. They found that high BP variability in the first 24 h following successful EVT was associated with an increased risk of symptomatic intracerebral hemorrhage (53). However, other investigators could not confirm this association (51).

Whether the relationship between high BPV and outcome is causative or an epiphenomenon of stroke-related factors and associated physiologic stressors remains unknown. Chang et al. demonstrated an inverse relationship between BPV parameters and the degree of recanalization (28). They hypothesized that lower recanalization success might increase the chances of insular and adjacent tissue destruction resulting in sympathetic overactivity. However, despite solid conceptual reasons to support a link between BPV and infarct location, other investigators found no association between BPV and injury to the structures of the central autonomic network, arguing against a central origin (51).

While evidence suggests that maintaining a stable BP with low variability after successful thrombectomy may be as important as controlling mean peak BP values, there has not been a clinical trial dedicated to reducing BPV in stroke patients. A summary of observational trials can be found in **Table 1**.

CLINICAL TRIALS EVIDENCE

The recently published Blood Pressure Target in Acute Stroke to Reduce hemorrhaGe After Endovascular Therapy (BP TARGET) was a prospective, randomized, multicenter, controlled, open-label trial aimed to evaluate if BP control with a goal of 100–129 mmHg could reduce the incidence of sICH and improve functional outcomes compared to a goal of 130–185 mmHg in successfully recanalized post-EVT patients (49). A total of 324 patients were enrolled and randomly assigned to either group within 1 h after EVT. Target BP range was maintained for 24 h after EVT. The choice of the antihypertensive agent was at the discretion of the medical provider. To assess the occurrence of sICH, a CT scan was obtained within 24–36 h of EVT. The study did not show any difference in functional outcome or reduction in the rates of sICH with more intensive BP control. Mazighi et al. (50) However, adherence to the assigned BP target was suboptimal, with only 50% of patients in the intense target group achieving the BP goal of 100–129 at 3 h. Moreover, the median percentage of time in range was only 61% for the 130–185 mmHg group and 66% for the 100–129 mmHg group. The study protocol required a time within the assigned BP range of at least 80%. These results indicate that despite setting SBP targets, post-EVT blood pressure may be difficult to control in clinical practice. Furthermore, the frequent administration of antihypertensive

TABLE 1 | Summary of observational studies evaluating post-EVT static BP and dynamic BP (BPV).

References	Sample size and reperfusion status	Monitoring duration and frequency of BP recording	Blood pressure measurements and comparisons	Main results and conclusions
Fixed blood pressures thresholds				
Goyal et al. (34)	217 patients, 67% achieved TICI 2b-3	BP was recorded hourly for 24 h after EVT.	SBP groups of <180/110, <160/90, or <140/90	A 10 mmHg increase in maximum SBP was associated with a lower likelihood of 3-month functional independence (OR 0.70; 95% CI 0.56–0.87, $p < 0.001$) and a higher odds of 3-month mortality (OR 1.49; 95% CI 1.18–1.88; $p < 0.001$). A BP target of <160/90 mmHg was associated with lower mortality than permissive hypertension (OR 0.08; 95% CI 0.01–0.54; $p = 0.01$).
Mistry et al. (41)	228 patients, 76% achieved TICI of 2b-3	BP was recorded hourly for 24 h after EVT.	Mean, maximum, and minimum, SBP	The maximum SBP independently correlated with worse 90-day mRS (OR 1.02; 95% CI 1.01–1.03; $p = 0.004$) and hemorrhagic complications within 48 h (OR 1.02; 95% CI 1.01–1.04; $p = 0.002$).
Goyal et al. (54)	88 patients with TICI 0-2a	BP was recorded hourly for 24 h after EVT.	Mean, maximum, and minimum SBP, and DBP	Maximum SBP was lower in patients with good outcome (mRS 0-2) at 3 months (160 vs. 179 mmHg, $p = 0.001$). Higher maximum SBP was independently associated with lower odds of functional independence (OR per 10 mmHg 0.55; 95% CI 0.39–0.79; $p = 0.001$),
Anadani et al. (55)	298 patients, 92.6% achieved TICI of 2b-3	BP was recorded hourly for 24 h after EVT.	Mean and maximum SBP within 24 h post EVT	Patients with average SBP of <120 mmHg had better 90-day outcomes (median mRS 2 vs. 3, $p < 0.001$) and lower mortality (12 vs. 26%, $p < 0.01$) compared to patients >120 mmHg. Higher mean SBP was associated with a lower chance of good outcome (OR 0.97; 95% CI 0.94–0.99, $p = 0.026$) No association was found between BP and hemorrhagic transformation.
Anadani et al. (42)	1,245 patients from 10 stroke centers with mTICI score of 2b-3	BP was recorded hourly for 24 h after EVT.	Mean, maximum, and minimum SBP, and DBP	Elevated admission SBP, mean SBP, maximum SBP, SBP range, and SBP SD were associated with increased risk of sICH and the need for hemicraniectomy. Elevated mean SBP, maximum SBP, and SBP range were associated with worse outcomes. Patients with SBP 101–120 mmHg had the highest rate of good outcome (mRS 0-2) and lowest rates of mortality, ICH, and hemicraniectomy.

(Continued)

TABLE 1 | Continued

References	Sample size and reperfusion status	Monitoring duration and frequency of BP recording	Blood pressure measurements and comparisons	Main results and conclusions
McCarthy et al. (39)	212 patients, 85.4% achieved TICI of 2b-3	BP was recorded hourly while patients were in the ICU. BP parameters were retrospectively abstracted from the data available in the medical record.	Admission SBP/DBP, peak intraoperative SBP/DBP, daily peak SBP/DBP measured for first 3 days post-EVT	Incremental 10 mmHg increases in peak 24-h SBP were independently associated with increased likelihood of sICH (OR 1.2; 95% CI 1.01–1.49, $p = 0.048$) and a lower probability of functional independence (OR 0.85, 95% CI 0.73–0.98; $p = 0.031$).
Chang et al. (40)	102 patients, 88.2% achieved TICI of 2b-3	After EVT, BP was measured every 15 min for 2 h, every 30 mins for 6 h, then every hour for 16 h.	24-h mean SBP >130 mmHg vs. <130 mmHg	A mean SBP >130 mmHg during the 24 h after EVT was associated with a shift toward a worse outcome on the mRS at 3 months (OR 2.66; 95% CI 1.11–6.41; $p = 0.03$)
Mistry et al. (56)	485 patients from 12 centers, 76% achieved TICI 2b or 3	BP was recorded for 24 h after EVT, frequency of recordings was institution dependent	Maximum SBP	Higher peak SBP associated with poor outcome in unadjusted (OR 1.02; 95% CI 1.01–1.03; $p < 0.001$) but not in adjusted analysis (OR 1.0; 95% CI 0.99–1.01; $p = 079$) A peak SBP of 158 mmHg best discriminated between good (mRS 0-2) and poor (mRS 3-6) outcomes.
Anadani et al. (57)	1,019 patients from 8 stroke centers, with mTICI score of 2b-3	BP was recorded for 24 h after EVT, frequency of recordings was institution dependent	SBP groups of <140, <160, or <180 mmHg	SBP of <140 mmHg was associated with a higher likelihood of good outcome (mRS of 0-2 at 90 days) and a lower likelihood of hemicraniectomy compared to SBP goal of <180 mmHg (OR 1.53; 95% CI 1.07–2.19 and OR 0.18; 95% CI 0.16–0.2, respectively). SBP goal of <160 mmHg was associated with lower odds of 90 day mortality compared to SBP goal of <180 mmHg (OR 0.41; 95% CI 0.18–0.96).
Matusevicius et al. (36)	3,631 patients, 80.4% achieved TICI 2b-3	SBP was recorded before EVT, at the end of EVT, and 2, 4, 12, and 24 h after EVT	Mean SBP and DBP, SBP categorized in 20 mmHg increments	In the TICI 2b-3 group, SBP of >160 mmHg was associated with less functional independence (OR 0.28; 95% CI 0.15–0.53) and increased rates of sICH (OR 6.28; 95% CI 1.53–38.09) compared to the reference group with <120 mmHg. In the TICI 0-2a group, SBP>160 mmHg was associated with an increased likelihood of sICH (OR 6.62; 95% CI 1.07–51.05).
Blood pressure variability				
Chang et al. (28)	303 patients, 79.9% achieved TICI of 2b-3	After EVT, BP was recorded every 15 min for 2 h, every 30 mins for 6 h, then every hour for 16 h.	SBP mean, SD, CV, and VIM	BPV parameters (SD, CV, and VIM) over 24 and 48 h decreased with a higher degree of recanalization. Higher BPV was associated with early neurological deterioration and poor functional outcomes at 3 months. (OR range 1.26–1.64; all $p < 0.05$)

(Continued)

TABLE 1 | Continued

References	Sample size and reperfusion status	Monitoring duration and frequency of BP recording	Blood pressure measurements and comparisons	Main results and conclusions
Bennett et al. (29)	182 patients, 54.9% achieved TICI of 2b-3	After EVT, BP was recorded every 15 mins for 2 h, every 30 mins for 6 h, then every hour for 16 h.	SBP SD, CV, and SV	Increased BPV parameters (SD, CV, and SV) were associated with a 1-point increase in 90-day mRS (OR range 2.30–4.38; all $p < 0.002$). SV was the strongest and most consistent predictor of worse mRS (OR range 2.63–3.32; all $p < 0.007$)
Kim et al. (53)	211 patients with TICI 2b-3	BP was recorded hourly for 24 h after EVT.	SBP and DBP mean, maximum, minimum, range, SD, CV, SV, and TR	The TR of SBP variation was independently associated with sICH (OR 1.71; 95% CI 1.01–2.89)
Cho et al. (51)	378 patients, 82.8% achieved TICI of 2b-3	BP was recorded hourly for 24 h after EVT.	SBP and DBP mean, SD, CV, and SV	Higher mean SBP and SBP SV during the first 24 h after EVT was associated with a reduced probability of a favorable 3-month outcome (each 10 mmHg increase OR 0.82; 95% CI 0.69–0.97 and each 10% increase OR 0.37; 95% CI 0.18–0.76, respectively). Effects of mean SBP and SBP SV on outcomes were more pronounced on patients with successful reperfusion.
Mistry et al. (37)	443 patients, 88.4% achieved TICI 2b or 3	BP was recorded hourly for 24 h after EVT.	SBP and DBP SD, CV, ARV, SV, and rSD	The highest tertile of systolic BPV (SD, CV, SV, and rSD) was associated with an increased risk of poor outcome (mRS 3-6) and death (adjusted OR range 1.6–2.9, all $p < 0.05$). The association was strongest in patients with complete reperfusion.
Huang et al. (52)	502 patients from 3 stroke centers with mTICI score of 2b-3	BP was recorded hourly for 24 h after EVT.	SBP and DBP SD, maximum, minimum, CV, and SV	Higher CV (OR 1.09; $p = 0.035$), SV (OR 1.08; $p = 0.004$), and SD (OR 1.07; $p = 0.027$) were associated with lower likelihood of a good outcome (mRS 0-2) and increased odds of sICH. The relationship between BPV (SBD SD) and outcome depended on recanalization status.

OR, odds ratio; CI, confidence interval; mTICI, modified Thrombolysis in Cerebral Ischemia; BP, blood pressure; SBP, systolic blood pressure; SBPV, systolic blood pressure variability; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage; DBPV, diastolic blood pressure variability; SITS-TBYR, Safe implementation of treatments in stroke international thrombectomy registry; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; SV, successive variation; ARV, average real variability; rSD, residual standard deviation; TR, time rate.

medication with more intensive BP control could have induced higher BPV, potentially offsetting the benefits of BP lowering.

Several ongoing prospective randomized control trials are further evaluating the impact of BP after successful EVT. The Blood pressure After Endovascular Stroke Therapy (BEST-II, NCT04116112) is a phase 2 clinical trial that randomly assigns patients with TICI 2b-3 to BP targets of ≤140, ≤160, and ≤180 mmHg. These BPs will be maintained for 24-h post-EVT, and the outcomes measures will be final infarct volume at 36-h and 3-month mRS. The Outcome in patients Treated with Intraarterial Thrombectomy- Optimal Blood Pressure Control (OPTIMAL_BP; NCT04205305) is a clinical trial evaluating the impact of SBP targets <140 vs. <180 mmHg on 36-h sICH, 90-day mRS, and mortality on patients with successful reperfusion after EVT. Similarly, the Second Enhanced Control of Hypertension and Thrombectomy Stroke Study (ENCHANTED 2; NCT04140110) trial will assign patients to an SBP target of <120 vs. 140–180 mmHg during the first 72 h after EVT to evaluate the effect on 90-day mRS. Finally, the Invasive Control of Blood Pressure in Acute Ischemic Stroke

After Endovascular Therapy on Clinical Outcomes (CRISIS I; NCT04775147) trial will compare SBP targets of <140 and <120 mmHg on 90-day sICH and mRS. All ongoing clinical trials will evaluate patients with successful EVT with TICI 2b-3, which is achieved in over 80% of patients with modern EVT techniques. The results of these trials will provide much-needed high-quality evidence and inform blood pressure management after thrombectomy. A summary of completed and ongoing prospective studies can be found in **Table 2**.

INDIVIDUALIZED BP TARGETS

Despite the consistent findings of better outcomes with lower post-thrombectomy BP, reducing BP to the same fixed target may be an oversimplification of the complex physiology. The neutral results of the BP TARGET trial suggest that stratification by reperfusion status may be inadequate for the heterogenous EVT patient population. A one-size-fits-all approach does not account for individual patient factors such a collateral status, infarct size, or history of hypertension. For example, a patient with chronic hypertension may have a rightward shifted autoregulatory curve (58), and aggressive BP lowering could result in cerebral hypoperfusion and infarct expansion. Similarly, a patient with TICI 2b reperfusion may still have significant residual tissue at risk and thus require different BP targets post-EVT than a patient with TICI 3 reperfusion. In contrast, a patient with a large infarct despite successful EVT who also received intravenous thrombolytics is at increased risk of reperfusion injury related to hyperperfusion of vascular beds with failed autoregulation. This patient may require strict BP control. In clinical practice, not all thrombectomy patients are treated equally, and survey data indicate that physicians often select BP parameters on a per-patient basis (48). While it may be reasonable to aim for a lower BP, particularly after successful reperfusion, the optimal target remains unknown.

Besides maintaining BP below a fixed, predetermined value, there is a strong rationale for a more personalized BP management. We recently compared fixed vs. personalized autoregulation-oriented BP thresholds after EVT (59). Near-infrared spectroscopy-derived tissue oxygenation (NIRS) was used as a surrogate of CBF and compared to changes in mean arterial pressure (MAP) to calculate the autoregulatory index and the BP range at which autoregulation is most preserved. This study showed that exceeding this blood pressure range was associated with an increased risk of hemorrhagic transformation and worse functional outcomes. Using the same dataset, the association was not seen when applying fixed blood pressure thresholds. Currently, there are no clinical trials to support autoregulation-guided BP management as a potential post-EVT neuroprotective strategy. An impediment to testing autoregulation-guided blood pressure management has been the complex task of acquiring, integrating, and real-time processing of high-frequency physiologic data. Commercially available software and hardware solutions are emerging, which may help to implement a personalized approach to BP management in the clinical setting. A phase II clinical trial of autoregulation-oriented BP management after severe TBI has recently been completed, and the results are expected soon. The study will provide further data regarding the feasibility of a personalized BP management approach that would also apply to other forms of acute brain injury such as ischemic stroke.

Another easily implementable and generalizable approach to personalized BP management is currently being tested in the Effect of Individualized vs. Standard Blood Pressure Management during Mechanical Thrombectomy for Anterior Ischemic Stroke Trial (DETERMINE; NCT04352296). The study will compare maintaining the BP within 10% of the first MAP measured in the angiography suite vs. a fixed blood pressure goal of 140–180 mmHg. Selecting BP targets based on an individual patients' baseline BP could represent a valid method to incorporate patient-specific factors without the need for advanced monitoring. A similar approach could potentially also be implemented in the post-EVT setting.

FUTURE DIRECTIONS

Management of hemodynamics in the post-EVT patient is complex and requires careful BP control to ensure adequate CBF to supply the ischemic penumbra while avoiding reperfusion injury. Several clinical trials are underway to evaluate different fixed BP thresholds after EVT with successful recanalization. These studies will provide insight and guidance on the optimal post-EVT BP target. Still, future *post-hoc* analyses of these trials will be necessary to assess if stroke or patient characteristics have any effect on outcome.

Patients with high SBP trajectories during the first 24 h after mechanical thrombectomy are at increased risk of an unfavorable outcome. Future research should focus on the early identification of patients with high-risk trajectories that are most likely to benefit from intense post-EVT BP management. Autoregulation-guided blood pressure management may present an elegant alternative over the classical approach of maintaining blood pressure below a fixed, predetermined value. Clinical trials are needed to test autoregulation-based treatment strategies, including tailored pharmacologic blood pressure augmentation and lowering therapies based on patients' real-time autoregulatory status. Parallel lines of inquiry have begun in Europe targeting autoregulation in traumatic brain injury, further suggesting that this approach is timely and feasible in a multicenter clinical trial.

Other approaches to post-EVT BP management include the reduction of potentially harmful BP fluctuations. There is ample evidence showing that higher BPV is associated with worse functional outcomes and increased ICH risk. Although it is unclear if this is causative or an epiphenomenon related to the stroke itself, studies aiming to decrease BPV should be pursued (28, 29, 51, 53). The main challenge of assessing and manipulating BPV is the lack of bedside techniques to measure BPV in real-time and determine ideal candidates for clinical trials. Short-term BP variability has traditionally been measured as minute-to-minute or hour-to-hour oscillations. It requires a minimum 24-h period, which limits its usefulness for bedside clinical decision

TABLE 2 | Summary of completed and ongoing prospective studies evaluating post-EVT static BP and dynamic BP (BPV).

References	Year	Trial name and type	Status	Sample size	Blood pressure comparisons	Outcomes/goals
Mazighi et al. (49, 50)	2021	BP TARGET; Randomized, controlled, open-label trial. Patients were enrolled at 4 clinical sites.	Completed	324 patients post EVT with TICI 2b-3	Patients were randomized within 1 hour after EVT to BP target of 100–129 mmHg vs. 130–185 mmHg	Primary outcome: Radiographic ICH Secondary outcome: NIHSS at 24 h, and 3-month mRS Results: There was no difference in the rate of radiographic ICH or any of the secondary clinical efficacy outcomes.
PI: Mistry NCT04116112	Estimated completion: 2023	BEST-II; prospective, randomized trial	Ongoing	120 patients post EVT with TICI 2b-3	Assigned to SBP target of <180, <160, or <140 mmHg during first 24 h after EVT	Primary outcomes: Final infarct volume and utility-weighted mRS at 90 days
PI: Nam NCT04205305	Estimated completion: 2024	OPTIMAL BP; prospective, multicenter randomized trial	Ongoing	644 patients post EVT with TICI 2b-3	SBP target of <140 vs. <180 mmHg during the first 24 h after EVT	Primary outcomes: 90-day mRS, symptomatic ICH at 36 h, death at 90 days ASPECTS at 36 h
PI: Song NCT04140110	Estimated completion: 2023	ENCHANTED 2; prospective, randomized trial	Ongoing	2,236 patients post EVT with TICI 2b-3	SBP target of <120 vs. 140–180 mmHg during first 72 h after EVT	Primary Outcome: 90-day mRS
PI: Zhou NCT04775147	Estimated completion: July 2023	CRISIS I; prospective, randomized trial	Ongoing	500 patients post EVT with TICI 2b-3	SBP target of <120 vs. <140 mmHg during first 72 h after EVT	Primary Outcome: 90-day mRS

EVT, endovascular thrombectomy; TICI, thrombolysis in cerebral infarction; SBP, systolic blood pressure; BP, blood pressure; SBPV, systolic blood pressure variability; DBPV, diastolic blood pressure variability; BEST, Blood Pressure After Endovascular Stroke Therapy; mRS, modified Rankin Scale; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; DBP, diastolic blood pressure; ASPECTS, Alberta Stroke Program Early CT Score; PI, Primary Investigator.

making (29, 51–53). One promising approach that warrants further investigation is the use of spectral analysis of beat-to-beat blood pressure to detect harmful patterns of BP variability within minutes (60). Ferreira et al. performed 5-min BP recordings recorded using non-invasive finger plethysmography immediately following TICI 2b-3 revascularization and found that a high-frequency BPV was correlated with lower rates of early neurological recovery and worse functional outcomes (60).

Cerebral perfusion optimization in the immediate post-EVT period is a research priority in acute stroke. Current research is focused on elucidating the best hemodynamic biomarker for defining and monitoring the ideal BP target after stroke. Results from ongoing and future clinical trials will be critical to reduce reperfusion injury and maximize neurological recovery for all stroke patients undergoing endovascular therapy.

AUTHOR CONTRIBUTIONS

NP conceived the review. TP drafted the manuscript. SO-G, AH, and NP made critical revisions to the manuscript. All authors contributed to the article and approved the submitted version.

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End-of-Life Care Decision-Making in Stroke

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Stroke is one of the leading causes of death and long-term disability in the United States. Though advances in interventions have improved patient survival after stroke, prognostication of long-term functional outcomes remains challenging, thereby complicating discussions of treatment goals. Stroke patients who require intensive care unit care often do not have the capacity themselves to participate in decision making processes, a fact that further complicates potential end-of-life care discussions after the immediate post-stroke period. Establishing clear, consistent communication with surrogates through shared decision-making represents best practice, as these surrogates face decisions regarding artificial nutrition, tracheostomy, code status changes, and withdrawal or withholding of life-sustaining therapies. Throughout decision-making, clinicians must be aware of a myriad of factors affecting both provider recommendations and surrogate concerns, such as cognitive biases. While decision aids have the potential to better frame these conversations within intensive care units, aids specific to goals-of-care decisions for stroke patients are currently lacking. This mini review highlights the difficulties in decision-making for critically ill ischemic stroke and intracerebral hemorrhage patients, beginning with limitations in current validated clinical scales and clinician subjectivity in prognostication. We outline processes for identifying patient preferences when possible and make recommendations for collaborating closely with surrogate decision-makers on end-of-life care decisions.

Keywords: stroke, end-of-life, palliative care, goals-of-care, advance care planning, surrogate decision-maker, shared decision-making

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INTRODUCTION: EPIDEMIOLOGY OF LIFE-SUSTAINING THERAPY FOR SEVERE STROKE PATIENTS

Stroke is a leading cause of death and long-term disability in the United States (US) (1, 2). The term "stroke" for this review focuses on two subtypes: acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH). Clinicians are often confronted with issues related to end-of-life (EOL) care for stroke patients, such as code status, dysphagia care, and airway management (3). In order to tailor these decisions to patients' wishes, goals-of-care (GOC) discussions regarding acceptable quality of life (QoL) that require collaboration with surrogate decision-makers of incapacitated patients are needed.

Code status changes are among the earliest decisions that may occur during hospitalization for severe stroke. In practice, do-not-resuscitate (DNR) orders are often placed as early as within 24 hours of emergency department admission for both ICH (4) and AIS (5) patients. Approximately 13–26% of stroke patients receive DNR orders within 24 hours of admission (4, 5), with higher

proportions of DNR status among those who later die of stroke (6, 7). There is concern that the act of making a patient DNR by itself affects clinicians' impressions of prognosis and independently increases the likelihood of mortality in AIS (5) and ICH (8, 9). This possible "self-fulfilling prophecy" is a well-established concern in stroke care (10).

In the days to weeks after admission, issues of nutrition and airway management often come to the forefront of decision-making. Percutaneous endoscopic gastrostomy (PEG) placement is currently performed throughout the US in 8.8% of patients with AIS (11) and 10.4% for ICH (12), with variation amongst institutions (11, 12). Over half of PEG placements for AIS occur in the first week of admission (13). For stroke patients who have difficulty maintaining an open airway or who require prolonged mechanical ventilation, tracheostomy in the US is commonly performed 6–14 days after stroke onset (14, 15), with increasing numbers over the past two decades (14). Rates of life-sustaining interventions are higher in minority patients than white patients (16), including PEG (17, 18) and tracheostomy (18).

In conjunction with these decisions, surrogates and clinical teams often decide to forgo life-sustaining measures and instead pursue comfort measures only (CMO). Withdrawal of life-sustaining therapy (WLST) is more common in neuro-intensive care units (Neuro-ICUs) than medical intensive care units (MICUs) (19), with up to 26% of all ICH patients in one single-center series undergoing WLST (20). Almost half of all stroke deaths occur inpatient (21), and hospitalized stroke patients have extensive palliative care needs (22, 23) that may not always be met. In one single-center US study from 2009-2015, about 4% of AIS patients were discharged to hospice (22).

In this brief review, we discuss the issues that arise when making EOL care decisions regarding stroke patients. We discuss prognostication tools, their limitations, methods to determine an incapacitated patient's wishes including advance care planning documentation (ACP) and best practices for shared decision-making with surrogates.

PROGNOSTICATION: LIMITATIONS OF CLINICAL SCALES

One factor in EOL decision-making involves prognostication of long-term outcome or natural disease history. Multiple clinical scales have been developed to predict mortality and functional outcome after stroke (24–26), several of which have been externally validated (**Table 1**).

Common predictor variables in AIS scales include age, stroke severity, pre-stroke functional status, comorbidities, and stroke subtype (24), with some scales utilizing imaging characteristics (36).

For ICH, many prognostication scales are based on variations of the "original" ICH score (33, 37–40), which was initially published with 30-day mortality data utilizing age, Glasgow Coma Scale at admission, ICH location, ICH volume, and presence of intraventricular hemorrhage (31).

Some published data suggest that scales largely outperform the "subjective" opinion of clinicians at predicting mortality and functional disability (41–43). However, these studies generally involved asking clinicians to prognosticate expected outcomes from hypothetical patient vignettes, which simplify and distill information that would otherwise be available in real-world clinical practice. In a comparison of the predictions of clinicians against common prognostication scales for 3-month functional status in real-world ICH patients, clinicians outperformed scales with regards to predictive accuracy (44).

This finding points towards the first of several limitations of prognostication scales—scales generate predictions using cohort data, yet prediction for individual patients may depend on variables not captured by scales. Furthermore, few models have been assessed for calibration (45) and robust external validation (25, 46), limiting their generalizability. Most scales were developed retrospectively, and data used to generate them include local practice patterns with regards to WLST, potentially incorporating the self-fulfilling prophesy. Finally, scales may not predict outcomes that are most important to patients and families, as the same functional outcome may lead to different perceptions of QoL for different patients. Clinicians have been shown to be poor at predicting a patient's future QoL, an inherently subjective quality, after stroke (47–49).

Despite these limitations, disclosing the results of a prognostication scale for a patient to a clinician impacts that clinician's clinical impression (50). Awareness of the limitations of scales can help ensure that the clinician utilizes these tools to complement clinical judgment rather than replace it. Recent studies suggest that making predictions based on clinical data from hospital day 5 rather than at admission may improve prognostication accuracy (51). Given the lack of objective tools for accurate prognostication and the potential for clinician bias to factor into decision-making, delaying prognostication may lead to improved prediction accuracy and clinical outcomes.

GOALS-OF-CARE CONVERSATIONS: DETERMINING PATIENTS' WISHES

Besides accurate neuro-prognostication, the ideal timing of GOC discussions regarding acceptable QoL for hospitalized stroke patients requires several considerations. GOC discussions, once initiated, are often iterative (1). Prognostic information should be tailored by amount and timing to the preferences of patients and families (52).

The aim of GOC discussions should be to ascertain the patient's wishes, or best estimates thereof, in order to provide goal-concordant care. As a means to this end, ACPs and surrogate decision-makers represent two sources of information for clinicians.

Advance Care Planning Documentation

Several types of ACPs (i.e. power of attorney, guardianship, living will, and Physician/Medical Orders for Life-Sustaining Treatment, or POLST/MOLST) exist, with variations in jurisdiction, applicability, and impact on decision-making (53). The only legally binding of these is POLST/MOLST, which serves

TABLE 1 | Selected clinical scales developed for acute ischemic stroke and intracerebral hemorrhage.

Scale	Original study	Predictors	Outcome variables
Acute Ischemic Stroke			
THRIVE	Flint et al., 2010 (27)	NIHSS score, age, presence of hypertension, diabetes, atrial fibrillation	Mortality and mRS 90 days after stroke with endovascular treatment
iScore	Saposnik et al., 2011 (28)	Age, sex, stroke severity, stroke subtype, comorbid conditions, preadmission level of function, glucose on admission	Death at 30 days or mRS = 3–5 at discharge/Death at 30 days or institutionalization at discharge
DRAGON	Strbian et al., 2012 (29)	Early infarct signs on admission CT, pre-stroke mRS, age, baseline glucose, onset to treatment time, baseline NIHSS	mRS 3 months after stroke treated with IV tPA
SOAR	Myint et al., 2014 (30)	Age, gender, ischemic vs hemorrhagic stroke, vascular territory, pre-stroke mRS	Inpatient and 7-day mortality
Intracerebral hemorrhage			
ICH score	Hemphill et al., 2001 (31)	GCS score, age, infratentorial origin, ICH volume, IVH	30-day mortality
Modified ICH score	Cheung and Zou, 2003 (32)	NIHSS, age, infratentorial origin, ICH volume, IVH	30-day mortality or mRS score ≤ 2
New ICH score	Cheung and Zou, 2003 (32)	NIHSS, temperature, pulse pressure, IVH, subarachnoid extension	30-day mortality or mRS score ≤ 2
ICH-GS	Ruiz-Sandoval et al., 2007 (33)	GCS score, age, ICH location, ICH volume, IVH	30-day mortality and GOS ≥ 4
FUNC	Rost et al., 2008 (34)	Age, GCS score, ICH location, ICH volume, pre-ICH cognitive impairment	90-day GOS ≥ 4
max-ICH	Sembill et al., 2017 (35)	ICH volume, age, NIHSS, IVH, oral anticoagulation	12-month mortality and mRS score in maximally treated patients

GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; tPA, tissue plasminogen activator.

as a standing medical order indicating a patient's wishes for treatment (54).

ACPs have variable effects on decision-making and come with several limitations. In a prospective study of hospitalized stroke patients, the presence of ACP documents and informal ACP conversations was associated with earlier transitions to CMO (55). However, other studies also specifically targeting stroke patients have suggested that the presence of ACPs does not affect clinicians' judgment for most decisions (56), implying other factors aside from ACPs play a greater role in decision-making. For instance, clinicians may endorse family members' choices for tube feeding despite contrary wishes expressed in living wills (57, 58).

Additionally, prevalence of ACPs in stroke patients is low (59); in studies of patients who died from stroke, fewer than half had completed ACPs (60, 61). Not all ACPs are readily available (61) or consistently documented (59). Though up to a quarter of strokes in the US are repeat strokes (62), ACP completion rates in stroke survivors are no different than that of the average older adult population (63). Some patients may experience financial and language barriers, as well as cultural factors, impacting ACP completion (64–66). This may also be due to the acute nature of stroke itself, making it difficult to have pre-emptive GOC conversations (67). Furthermore, ambiguous words, such as "incurable" (68) and states of "irreversible coma" are difficult to interpret in stroke (61). Most ACPs focus on specific procedures without clear-cut descriptions of scenarios pertinent to stroke (61), thus limiting their utility in determining patients' wider GOC.

Identifying Surrogate Decision-Makers

A second source of information for clinicians to ascertain a patient's GOC is the patient's surrogate. Patients with severe stroke often do not have capacity to participate in decision-making (58, 69). Though tools such as communication boards exist to aid select intubated patients in communicating their wishes (70), the vast majority of EOL cases in the Neuro-ICU require identifying surrogates (53).

In the absence of ACPs, clinicians typically follow a prioritized list of relatives according to state law (71). When no surrogate is available, protocols may involve committees or judiciary involvement (71). Great variation exists in the use of these resources by clinicians who make decisions to limit life-sustaining treatment in the ICU, suggesting further work is needed to develop procedures in these cases (72).

SHARED DECISION-MAKING WITH SURROGATES: POTENTIAL PITFALLS

Complexity of Decision-Making Factors

After surrogates are identified, several factors play a role in shared EOL care decision-making. Generally, few surrogates of critically ill patients depend solely upon clinician prognoses when estimating their loved ones' prognoses themselves (73). Many endorse being influenced by a patient's physical appearance, their faith, and their understanding of the patient's will to live in addition to, and sometimes above, the clinician's prognostication (73).

In qualitative studies, surrogates of stroke patients have endorsed reluctance in deciding to pursue CMO for loved ones (74). A recent study of nearly 800 US residents suggested that, when presented with a hypothetical scenario of a relative hospitalized with severe acute brain injury (requiring tracheostomy and PEG for survival), potential surrogates acknowledged a variety of competing concerns (75). While most surrogates prioritized respecting patients' perceived wishes and reducing suffering, surrogates may belong to different subgroups characterized by varying other top concerns: patient age, family agreement, prognostication, and cost of long-term care (75). Both non-white race and high religiosity may predict a surrogate choosing life-sustaining therapy over CMO (76). However, such a decision is still fraught with uncertainty; for example, respondents in the aforementioned study of US residents who were most concerned about cost of care were still more likely to choose tracheostomy and PEG placement over CMO compared with those less concerned (77). Clinicians must recognize that a variety of factors may influence surrogates in stroke-related GOC discussions.

Cognitive and Emotional Biases

Potential biases exist for both clinicians and surrogates collaborating to make shared EOL decisions. Towards recommending what (if any) additional treatments to pursue in stroke patients, a clinician may be influenced, for instance, by a desire to avoid personal or legal accusations by families of patients (78) in addition to patient factors (7, 20). The clinician's prior experiences also affect these decisions; for instance, clinicians with experience in rehabilitation medicine tend to suggest continuation of life-sustaining therapy, perhaps due to a tendency to make positive prognoses (79). In these cases, clinicians may be biased towards what they would personally want in a similar situation rather than what the patient would want. In a study in which clinicians were presented vignettes of hypothetically critically-ill patients, clinician recommendations did not differ between groups who were provided the patient's values as expressed by family members vs. those who were not (80).

Several common surrogate biases warrant discussion. First, in experimental settings, surrogates' interpretations of clinician prognostications were affected by numeracy skills (81) and were often overly optimistic (82). Second, surrogates may be subject to recall bias, remembering patients as more independent than they really were prior to illness (83).

Third, surrogates may be biased by their own perceptions of acceptable QoL in contrast to patients' own wishes. In a hypothetical scenario of stroke, surrogates' ratings of a patient's QoL were not reflective of the patient's own perceptions and desire for treatment (84). Levels of patient-proxy concordance varies by decision type, with surrogates accurately predicting patient preferences for reperfusion treatment (85, 86) but not clinical trial enrollment (86). When examining withdrawal of mechanical ventilation in stroke scenarios, patient-proxy agreement varied, with lowest levels of agreement when patients wanted everything done for treatment (87). Notably, despite these discrepancies, patients continue to exhibit high levels of trust in their surrogates (87–89).

Clinicians and surrogates alike may both be subject to the "disability paradox" bias—where people with serious disabilities may report greater QoL compared to healthy individuals envisaging similar circumstances (83, 90). However, clinicians must take into consideration long-term caregiver burden and take care not to offer an overly positive prognosis that is not warranted by objective clinical data.

SHARED DECISION-MAKING WITH SURROGATES: IDEAL PROCESSES

Essential elements of shared-decision making models are outlined by the Agency for Healthcare Research and Quality (91, 92). A recent survey of surrogates in the Neuro-ICU showed significant room for improvement in their inclusion in decision-making and clinician communication (93). For stroke patients specifically, caregivers may not comprehend the interventions that occurred (85) and feel overwhelming uncertainty (94, 95) throughout the decisional process. Families of stroke patients tend to have relatively low satisfaction with the attention given to communication and the needs of the family despite overall high satisfaction with palliative care administration (60). Almost a third of surrogates in the Neuro-ICU experience clinically significant grief and stress reactions (96). Surrogates may feel guilty about their decisions (1, 97) and often lack time to adapt during acute stroke when rapid treatment decisions are made (74).

Best Practices for Communication

Given these considerations, clinicians should approach the decision-making process collaboratively, negotiating the role of the clinician with surrogates (98) rather than taking a default paternalistic approach (99). Though few providers enquire about the surrogate's preferred role in decision-making (98), providers should ascertain a decision-maker's preferred level of control over EOL care decisions. Surrogates may want to make the final decision or consent to clinicians making decisions for the patient (100). Clear communication on the roles of the clinician and surrogate is key as discordancy between family members' preferred and actual decision-making roles is associated with increased depressive and post-traumatic stress disorder symptoms (101).

Our recommendations for family meetings are summarized in **Table 2**. Key participants to consider include interpreters (108), social workers (1, 104), spiritual care (1, 104, 109), speech therapists (110), and case managers (1, 104). Neuro-ICU nurse-led family meetings can lead to greater feelings of control by families and higher satisfaction with care (111).

Clinicians should ensure consistent information from different providers (104, 105, 112), use an "ask-tell-ask" approach (104) and give concrete descriptions of deficits (1). Using consistent terminology avoids confusion regarding seemingly interchangeable terms such as "brain bleed", "stroke", and "brain hemorrhage" (105). When prognosticating, acknowledging uncertainties is important, in addition to preparing families for worst-case scenarios while using "I wish" statements to preserve hope (113). Families of stroke patients are often aware

TABLE 2 | Recommendations for shared decision-making with surrogate decision-makers after acute stroke.

Setting the Stage for Goals-of-care	• Ensure relevant participants are involved in family meetings (i.e. patient, family, other services) (102) • Ask the surrogate decision-maker their preferences in terms of their role and that of the clinician in the shared decision-making process (98) • Utilize the ask-tell-ask approach by getting permission to present information, communicating information clearly, and checking for understanding (103)
Communicating Prognostic Uncertainty	• Acknowledge uncertainty and explain why uncertainty exists (95) • Communicate that prognosis can be altered by treatment decisions (1) • Describe possible best and worst-case scenarios of survival and future quality of life (102)
Eliciting Patient Preferences	• With open-ended questions, ask what the patient valued in life (102) (i.e. "Tell me more about what [patient] liked to do before they got sick") (103) • Review advance care planning documents or the patient's verbally expressed wishes (1, 102)
Address Cognitive Biases	• Consider discussing common recall and/or affective forecasting biases with decision-makers (102) • Providing concrete descriptions of stroke survivors' functional outcomes after discharge may be helpful for de-biasing (83)
Ongoing Communication	• Demonstrate empathy in response to emotions (103) • Continue to assess goals-of-care over time with regular meetings (1) • Maintain consistency in communication across team members (104) and use consistent terminology to avoid confusion (105)
Consider Time-Limited Trials	• Can be used to reach consensus with families by giving patients who have a high likelihood of deteriorating a chance to respond to treatments (106) • Successful time-limited trials require defining the (1) intervention; (2) duration of intervention; (3) desired outcome; and (4) follow-up plan that may include extending the trial and pursuing or forgoing further treatment (107)

of uncertainties in prognostication but require clarification as to why such uncertainty exists (95). Given concerns of numeracy skills (81), multiple portrayals of data should be offered if quantitative estimates of prognosis are offered; risks may be perceived as higher when presented as frequencies (e.g., 1 in 10) rather than equivalent percentages (e.g., 10%) (114). Alternatively, some specialists recommend focusing on functional outcomes – with less emphasis on numerical estimates – using visual aids that illustrate the best, worst, and most likely scenarios (115). Time-limited trials can assess progress over time (106, 113) and help families come to terms with a patient's poor prognosis or manage uncertainty (**Table 2**).

How best to discuss prognostication and GOC after stroke remains a subject of ongoing discussion (92, 102). Decision aids, evidence-based interventions that outline the benefits/harms of decisions and their concordance with personal values (116), have been tested to assist in shared decision-making in ICUs (92, 117). A recent clinical trial using web-based decision aids for prolonged mechanical ventilation reduced surrogates' levels of decisional conflict, but did not improve prognostic concordance between clinicians and surrogates (118). Neuro-ICU-specific decision aids are currently few in number but are in development (92, 119–122). Future efforts could aim to identify different subgroups of surrogates in developing aids tailored to their priorities to facilitate shared decision-making after stroke (92).

Expert Consultations

Traditional palliative care needs are present in over half of Neuro-ICU patients (123, 124) and consults to palliative care services are used infrequently (52, 125). Even in those who die of stroke, palliative care involvement varies greatly from 26–90% (52, 126–128). Stroke may not trigger palliative care requests from family as other diagnoses, such as cancer, might (95). Despite recognizing the importance of palliative care in stroke, clinicians may feel uncertain about when to begin addressing palliative care needs (129). As such, palliative care specialists are often only brought in during the last days of life for symptomatic management of pain, dyspnea, and mood (128, 130, 131).

It is recognized that having enough consultants to handle all palliative care needs in the Neuro-ICU may not be practical or appropriate in many situations. Palliative care consultations should not be initiated as a replacement for GOC conversations with the primary team (132). Neuro-ICU clinicians should be trained in and provide primary palliative care, including eliciting GOC and providing palliative treatments at EOL (113). However, expert palliative care consultants can help with symptom management, complicated conflict resolution, and eliciting further patient values/needs (133). Current palliative Neuro-ICU screening tools (123) and new models of palliative care delivery (102, 134–137) are being explored to assist clinicians with thresholds for consulting expert palliative care.

Conflicts may occur surrounding decisions of artificial nutrition/hydration (60, 74, 112, 138), resuscitation (112), and care transitions (112), particularly when impressions of prognosis are different between surrogates and clinicians despite multiple attempts at family conferences (52, 138, 139). Though protocols differ, ethics consultations can help resolve conflicts between decision-makers and providers (140). Should providers believe that inappropriate treatment has been requested, a series of steps are recommended for conflict resolution by the American Thoracic Society (141, 142).

CONCLUSION

In this brief review, we discussed factors to consider when engaging in EOL decision-making, including prognostication, determining patient wishes, and interacting with surrogates with the goal of shared decision-making.

It is important to note that even after decisions to WLST, families require ongoing support (95). Expectations must be discussed after WLST, which does not always mean imminent death (1, 143), as families often expect death early on and are distressed by prolonged dying processes (138).

AUTHOR CONTRIBUTIONS

LG, CZ, and DH all discussed the content of this manuscript in its planning stages. LG and CZ drafted this article, with subsequent revisions from DH. All authors contributed to the article and approved the submitted version.

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Measuring Patient Safety Climate in Acute Stroke Therapy

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Background: Treatment of acute stroke is highly time-dependent and performed by a multiprofessional, interdisciplinary team. Interface problems are expectable and issues relevant to patient safety are omnipresent. The Safety Attitudes Questionnaire (SAQ) is a validated and widely used instrument to measure patient safety climate. The objective of this study was to evaluate the SAQ for the first time in the context of acute stroke care.

Methods: A survey was carried out during the STREAM trial (NCT 032282) at seven university hospitals in Germany from October 2017 to October 2018. The anonymous survey included 33 questions (5-point Likert scale, 1 = disagree to 5 = agree) and addressed the entire multiprofessional stroke team. Statistical analyses were used to examine psychometric properties as well as descriptive findings.

Results: 164 questionnaires were completed yielding a response rate of 66.4%. 67.7% of respondents were physicians and 25.0% were nurses. Confirmatory Factor Analysis revealed that the original 6-factor structure fits the data adequately. The SAQ for acute stroke care showed strong internal consistency ($\alpha = 0.88$). Exploratory analysis revealed differences in scores on the SAQ dimensions when comparing physicians to nurses and when comparing physicians according to their duration of professional experience.

Conclusion: The SAQ is a helpful and well-applicable tool to measure patient safety in acute stroke care. In comparison to other high-risk fields in medicine, patient safety climate in acute stroke care seems to be on a similar level with the potential for further improvements.

Trial registration: www.ClinicalTrials.gov Identifier: NCT032282.

Keywords: critical care, stroke, patient safety, safety attitudes questionnaire, neurology, CRM, acute stroke care, emergency care

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INTRODUCTION

Ensuring patient safety has a tremendous value in medicine and is especially demanding in time-critical operations like acute stroke care with critically ill patients and the involvement of interdisciplinary, multiprofessional teams. The fast growing implementation of endovascular therapies in acute stroke care enforces this development and challenges local stroke teams every day. Thus, current guidelines on the management of acute ischemic stroke recommend the establishment of dedicated multidisciplinary stroke teams and the implementation of education programs focusing on team performance and patient safety (1).

In line with safety concepts developed in non-medical high-risk environments, it has been established that patient safety largely depends on human and organizational factors (2–4) and is often challenged at organizational interfaces such as handovers that increase the risk for potential error (5). Safety culture is seen as the basis for ensuring patient safety through successful team performance in emergency medicine (4, 6).

Healthcare professionals' perceptions of safety culture (i.e., patient safety climate) has been shown to correlate with safety outcomes in hospital settings (7–10). Thus, measuring the perceived patient safety climate is important for understanding and effectively addressing patient safety issues. From that future patient safety improvement programs in acute stroke therapy might benefit.

To gauge patient safety climate, the Safety Attitudes Questionnaire (SAQ) has been developed (11). Adopted to various clinical settings and validated in different languages, it is the most widely used instrument for measuring patient safety climate at the team or department level (12). The initial version of the SAQ has 60 items, including 34 core items, which are independent of the clinical setting. The short version of SAQ only includes the core items. Psychometric properties data from the SAQ identified six factors for safety culture: teamwork climate, job satisfaction, safety climate, stress recognition, perception of management and working conditions (**Table 1**). For intensive care units (ICU), the SAQ factors have already proven to be sensitive for changes by a quality improvement program, associated with reductions in medication errors and with shorter lengths of stay (13). It has been also shown that critical care units with highest scores on SAQ factors had the lowest rates of blood-stream infections (11, 14). Based on real-life studies targeting safety climate (7–10), the proposed cut-off for each SAQ factor should be 60 point (on a 100 point scale), respectively, 3.4 points on the 5-point Likert scale (5, 11).

Based on these results, the SAQ might be a valuable tool for assessing patient safety climate in acute stroke therapy. Providing measurable positive effects on patient safety climate might facilitate the long-term organizational anchoring of quality improvement programs. Thus, the aim of this study was to evaluate the SAQ in the setting of acute stroke therapy. To the best of our knowledge, this is the first study using SAQ in the context of clinical neurology.

TABLE 1 | SAQ factors, items and dimensions.

	SAQ factors, items and dimensions
	Teamwork climate (6 items)
1	Nurse input is well received in this clinical area.
2	In this clinical area, it is difficult to speak up if I perceive a problem with patient care.
3	Disagreements in this clinical area are resolved appropriately (i.e., not who is right, but what is best for the patient)
4	I have the support I need from other personnel to care for patients.
5	It is easy for personnel in this clinical area to ask questions when there is something that they do not understand.
6	The physicians and nurses here work together as a well-coordinated team.
	Safety climate (7 items)
7	I would feel safe being treated here as a patient.
8	Medical errors are handled appropriately in this clinical area.
9	I know the proper channels to direct questions regarding patient safety in this clinical area.
10	I receive appropriate feedback about my performance.
11	In this clinical area, it is difficult to discuss errors.
12	I am encouraged by my colleagues to report any patient safety concerns I may have.
13	The culture in this clinical area makes it easy to learn from the errors of others.
	Job satisfaction (5 items)
14	I like my job.
15	Working in this hospital is like being part of a large family.
16	This hospital is a good place to work.
17	I am proud to work at this hospital.
18	Moral in this clinical area is high.
	Stress recognition (4 items)
19	When my workload becomes excessive, my performance is impaired.
20	I am less effective at work when fatigued.
21	I am more likely to make errors in tense or hostile situations.
22	Fatigue impairs my performance during emergency situations (e.g., emergency resuscitation, seizure).
	Perception of Management (8 items)
	Unit level:
23	Management supports my daily efforts.
24	Management does not knowingly compromise the safety of patients.
25	Problem personnel are dealt constructively in hospital.
26	I am provided with adequate, timely information about events in the hospital that might affect my work.
	Hospital level:
27	Management supports my daily efforts:
28	Management does not knowingly compromise the safety of patients.
29	Problem personnel are dealt constructively in hospital.
30	I am provided with adequate, timely information about events in the hospital that might affect my work.
	Working conditions (4 items)
31	The levels of staffing in this clinical area are sufficient to handle the number of patients.
32	This hospital does a good job of training new personnel.
33	*All the necessary information for diagnostic and therapeutic decisions is routinely available to me (excluded).*
34	Trainees in my discipline are adequately supervised.

METHODS

Design and Setting

From October 1st 2017 to July 1st 2018 a cross sectional survey was conducted at seven stroke centers of tertiary care university hospitals with 24/7 capacity for thrombectomy (University Hospital Augsburg, University Hospital Tuebingen, University Hospital Heidelberg, Ludwig Maximilians-University Munich, Centre for Stroke Research Berlin Charité, University Medical Centre Hamburg, University Hospital Cologne) as part of the Simulation STREAM trial (NCT 032282). The trial was coordinated by the University Hospital Frankfurt (Goethe University) and had the approval of the ethics committee

of Frankfurt University Hospital (ID 433/16) with secondary approvals from the ethics committees of all participating centers. The trial intervention itself did not require individual consent.

Safety Attitudes Questionnaire – German Version

The SAQ was first developed by Sexton and colleagues (11). Zimmermann et al. translated and validated the short version of the SAQ into the German language version (15). Items and dimensions are illustrated in **Table 1**. By decision of an interdisciplinary expert group, item 33 of the SAQ was not applicable to acute care of stroke patients and excluded before the start of the trial. Answers to the 33 SAQ items are given on a 5-point Likert scale (1 = disagree strongly, 2 = disagree slightly, 3 = neutral, 4 = agree slightly, 5 = agree strongly).

Data Collection

In each participating center, all members of the stroke teams (professionals involved in acute stroke care: neurologists, neuroradiologists/-interventionalists, nurses, medical technical assistants) received an invitation and two e-mail reminders to fill out the German version of SAQ in a paper and pencil version. Questionnaires (n = 247) were administered by a local principle investigator (PI), collected and sent back to the sponsor (University Hospital Frankfurt) for central data collection and analysis.

Statistical Analysis

Psychometric Testing

Factor scale scores were calculated for individual respondents by the taking the average of the specific items per factor. For reliability analysis, Cronbach's alpha was calculated to assess the internal consistency of the overall SAQ. Cronbach's alpha was calculated for each factor of the SAQ (>0.7 indicates adequate internal consistency (16). Separately, scale reliability analysis for each item and dimension resulted in a corrected item-total correlation and Cronbach's alpha. Inter-item correlations were examined for internal consistency reliability of the questionnaire.

Based on the identified factor structure during the testing of the validated original SAQ version and the German translation, a confirmatory factor analysis (CFA) was performed to verify the factor structure in context of acute stroke care (11, 15). CFA based on participants who fully completed the instrument (n = 151) with analysis of moment structures (AMOS 26.0.0, IBM, Chicago, USA) software. A Root Mean Square Error of Approximation (RMSEA) < 0.08, a Tucker-Lewis Index (TLI) close to 0.95 and a Comparative Fit Index/CFI) > 0.9 (17) are deemed for a successful model (18). Additionally χ^2 statistics are given (19). Modification indices (MI) were examined to identify any additional adjustments. Factor loadings of individual items were estimated based on the six-factor CFA model.

Descriptive Statistics

Frequency tables were used to analyse data and missing values (MV). Scores were reversed for all negatively worded items. Despite the ordinal scaling of SAQ data, the established method is to present results as mean values or percentages (agree/disagree) (9, 20). Screening for outliers and normal distribution was done with boxplots and q-q plots. To illustrate percentages of participants that agreed or disagreed with each specific item on the 5-point Likert scale, values of 1 and 2 were recoded as 'disagree', 3 as 'neutral' and 4 and 5 as 'agree'. A threshold score of 3.4 points on the 5-point Likert scale (representing 60% agreement on the 0–100-point scale where disagree strongly becomes 0, disagree slightly becomes 25, neutral becomes 50, agree slightly becomes 75 and agree strongly becomes 100) should be exceeded, with a "goal zone" of 4.2–5 points (5).

For interpretation of group differences, multivariate analysis of variance (MANOVA) was used to analyse mean scores. Three separate MANOVA's (Wilks Lambda) were performed with professional position, department and work experience of physicians (≤5 vs. >5 years for medical doctors, 5 years as cut-off for separation resident/ specialist) as independent variables. *post-hoc* univariate ANOVAs were conducted for every dependent variable. Additionally, Tukey HSD *post-hoc* analysis explored differences between two groups. For the correlation analysis of relations between SAQ dimensions, Pearson's correlation was used with a two-tailed test of significance. A $p < 0.05$ was deemed to indicate significance. Data was analyzed with SPSS 26 (IBM; Armonk, BY, USA).

RESULTS

Study Sample and Descriptive Statistics

In total 164 questionnaires were returned by participants representing an overall response rate of 66.4%. The complete data set consisted of 111 physicians, 41 nurses and 10 medical technical assistants with regular patient contact (**Table 2**).

SAQ Factor Structure and Reliability

Confirmatory factor analysis based on the retained 33 items with six factors showed good model fit (RMSEA = 0.044, 90% CI 0.032, 0.056; TLI = 0.94, CFI = 0.95, $\chi^2_{(376)} = 486.74$, $p < 0.001$) (21). Item loadings on the respective factor are presented in **Supplementary Table 2**.

The internal consistency of the questionnaire is satisfactory, with Cronbach's alpha 0.88. Cronbach's alpha for all factors was above 0.7 (0.73–0.85), except for the factor "perception of management" where Cronbach's alpha was 0.22 (**Table 3**) indicating heterogeneity in relation to the confidence in adequate institutional management.

SAQ Response Pattern

Missing values did not exceed 2.5% (range 0–2.4%). We found no statistical significant difference for MV rates between trial centers, departments or professions. Item 24 (unit level) and 28 (hospital level) presented a bimodal response pattern (**Supplementary Table 1**). *Post-hoc* feedback concerning item 24 and 28 suggest that these items were not clear to participants. Negative Item-Total-Correlation enforced these findings, so these items were excluded from individual factor analysis. Demographics are presented in **Table 3**. Mean values and SD for individual SAQ factors are depicted in **Figure 1**.

TABLE 2 | Participant characteristics.

	In total (n = 164)	Physicians (n = 111)			Nurses (n = 41)	MTA† (n = 10)	Neurology (n = 111)	Neuroradiology (n =35)
		In total (n = 111)	≤5 years‡ (n = 60)	>5 years‡ (n = 50)				
Age (years), median (IQR)	33 (29–39)	33 (30–37)	30 (29–31)	39 (35–42)	33 (28–44)	30 (27–46)	31 (29–36)	35 (31–43)
Female, n (%)	86 (52.5)	44 (4)	32 (53.3)	11 (22.0)	32 (78.0)	8 (80.0)	61 (55.5)	12 (36.4)
Duration of professional experience (years), median (IQR)								
- *as physician/ nurse*	7 (3-13)	5 (3-10)	3 (2-4)	10 (8-15)	10 (4-23)	8 (3-20)	5 (2-19)	9 (4-18)
- *in acute stroke care*	4 (2-10)	4 (2-8)	2 (1-3)	8 (6-13)	6 (2-10)	4 (2-14)	4 (1-9)	5 (3-10)

† *MTA, Medical technical assistant;* ‡ *Duration of professional experience (years) as physician.*

TABLE 3 | SAQ factors correlations and Cronbach's alpha.

	Teamwork climate	Safety climate	Job satisfaction	Stress recognition	Perception of management	Working conditions
Correlation (Pearson) and Cronbach's alpha (alpha = 0.88)						
Teamwork climate	0.748					
Safety climate	0.734	0.816				
Job satisfaction	0.629	0.552	0.824			
Stress recognition	−0.002	−0.052	−0.014	0.845		
Perception of management	0.12	0.294	0.085	0.032	0.215	
Working conditions	0.499	0.593	0.499	−0.142	0.238	0.729

Cronbach's alpha is highlighted on the diagonal.

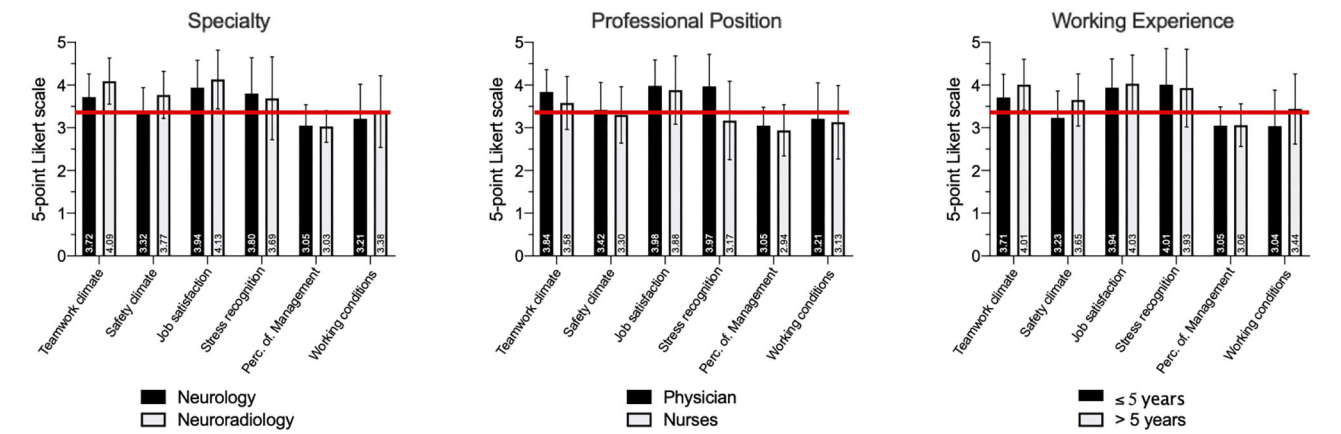

FIGURE 1 | Perceptions of patient safety climate depending on specialty, professional position and duration of professional experience. The six SAQ factors with mean values and standard deviation (SD) are depicted for each subgroup. Individual mean values are written vertical per column. The red lines reflect the proposed benchmark of 3.4 points. Perc. of Management: Perception of Management.

Differences in Patient Safety Climate Across Departments

Comparing the results for the respective SAQ factors, we generally found higher scores for neuroradiology than for neurology or other departments (e.g., anesthetics, neurosurgery). A one-way MANOVA showed a statistically significant difference between departments (neurology, neuroradiology, others) on the combined dependent variables, $F_{(12,306)} = 3.327$, $p < 0.001$, partial $\eta^2 = 0.115$, Wilk's $\Lambda = 0.782$.

Post-hoc univariate ANOVAs show a statistically significant difference between the departments for teamwork climate, $F_{(2,158)} = 8.049$, $p < 0.001$, partial $\eta^2 = 0.092$, safety climate, $F_{(2,158)} = 7.866$, $p = 0.001$, partial $\eta^2 = 0.091$ and working condition $F_{(2,158)} = 2.193$, $p = 0.044$, partial

$\eta^2 = 0.039$, but not for job satisfaction $F_{(2,158)} = 2.808$, $p = 0.195$, partial $\eta^2 = 0.034$, stress recognition, $F_{(2,158)} = 1.654$, $p = 0.195$, partial $\eta^2 = 0.021$, and perception of management $F_{(2,158)} = 2.675$, $p = 0.072$, partial $\eta^2 = 0.033$ (**Table 4**).

Additional Tukey HSD *post-hoc* analysis on *teamwork climate* revealed a significant difference between neurology and neuroradiology, $p = 0.001$ ($M_{\text{Diff}} = -0.3802$, 95%–CI[−0.6313, −0.1291]), and between neuroradiology and others, $p = 0.003$ ($M_{\text{Diff}} = 0.5379$, 95%–CI[.1583, 0.9393]), but not between neurology and others, $p = 0.483$ ($M_{\text{Diff}} = 0.1686$, 95%–CI[−0.1776, 0.5148]).

Tukey HSD *post-hoc* analysis on *safety climate* revealed a significant difference between neurology and neuroradiology, $p = 0.001$ ($M_{\text{Diff}} = -0.4460$, 95%–CI[−0.7262, −0.1659]), and between neuroradiology and other, $p = 0.011$ ($M_{\text{Diff}} = 0.5379$, 95%–CI[.1023, 0.9736]), but not between neurology and others, $p = 0.840$ ($M_{\text{Diff}} = 0.0919$, 95%–CI[−0.2944, 0.4781]).

Tukey HSD *post-hoc* analysis on *working conditions* revealed a significant difference between neuroradiology and other, $p = 0.034$ ($M_{\text{Diff}} = 0.25046$, 95%–CI[.0384, 1.2235]) but not between neurology and neuroradiology, $p = 0.513$ ($M_{\text{Diff}} = -0.1779$, 95%–CI[−0.5590, 2032]), and between neurology and others, $p = 0.106$ ($M_{\text{Diff}} = 0.4530$, 95%–CI[−0.0724, 0.9784]).

Differences in Patient Safety Climate Across Professions

While teamwork climate was scored higher by physicians and medical technical assistants than by nurses, patient safety, working conditions and job satisfaction did not differ significantly between profession. A one-way MANOVA showed a statistically significant difference between professions on the combined dependent variables, $F_{(18,433)} = 3.393$, $p < 0.001$, partial $\eta^2 = 0.117$, Wilk's $\Lambda = 0.689$. *post-hoc* univariate ANOVAs showed a statistically significant difference between the professions for teamwork climate, $F_{(3,158)} = 6.502$, $p < 0.001$, partial $\eta^2 = 0.110$ and stress recognition, $F_{(3,158)} = 11.056$, $p < 0.001$, partial $\eta^2 = 0.174$, but not for safety climate, $F_{(3,158)} = 1.652$, $p = 0.180$, partial $\eta^2 = 0.030$, job satisfaction $F_{(3,158)} = 1.094$, $p = 0.354$, partial $\eta^2 = 0.020$, perception of management $F_{(3,158)} = 0.548$, $p = 0.548$, partial $\eta^2 = 0.010$ and working conditions $F_{(3,158)} = 0.877$, $p = 0.454$, partial $\eta^2 = 0.016$.

Additionally Tukey HSD *post-hoc* analysis on *teamwork climate* revealed a significant difference between physicians and nurses, $p = 0.032$ ($M_{\text{Diff}} = 0.2543$, 95%–CI[.0171, 0.4915]), and between nurses and medical technical assistants, $p = 0.041$ ($M_{\text{Diff}} = -0.4728$, 95%–CI[−0.9300, −0.0155]), but not between physicians and medical technical assistants, $p = 0.451$ ($M_{\text{Diff}} = -0.2185$, 95%–CI[−0.6467, 0.2097]). Tukey HSD *post-hoc* analysis on *stress recognition* revealed a significant difference between physicians and nurses, $p < 0.001$ ($M_{\text{Diff}} = 0.8025$, 95%–CI[.453, 0.1.1515]), but not between nurses and medical technical assistants, $p = 0.529$ ($M_{\text{Diff}} = -0.3063$, 95%–CI[−0.9789, 0.3663]) and between physicians and medical technical assistants, $p = 0.153$ ($M_{\text{Diff}} = 0.4962$, 95%–CI[−0.1337, 1.1261]).

Differences in Patient Safety Climate According to the Duration of Professional Experience

Concerning all individual SAQ factors, experienced physicians only scored higher for teamwork climate and working conditions than physicians with less working experience (< 5 years). A one-way MANOVA showed a statistically significant influence of the duration of professional experience (physicians with more or <5 years working experience) on the combined dependent variables, $F_{(6,102)} = 3.350$, $p = 0.005$, partial $\eta^2 = 0.165$, Wilk's $\Lambda = 0.835$.

Post-hoc univariate ANOVAs showed a statistically significant difference between the levels of experience for teamwork climate, $F_{(1,107)} = 2.745$, $p = 0.001$, partial $\eta^2 = 0.095$, safety climate, $F_{(1,107)} = 4.794$, $p < 0.001$, partial $\eta^2 = 0.109$ and working conditions $F_{(1,107)} = 4.588$, $p = 0.009$, partial $\eta^2 = 0.062$, but not for job satisfaction, $F_{(1,107)} = 0.580$, $p = 0.448$, partial $\eta^2 = 0.005$, stress recognition $F_{(1,107)} = 0.335$, $p = 0.564$, partial $\eta^2 = 0.003$ and perception of management $F_{(1,107)} = 0.038$, $p = 0.847$, partial $\eta^2 = 0.000$.

DISCUSSION

The increasing implementation of endovascular therapies requires fast interdisciplinary decision-making and the involvement of neurointerventionalists, neurointensive care specialists and anesthetists. Consequences are larger team sizes and an increased number of handovers. Therefore, a good teamwork climate is essential for patient safety. This study explored for the first time the SAQ as a potential assessment tool for safety culture in acute stroke care. The results showed a good reliability and CFA confirmed the proposed factor model for this survey (11). In comparison to benchmarking data from emergency departments and intensive care units from other disciplines than neurology, our results indicate comparable results for teamwork climate and patient safety in the field of acute stroke care with the potential for future refinements (7–10). Noteworthy are particularly high scores for job satisfaction. Our results indicate that the SAQ has the potential to validly depict changes of the safety climate induced by dedicated improvement programs targeting patient safety in acute stroke care.

For quantitative analysis of hospitals' safety climate, several measurement methods have been developed, the most frequently used are the Hospital Survey on Patient Safety Culture (HSPSC), the Safety Organizing Scale (SOS) and the SAQ (11, 22). We chose the SAQ because of its well-characterized psychometric properties, available benchmarking data and verification of the original factor analysis (10, 11, 23). One strength of the SAQ is the possibility to differentiate between different factors of patient safety climate (15, 24). Nevertheless, additional qualitative safety climate measurements, like structured interviews, could be necessary to explore causality of findings (10).

The mean values for the perception of safety climate in the present study were similar to former SAQ studies targeting safety climate at intensive care units or emergency rooms [**Table 4**, (25)]. Referring to benchmarking data from Sexton and colleagues comparing results of six SAQ versions from

TABLE 4 | Perceptions of patient safety climate per specialty, professional position and working experience.

	Teamwork climate	Safety climate	Job satisfaction	Stress recognition	Perception of management	Working conditions
Specialty						
Neurology (n =111)	3.72* (0.54)	3.32* (0.62)	3.94 (0.62)	3.80 (0.84)	3.05 (0.49)	3.21* (0.81)
Neuroradiology (n = 35)	4.09* (0.54)	3.77* (0.55)	4.13 (0.69)	3.69 (0.97)	3.03 (0.37)	3.38* (0.84)
Others (n = 16)	3.54 (0.65)	3.23 (0.69)	3.68 (0.63)	3.38 (0.80)	2.76 (0.62)	2.75 (0.84)
Professional position						
Physician (n = 111)	3.84* (0.52)	3.42 (0.64)	3.98 (0.61)	3.97* (0.75)	3.05 (0.43)	3.21 (0.84)
Nurse (n = 41)	3.58* (0.62)	3.30 (0.66)	3.88 (0.80)	3.17* (0.92)	2.94 (0.60)	3.13 (0.86)
MTA (n = 10)	4.05* (0.54)	3.73 (0.51)	4.10 (0.68)	3.48* (0.90)	2.99 (0.47)	3.37 (0.88)
Physician's working experience						
≤5 years (n = 60)	3.71* (0.54)	3.23* (0.63)	3.94 (0.67)	4.01 (0.84)	3.05 (0.44)	3.04* (0.84)
>5 years (n = 50)	4.01* (0.59)	3.65* (0.61)	4.03 (0.67)	3.93 (0.91)	3.06 (0.50)	3.44* (0.82)
Overall (n = 164)	**3.77 (0.57)**	**3.40 (0.64)**	**3.95 (0.67)**	**3.74 (0.88)**	**3.01 (0.47)**	**3.19 (0.85)**

*Between groups difference significant $p < 0.05$ (post-hoc univariate ANOVA respectively Tukey-HSD).

different departments and sites (ICU-UK, ICU-NZ, ICU-USA, inpatient-USA, OR-UK, ambulatory-USA) teamwork climate (factor means from the six SAQ versions (range) 3.57–3.97 vs. actual SAQ overall mean 3.77), safety climate (means 3.42–3.80 vs. actual overall mean 3.4), stress recognition (means 3.19–3.98 vs. actual overall mean 3.74), perception of management (means 2.53–3.21 vs. actual overall mean 3.01) and working conditions (means 2.97–3.46 vs. actual overall mean 3.19) were on a similar level. Only job satisfaction scored higher in the present study than in the afore mentioned studies (means 3.38–3.82 vs. actual overall mean 3.95). To the best of our knowledge, this is the first study benchmarking safety climate in acute stroke care against existing data from other clinical areas (11, 12).

In comparison to other studies targeting patient safety climate (7–10), the present study reached the proposed threshold of 3.4 points for the factors teamwork climate, safety climate and stress recognition (5, 11). Nevertheless, the cut-off was not achieved for the factors perception of management and working conditions. Both factors are strongly influenced by hospital management setting the local frame for work and communication. Because of the low internal consistency of the factor "perception of management" (Cronbach's alpha 0.22) further interpretations should be done carefully. A possible explanation for the low internal consistency could be the involvement of different management entities due to the multiprofessional and interdisciplinary composition of the stroke team.

Concerning results for individual SAQ factors in our explorative analysis, physicians scored higher than nurses in most items, especially in items concerning teamwork climate (3.84 ± 0.52 vs. 3,58 ± 0.62, $p = 0.032$) and stress recognition (3.97 ± 0.75 vs. 3.17 ± 0.92, $p < 0.001$), where higher scores indicate a better sensitivity for the impact of stress (**Figure 1**). Similar results were found elsewhere (25, 26). These might indicate different perceptions of teamwork and stress identify nurses as a particularly vulnerable group. This should be taken into account during team trainings.

Concerning the influence of the duration of professional experience on perceived safety climate, our data suggest that for physicians, a working experience of more than 5 years results in significantly higher scores for teamwork climate (>5 years: 4.01 ± 0.59 vs. ≤5 years: 3.71 ± 0.54, $p = 0.001$), safety climate (3.65 ± 0.61 vs. 3.23 ± 0.63, $p < 0.001$) and working conditions (3.44 ± 0.82 vs. 3.04 ± 0.84, $p = 0.009$). This cut-off was chosen because 5 years is the duration of specialty training for neurology in Germany. The achievement of specialist status often confers more work autonomy and a relief from procedural tasks, resulting in more satisfaction as reported elsewhere (20). Interestingly, job satisfaction and stress recognition were independent from working experience with job satisfaction being particularly high in acute stroke care as compared to published results from other clinical environments. When looking at the speciality, we found differences in teamwork climate, safety climate and working conditions with higher scores for neuroradiology. Since the number of respondents and their baseline parameters are significantly different, these findings should be interpreted with caution.

We acknowledge that there are some limitations that we could not circumvent when designing this study: First, we recruited only experienced high-volume stroke centers. Therefore, our findings might not be representative for stroke units in general and a potential selection bias should be considered although we addressed this issue at least partially by employing a multicenter approach. Second, the overall response rate of 66.4% equalled that of previous studies based on the SAQ and was deemed acceptable (11). In studies with voluntary participation, as in the present study, the response rate plays a major role regarding representative statements. This should be considered in future studies to circumvent a possible selection bias. Third, sample size for confirmatory factor analysis was limited due to study design and number of study centers, but results were similar to former factor analysis (25). Fourth, psychometric properties of the SAQ factor perception of management showed lower values than benchmarking data, but patterns were similar (15). Therefore,

interpretation of this factor should be done with caution. Despite these restrictions, psychometric properties from similar studies using the SAQ demonstrated good model validity and reliability (15, 25). In principle, the SAQ cannot exclude recall bias, since it asks for a self-assessment. This aspect must be taken into account when assessing the results.

CONCLUSIONS

The German SAQ is a reliable instrument to measure safety climate of stroke services. We found comparatively high rates for job satisfaction among all professions of the stroke team but also indicators for a higher vulnerability of nurses and physicians with <5 years work experience toward unfavorable teamwork climate and working conditions. Further studies are needed to evaluate the potential of interventional studies for improving patient safety climate in stroke medicine and neurocritical care.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The trial was coordinated by the University Hospital Frankfurt (Goethe University) and had the approval of the ethics committee of Frankfurt University Hospital (ID 433/16) with secondary approvals from the ethics committees of all participating centers. The trial intervention itself did not require individual consent.

AUTHOR CONTRIBUTIONS

FB, JG, and WP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, concept and design, and statistical analysis. FB and JG acquisition, analysis, or interpretation of data. FB and WP drafting of the manuscript. FB, JG, KG, TM, HS, and WP critical revision of the manuscript for important intellectual content. FB, WP, and HS supervision. All authors contributed to the article and approved the submitted version.

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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.2021.686649/full#supplementary-material

Supplementary Table 1 | STREAM collaborators.

Supplementary Table 2 | Items response rate, means, reliability characteristics and factor loading.

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Prediction of Hematoma Expansion in Patients With Intracerebral Hemorrhage Using Thromboelastography With Platelet Mapping: A Prospective Observational Study

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Background and Purpose: The purpose of the study was to evaluate the usefulness of thromboelastography with platelet mapping (TEG-PM) for predicting hematoma expansion (HE) and poor functional outcome in patients with intracerebral hemorrhage (ICH).

Methods: Patients with primary ICH who underwent baseline computed tomography (CT) and TEG-PM within 6 h after symptom onset were enrolled in the observational cohort study. We performed univariate and multivariate logistic regression models to assess the association of admission platelet function with HE and functional outcome. In addition, a receiver operating characteristic (ROC) curve analysis investigated the accuracy of platelet function in predicting HE. A mediation analysis was undertaken to determine causal associations among platelet function, HE, and outcome.

Results: Of 142 patients, 37 (26.1%) suffered HE. Multivariate logistic regression identified arachidonic acid (AA) and adenosine diphosphate (ADP) inhibition as significant independent predictors of HE. The area under the ROC curves was 0.727 for AA inhibition and 0.721 for ADP inhibition. Optimal threshold for AA inhibition was 41.75% (75.7% sensitivity; 67.6% specificity) and ADP inhibition was 65.8% (73.0% sensitivity; 66.7% specificity). AA and ADP inhibition were also associated with worse 3-month outcomes after adjusting for age, admission Glasgow Coma Scale score, intraventricular hemorrhage, baseline hematoma volume, and hemoglobin. The mediation analysis showed that the effect of higher platelet inhibition with poor outcomes was mediated through HE.

Conclusions: These findings suggest that the reduced platelet response to ADP and AA independently predict HE and poor outcome in patients with ICH. Platelet function may represent a modifiable target of ICH treatment.

Keywords: intracerebral hemorrhage, hematoma expansion, thromboelastography, platelet function, stroke

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) accounts for 20% of all strokes and carries the highest stroke-related morbidity and mortality (1, 2). Hematoma expansion (HE) usually occurs within the first few hours and is the main cause of worse functional outcome (3, 4). Therefore, therapeutic intervention aimed at reducing HE could represent a treatment paradigm in efforts to improve neurological outcome after ICH (2). However, recent ICH trials with hemostatic drugs, such as recombinant activated coagulation factor VII (rFVIIa) and tranexamic acid, did not reveal beneficial effects (5, 6). Previous studies focused on the changes of coagulation and fibrinolysis and theorized that these may contribute to HE. Actually, the role of platelet function on the occurrence of HE is insufficiently established, which may be due to the lack of effective detection methods (7).

Thromboelastography (TEG), a whole-blood viscoelastic test, offers a rapid bedside assessment of coagulability and fibrinolysis (8). Furthermore, according to the combined effect of platelet and plasma coagulation factors that contribute to hemostasis, platelet function activated by different pathways is available through TEG with platelet mapping (TEG-PM) (9). TEG-PM has previously been shown to be comparable with optical platelet aggregometry and superior to PFA-100 (10, 11). It is widely used in the guidance of personalized antiplatelet treatment and the assessment of perioperative period platelet function (11–13). However, there is no validated data about the level of platelet function detected by TEG-PM in patients with ICH.

The purpose of this prospective cohort study was to test the hypothesis that platelet dysfunction correlates with subsequent occurrence of HE and unfavorable outcome and then explore whether HE is the pathophysiological mechanism underlying this association. TEG-PM may be used as a clinically useful method to predict patients who will suffer HE and poor outcome and provide a possible direction concerning appropriate therapeutic interventions.

MATERIALS AND METHODS

Patient Population

This prospective study included spontaneous ICH patients aged 18 years or older who were admitted to our center between November 2019 and February 2021. Inclusion criteria were as follows: (1) baseline computed tomography (CT) scan was obtained within 6 h of symptom onset and (2) follow-up CT scan was acquired within 24 h of the baseline CT scan.

Exclusion criteria were as follows: (1) the presence of vascular malformation, aneurysm, traumatic, brain tumor, ischemic stroke with hemorrhagic transformation, or any other cause of secondary ICH; (2) primary intraventricular hemorrhage; (3) preceding use of antiplatelet or anticoagulant drugs; (4) receiving any hemostatic agents before TEG-PM draw; (5) surgery or other neurosurgical intervention before follow-up CT scan; (6) evidence of coagulopathy on traditional laboratory testing (14), such as activated partial thromboplastin time (APTT) >50 s, international normalized ratio (INR) >1.5, or platelet (PLT) count $<50 \times 10^3/\mu l$; and (7) lost to follow-up. The Institutional Review Board of our hospital approved this study, and written informed consent was obtained from each patient or close relatives.

Clinical Data and Outcome

We prospectively collected baseline demographic and clinical data including age, sex, cerebrovascular risk factors (smoking

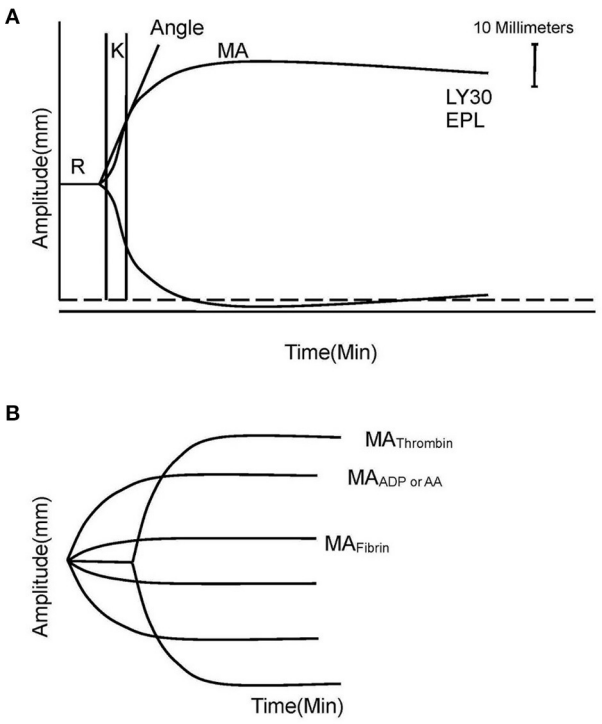

FIGURE 1 | Explanation of TEG and TEG-PM. **(A)** TEG parameters: *K*, angle, MA, EPL, and LY30. **(B)** TEG-PM parameters: $MA_{Thrombin}$, $MA_{ADP/AA}$, and MA_{Fibrin}. TEG, thromboelastography; TEG-PM, thromboelastography with platelet mapping; *R*, time from the start of the test to clot formation; *K*, kinetics of the rate of clot formation; angle, velocity of clot strength generation; MA, maximum amplitude; EPL, percent of clot dissolution 30 min after MA; LY30, percent of amplitude reduction at 30 min after MA; AA, arachidonic acid; ADP, adenosine diphosphate.

TABLE 1 | Comparison of baseline demographic, clinical characteristics, and TEG-PM parameters between patients with and without hematoma expansion.

	Hematoma expansion		
	Yes (*n* = 37)	**No (*n* = 105)**	***P* value**
Male, *n* (%)	26 (70.3)	70 (66.7)	0.687
Age (years), mean ± SD	63.0 ± 14.5	61.0 ± 15.1	0.483
Smoking, *n* (%)	17 (45.9)	43 (41.0)	0.597
Hypertension, *n* (%)	31 (83.8)	86 (81.9)	0.796
Diabetes mellitus, *n* (%)	3 (8.1)	8 (7.6)	0.924
SBP on admission (mmHg), mean ± SD	184.5 ± 24.6	168.2 ± 31.2	0.005
DBP on admission (mmHg), mean ± SD	97.5 ± 17.1	97.8 ± 19.7	0.952
GCS score, median (IQR)	12 (8–14)	14 (12–15)	<0.001
Intraventricular hemorrhage, *n* (%)	15 (40.5)	33 (31.4)	0.314
Time to baseline CT scan (h), median (IQR)	2 (1–2.5)	3 (2–4.5)	<0.001
Baseline hematoma volume (ml), median (IQR)	22 (10–34.5)	14 (4.5–26)	0.007
ICH locations			0.846
Infratentorial, *n* (%)	3 (8.1)	8 (7.6)	
Lobar, *n* (%)	9 (24.3)	21 (20.0)	
Deep, *n* (%)	25 (67.6)	76 (72.4)	
Hb (g/l), mean ± SD	136.3 ± 17.0	139.1 ± 18.1	0.412
PLT count (1,000 cells/μl), mean ± SD	196.1 ± 52.7	192.5 ± 59.9	0.750
APTT (s), median (IQR)	34.9 (32.1–38.5)	34.8 (32.4–37.2)	0.672
INR, median (IQR)	1.02 (0.96–1.07)	1.03 (0.97–1.12)	0.262
R (min), mean ± SD	6.7 ± 2.6	6.3 ± 1.7	0.446
K (min), median (IQR)	1.9 (1.6–2.9)	1.8 (1.6–2.3)	0.153
Angle (°), median (IQR)	62.1 (55.3–67.5)	64.4 (58.2–68.3)	0.192
MA (mm), mean ± SD	59.0 ± 6.8	60.9 ± 5.9	0.111
EPL (%), median (IQR)	0.1 (0.1–1.2)	0.2 (0.1–2.1)	0.108
LY30 (%), median (IQR)	0.1 (0.1–0.5)	0.1 (0.1–0.9)	0.359
AA inhibition (%), median (IQR)	77.9 (38.9–98.8)	23.5 (8.9–72.0)	<0.001
ADP inhibition (%), median (IQR)	80.3 (47.5–95.8)	51.5 (21.6–72.2)	<0.001

TEG-PM, thromboelastography with platelet mapping; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; CT, computed tomography; ICH, intracerebral hemorrhage; Hb, hemoglobin; PLT, platelet; APTT, activated partial thromboplastin time; IQR, interquartile range; INR, international normalized ratio; R, time from the start of the test to clot formation; K, kinetics of the rate of clot formation; Angle, velocity of clot strength generation; MA, maximum amplitude; EPL, percent of clot dissolution 30 min after MA; LY30, percent of amplitude reduction at 30 min after MA; AA, arachidonic acid; ADP, adenosine diphosphate.

status, hypertension, and diabetes mellitus), onset to first CT scan time, admission systolic blood pressure (SBP), diastolic blood pressure (DBP), and baseline Glasgow Coma Scale (GCS) score at arrival. Laboratory information included hemoglobin (Hb), PLT, APTT, and INR.

All participants received standard care according to the ICH treatment protocol of our hospital. Systolic blood pressure target was less than 140 mmHg after admission, according to the American Heart Association/American Stroke Association guidelines (15). Functional outcome scored with the modified Rankin Scale (mRS) at 3 months was obtained by a trained research staff. Poor functional outcome was defined as a dichotomized mRS score of 3–6 according to previous studies (16–18).

TEG-PM

TEG-PM testing was performed with whole blood drawn from a single clean puncture of the median cubital vein after the diagnostic CT scan. These samples were collected in heparinized or citrated tubes and processed within 2 h at room temperature. The tests were done using a computerized TEG-PM analyzer (Haemoscope, Model 5000) by a trained clinical scientist. Daily quality assurance checks were carried out to ensure the validity of calibration.

The standard TEG parameters were recorded as follows: time from the start of the test to clot formation (*R*, minutes), kinetics of the rate of clot formation (*K*, minutes), velocity of clot strength generation (angle, degrees), maximal clot strength contributed by fibrinogen activity and platelet function (MA, millimeters), percent of amplitude reduction at 30 min after MA (LY30), and percent of clot dissolution 30 min after MA (EPL) (**Figure 1A**) (8).

The platelet inhibition shows the degree of non-response of the platelet activated by exogenous arachidonic acid (AA) and adenosine diphosphate (ADP). $MA_{Thrombin}$ reflects the maximal clot strength with contribution of platelet and fibrinogen together measured by a kaolin-activated sample. MA_{AA} and MA_{ADP} reflect clot strength induced by stimulation of AA or ADP,

respectively. MA_{Fibrin} represents individual contribution of fibrin to the clot strength measured by a reptilase and activator F-activated sample. The platelet inhibitions in response to AA and ADP were calculated with computerized software according to the equation:

$$100 - \{[(MA_{AA} or MA_{ADP}) - MA_{Fibrin}]/(MA_{Thrombin} - MA_{Fibrin})\} \times 100$$ (**Figure 1B**) (19).

Imaging Analysis

According to trial protocol, a follow-up CT scan was performed within 24 h after the admission CT. The interval from symptom onset to admission CT was recorded. All CT scans were analyzed to determine the presence of intraventricular hemorrhage, ICH location (infratentorial, lobar, or deep), and hematoma volume. Hematoma volume measurement was performed using the 3D Slicer. Regions of interest of hematoma were identified using a semiautomatic method in each slice with a threshold range from 44 to 100 Hounsfield units. Then, we calculated hematoma volume by the accumulating volume of each slice (20–22). HE was defined as relative growth of more than 33% or an absolute growth greater than 6 ml from initial CT according to previous studies (3, 8).

Statistical Analysis

Quantitative variables were summarized as mean ± SD or as median with interquartile range (IQR) otherwise. Categorical variables were summarized as numbers with percentages. We compared baseline demographic, clinical, laboratory information, imaging characteristics, and TEG-PM parameters between patients with and without HE and then compared those between patients with good and poor outcome using *t* test (or Mann–Whitney *U* test for skewed distribution) for continuous variables and χ^2 test (or Fisher's exact test) for categorical variables. To determine the independent predictors of HE and poor outcome, variables associated with a $P < 0.10$ in univariate analyses were entered into the multivariable logistic regression models. In addition, we performed a multivariable analysis in two models because GCS and baseline hematoma volume were collinear. A mediation analysis was performed to estimate whether HE (as the mediator) was the driving factor for any relationship between platelet inhibition (independent variable) and poor outcome (dependent variable) by regressing all three variables together (23).

To obtain diagnostic threshold values of inhibition, we used receiver operator characteristic (ROC) curves considering an area under the curve (AUC) of 0.70 or higher as indicating an acceptable prediction. From the ROC curve, we determined the optimal cut-off value (with sensitivity and specificity) for discriminating the risk of HE by maximizing the Youden index (24). Statistical significance was set at a *P* value <0.05. Statistical analyses were performed using SPSS 19.0 software.

RESULTS

There were 142 ICH subjects meeting the inclusion criteria for analysis. The study population consists of 96 (67.6%) men and 46 (32.4%) women, with a mean age of 61.5 years. The median time from onset to first CT scan was 2.5 h (IQR, 2–4). The median baseline hematoma volume was 15 ml (IQR, 7–27 ml), and 48 patients (33.8%) had intraventricular hemorrhage on the first CT scan. HE occurred in 37 (26.1%) cases.

Intergroup differences between ICH patients with and without HE are shown in **Table 1**. Subjects with HE had higher systolic blood pressure, lower admission GCS score, shorter time

TABLE 2 | Multivariate analysis of predictors for hematoma expansion.

	OR	95% Wald CI	*P* value
Model 1			
SBP on admission, mmHg	1.016	0.999–1.032	0.061
Time to baseline CT scan, h	0.575	0.417–0.793	0.001
Baseline hematoma volume, ml	1.014	0.987–1.041	0.327
AA inhibition, %	1.020	1.006–1.033	0.004
ADP inhibition, %	1.026	1.008–1.045	0.004
Model 2			
SBP on admission, mmHg	1.012	0.995–1.029	0.167
Time to baseline CT scan, h	0.588	0.424–0.815	0.001
GCS score	0.861	0.732–1.013	0.072
AA inhibition, %	1.022	1.008–1.035	0.001
ADP inhibition, %	1.025	1.006–1.043	0.008

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; CT, computed tomography; AA, arachidonic acid; ADP, adenosine diphosphate.

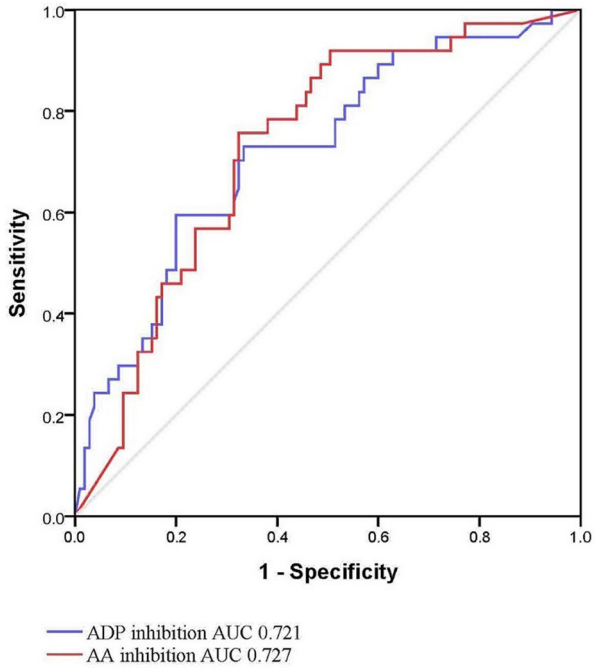

FIGURE 2 | Receiver operating characteristic curve for hematoma expansion with AA and ADP inhibition. AA, arachidonic acid; ADP, adenosine diphosphate; AUC, area under the curve.

TABLE 3 | Univariate comparison between patients with good outcome (mRS 0–2) and poor outcome (mRS 3–6).

	Good outcome ($n = 54$)	Poor outcome ($n = 88$)	*P* value
Male, *n* (%)	37 (68.5)	59 (67.0)	0.856
Age (years), mean ± SD	56.2 ± 12.0	64.8 ± 15.6	<0.001
Smoking, *n* (%)	24 (44.4)	36 (40.9)	0.679
Hypertension, *n* (%)	43 (79.6)	74 (84.1)	0.498
Diabetes mellitus, *n* (%)	4 (7.4)	7 (8.0)	0.906
SBP on admission (mmHg), mean ± SD	171.1 ± 32.0	173.3 ± 29.6	0.680
DBP on admission (mmHg), mean ± SD	101.1 ± 21.0	95.6 ± 17.4	0.110
GCS score, median (IQR)	14 (13–15)	13 (9–14)	<0.001
Intraventricular hemorrhage, *n* (%)	12 (22.2)	36 (40.9)	0.022
Time to baseline CT scan (h), median (IQR)	2 (2–4)	3 (1.25–4)	0.959
Baseline hematoma volume (ml), median (IQR)	7 (3–15)	22.5 (12–34.5)	<0.001
ICH locations			0.216
Infratentorial, *n* (%)	6 (11.1)	5 (5.7)	
Lobar, *n* (%)	8 (14.8)	22 (25.0)	
Deep, *n* (%)	40 (74.1)	61 (69.3)	
Hb (g/l), mean ± SD	141.5 ± 16.6	136.4 ± 18.3	0.095
PLT count (1,000 cells/μl), mean ± SD	196.7 ± 56.0	191.5 ± 59.3	0.606
APTT (s), median (IQR)	34.9 (32.6–37.1)	34.7 (32.0–37.5)	0.621
INR, median (IQR)	1.04 (0.97–1.11)	1.02 (0.97–1.10)	0.357
R (min), mean ± SD	6.3 ± 1.4	6.5 ± 2.2	0.456
K (min), median (IQR)	1.8 (1.6–2.3)	1.9 (1.6–2.8)	0.544
Angle (°), median (IQR)	65.6 (59.0–68.2)	63.5 (54.6–67.7)	0.242
MA (mm), mean ± SD	61.4 ± 6.6	59.8 ± 5.8	0.130
EPL (%), median (IQR)	0.1 (0.1–1.3)	0.2 (0.1–2.0)	0.329
LY30 (%), median (IQR)	0.1 (0.1–0.5)	0.1 (0.1–1.0)	0.162
AA inhibition (%), median (IQR)	18.5 (6.6–33.1)	56.3 (23.9–94.6)	<0.001
ADP inhibition (%), median (IQR)	38.6 (16.7–63.2)	69.3 (39.7–89.4)	<0.001

mRS, modified Rankin Scale; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; CT, computed tomography; ICH, intracerebral hemorrhage; Hb, hemoglobin; PLT, platelet; APTT, activated partial thromboplastin time; IQR, interquartile range; INR, international normalized ratio; R, time from the start of the test to clot formation; K, kinetics of the rate of clot formation; Angle, velocity of clot strength generation; MA, maximum amplitude; EPL, percent of clot dissolution 30 min after MA; LY30, percent of amplitude reduction at 30 min after MA; AA, arachidonic acid; ADP, adenosine diphosphate.

to baseline CT scan, and larger baseline hematoma volume compared to subjects without HE ($P < 0.05$). There were no statistically significant differences in TEG values of *R*, *K*, angle, MA, EPL, and LY30 ($P > 0.05$). In multivariate logistic analyses adjusted for relevant confounders, independent predictors of HE were time to baseline CT scan, AA, and ADP inhibition in both models 1 and 2 (**Table 2**). The ability of AA and ADP inhibition to predict early HE is shown in **Figure 2**. The AUC were 0.727 (95% CI 0.638 to 0.816) for AA inhibition and 0.721 (95% CI 0.625 to 0.816) for ADP inhibition. We identified the optimal cut-off values of AA and ADP inhibition as 42.75% (sensitivity 75.7%; specificity 67.6%) and 65.8% (sensitivity 73.0%; specificity 66.7%) for predicting HE, respectively.

Eighty-eight patients (62.0%) with ICH had unfavorable outcome. The results of bivariate analysis concerning predictors of 3-month outcomes are detailed in **Table 3**. The age, admission GCS score, intraventricular hemorrhage, baseline hematoma volume, and AA and ADP inhibition were associated with unfavorable outcome. The multivariate logistic analysis showed that the AA and ADP inhibition remained independent predictors of unfavorable outcome in patients with ICH (**Table 4**).

When regressing platelet inhibition, HE, and outcome together, the mediation analysis revealed that HE partially mediated the relationship between a high degree of AA inhibition and poor outcome. Additionally, HE also played a partially mediating role between ADP inhibition and poor outcome (**Figure 3**).

DISCUSSION

Our data indicate that a higher degree of AA and ADP inhibition on admission was independently associated with increased odds of HE. Furthermore, AUC suggested the acceptable performance of platelet function to predict HE. In addition, our study demonstrated that admission platelet dysfunction was associated with poor outcome at 3 months, after adjustment for age and measures of disease severity. This relationship seemed to be mediated partly by HE.

A previous study revealed that patients with HE showed longer *K* and a trend toward longer *R* compared with patients without HE (8). However, we were unable to identify an association of coagulation status with HE detected by TEG-PM. These differences may have been explained by the inclusion of ICH patients receiving anticoagulant or antiplatelet therapy in that study, and there were obviously more patients receiving aspirin and clopidogrel in the HE group, thus causing a slower clot formation. Additionally, the prior study did not include information on times from symptom onset to admission CT, a well-known predictor of HE. What is more, GCS score and baseline hematoma volume were not associated with HE in that study, which is not consistent with previously reported ICH cohorts (3, 25).

Antiplatelet medication has been demonstrated to be related to increased risk of HE and poor prognosis, due to the platelet dysfunction (26). Actually, high variability of platelet reactivity to ADP and AA in healthy volunteers has previously been reported (11, 27), but few studies concerned about the relationship between platelet function and HE in ICH patients without antiplatelet therapy before. In our cohort, the degree of ADP and AA receptor inhibition was similar to the clinical scenario of patients taking aspirin combined with clopidogrel (11). It is unknown whether ICH itself changes platelet activity, because it is not feasible to obtain platelet activity data before and after ICH in humans. Furthermore, our multivariable analysis suggested that both AA and ADP inhibition are independent predictors of HE. However, no difference was demonstrated in platelet count, coagulation, or fibrinolysis status between the two groups.

Although our study was not designed to investigate potential pathophysiologic mechanisms of platelet function in HE, multiple prior studies support a definitely mechanistic role for platelet function in hemostasis. When bleeding occurs, the platelet and fibrin polymer aggregate in the damaged vessel to form an immobile blood clot. Secondary mechanical shearing of peripheral vessels caused by the initial bleeding is responsible for ongoing bleeding, called HE (25, 28). Otherwise, the accumulation of platelets activated through AA and ADP pathway subsequently enhance the hemostatic effect to prevent HE (29). This could be a possible explanation of the present study that HE is more likely to occur in patients with high ADP or AA inhibition.

According to the role of platelet in hemostasis, we speculate that the effect of higher platelet inhibition on outcomes in ICH patients is mediated through larger admission hematoma volumes and HE. This in turn results in worse functional outcomes at 3 months. In the mediation analysis, we were able to demonstrate a HE-mediated mechanism contributing to the association between platelet inhibition and functional outcome. Moreover, it is possible that mechanisms unrelated to HE may also contribute to the association.

HE is a clear independent predictor of increased mortality and poor functional outcomes (17). Therefore, several agents that affect the coagulation and fibrinolysis status have been investigated to prevent HE, restricting the mass effect and secondary brain injury (30). Unfortunately, none of these clinical trials was able to reject the null hypothesis (31). In previous studies, tranexamic acid and rFVIIa reduced HE compared

TABLE 4 | Multivariate analysis of predictors for poor outcome.

	OR	95% Wald CI	*P* value
Model 1			
Age, years	1.070	1.029–1.112	0.001
Intraventricular hemorrhage	1.638	0.540–4.968	0.383
Baseline hematoma volume, ml	1.144	1.078–1.214	<0.001
Hb, g/l	1.006	0.977–1.036	0.694
AA inhibition, %	1.019	1.005–1.033	0.007
ADP inhibition, %	1.027	1.010–1.045	0.002
Model 2			
Age, years	1.045	1.012–1.080	0.007
GCS score	0.679	0.538–0.858	0.001
Intraventricular hemorrhage	1.710	0.627–4.664	0.294
Hb, g/l	1.000	0.974–1.026	0.973
AA inhibition, %	1.021	1.008–1.034	0.002
ADP inhibition, %	1.021	1.005–1.036	0.009

OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; Hb, hemoglobin; AA, arachidonic acid; ADP, adenosine diphosphate.

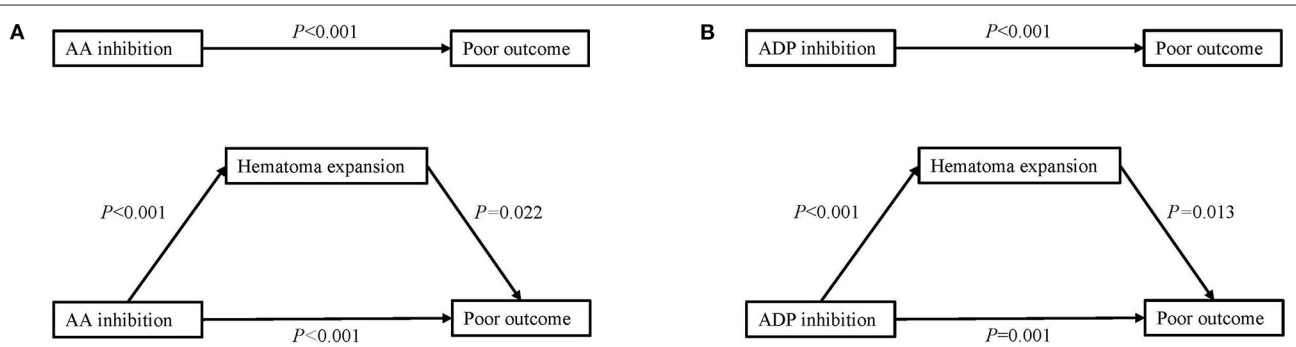

FIGURE 3 | Mediation analysis of the association of platelet inhibition with poor outcome with hematoma expansion as a mediator. **(A)** Mediation analysis of AA inhibition in poor outcome by hematoma expansion. **(B)** Mediation analysis of ADP inhibition in poor outcome by hematoma expansion. AA, arachidonic acid; ADP, adenosine diphosphate.

with placebo, but did not improve survival or functional outcomes (6, 32). Our data may suggest that improvement of platelet function can be considered in preventing the early occurrence of HE to improve outcome. However, a previous study showed that platelet transfusion did not reduce HE for people taking antiplatelet therapy before ICH. On the contrary, it was associated with increased mortality and dependence in 3 months (18). One possible explanation is that HE is more closely associated with platelet function than platelet count itself, as demonstrated in our multivariable analysis and a previous cohort study (33). Another possible explanation is that the harmful effects were partly caused by transfusing ABO-incompatible platelets (34). Two prior studies have investigated the effect of desmopressin on improving platelet function in ICH patients and found that intravenous desmopressin was well tolerated and obviously improved platelet activity (35, 36). According to the results of our study, it is reasonable to believe that desmopressin may be a potential pharmacological treatment in preventing HE to improve outcome.

Thus far, clinical trials aimed at restricting expansion have not led to improved neurological outcome (6, 18), perhaps because such therapies need to be targeted to patients at highest risk for expansion to show any benefit. So, effective biomarkers are needed to select patients and guide interventions to restrict HE. The computed tomographic angiography (CTA) spot sign, a novel radiographic marker, has proven to be a promising predictor of HE with a sensitivity of 51% and a specificity of 85% (3). In our study, the sensitivity and specificity of platelet inhibition for predicting expansion were 73.0 and 66.7% for ADP inhibition and 75.7 and 67.6% for AA inhibition, respectively. Compared with the CTA spot sign, platelet inhibition has a lower specificity, but it is more sensitive for predicting HE. Moreover, CTA spot sign was just an imaging sign that cannot be altered, while platelet function can be directly improved. Additionally, recent clinical trials did not show reduced HE or improved clinical outcomes in spot sign-positive ICH patients through the use of rFVIIa or tranexamic acid (37, 38). Thus, it may be infeasible to use CTA spot sign as a predictor to target hemostatic therapy in acute ICH patients. Our data may suggest that TEG-PM is useful to identify individuals in high risk for HE, and they should receive aggressive treatments such as desmopressin and hemostatic drugs.

Inherent limitations of our analysis should be clarified. Our study was a single-center observational cohort with limited sample size and will need to be replicated. In addition, TEG-PM was tested only once on admission. It is unclear whether there are dynamical changes in platelet function, which might explain the reason why HE often occurs in early stage. Finally, we did not perform CTA spot sign testing and the correlation of platelet function with the CTA spot sign was not analyzed.

Further investigation is warranted to confirm our findings of more HE after ICH in patients with lower platelet function, resulting in worse clinical outcomes. If confirmed, these findings may suggest the importance of accounting for and correcting platelet dysfunction in future ICH treatment strategies for HE in efforts to improve outcome.

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 human participants were reviewed and approved by Medical Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QH, YC, and SC conceived and designed the study. QH, YZ, CL, RW, and YW acquired the data, which ZC analyzed. QH, YZ, and ZX aided in data interpretation and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Impact of Chronic Obstructive Pulmonary Disease on Infectious Complications and Mortality in Patients With Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose: Chronic obstructive pulmonary disease (COPD) has been associated with several complications and mortality in acutely ill patients. For patients with aneurysmal subarachnoid hemorrhage (aSAH), the association between COPD and clinical outcomes remains unclear.

Methods: In this retrospective cohort study, we analyzed consecutive aSAH patients admitted to the West China Hospital between 2014 and 2019. Propensity score matching analysis and cox regression models was used to assess the association between COPD and mortality. The primary outcome was long-term mortality.

Results: Using a clinical database from a large university medical center, 2,925 patients with aSAH were identified, of whom 219 (7.5%) also had COPD. Patients were followed-up for a median of 3.8 years, and during follow-up 633 patients (21.6%) died. Long-term mortality was higher in patients with COPD compared to patients without COPD in the Cox regression models [adjusted hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.14–2.02]. Propensity score matching analysis also showed similar associations between COPD and mortality in hospital, at 1 year, at 2 years, and at long-term. Similarly, patients with COPD had significantly higher incidence of infections, such as pneumonia [odds ratio (OR) 3.24, 95% CI 2.30–4.56], urinary tract infection (OR 1.81, 95% CI 1.20–2.73), bloodstream infection (OR 3.83, 95% CI 1.84–7.99), and hospital infection (OR 3.24, 95% CI 2.28–4.61).

Conclusions: Among aSAH patients, COPD is associated with increased mortality. COPD represents a significant risk factor for infections. Given that these are preventable complications, our findings are of clinical relevance.

Keywords: intracranial aneurysm, chronic obstructive pulmonary disease, subarachnoid hemorrhage, risk factor, prognosis

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the world (1–3) and is currently characterized by systemic involvement and multiple comorbidities (4). Growing evidence indicated that COPD independently predicts mortality and morbidity in patients undergoing surgery and patients with critically ill (5–8). However, the impact of COPD on outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH) remains unclear (9). Only one observational study has addressed the association between COPD and mortality in patients with aSAH (10). That study demonstrated that COPD did not increase in-hospital mortality after adjusting confounders. The published literature is sparse with respect to the long-term mortality of patients with COPD after aSAH.

Moreover, there is no data identifying the impact of COPD on infectious complications in patients with aSAH. The question of the potential impact of COPD on infectious complications in patients with aSAH is important because if COPD was indeed associated with infections, patients with COPD after aSAH would benefit from prophylactic antibiotics. A Cochrane review concluded that use of prophylactic antibiotics results in a benefit in reducing exacerbations in COPD patients (11). However, evidence from two large randomized clinical trials did not found the benefits of use of prophylactic antibiotics in lower risk of pneumonia or death for patients with stroke (12, 13). A possible explanation for the failure is that the included patients in the trials have low risk of infection, with 7 and 16% patients developing pneumonia, respectively. For patients with aSAH, about 20% of them develop pneumonia (14). COPD is also one of the most frequent comorbid conditions and a risk factor for developing pneumonia in critically ill patient (15).

With the increasing global incidence of COPD (16) and its high prevalence in patient with aSAH (10), we assessed the impact of COPD on outcomes in patient with aSAH, using propensity score matching (PSM) to form groups for comparison with near-identical distributions of background and potential confounder variables.

MATERIALS AND METHODS

Study Design

We performed a retrospective cohort study. We consecutively evaluated the electronic health record of patients with aSAH admitted to the West China Hospital, Sichuan University, from January 2014 to June 2019, which is the largest hospital in Sichuan province, with a population of 91 million. This study was approved by the ethics committee of West China hospital (No. 20191133). The ethics committee has exempted written informed consent of patients included in the study because this study posed minimal-risk research and used only observational data.

Study Population

Patients were eligible if they had an intracranial aneurysm identified by imaging in the presence of SAH. Intracranial aneurysms were identified by cerebral angiography, MRA, CTA, or operation. SAH was confirmed with neuroimaging (including CT, MRI, or angiography), cerebrospinal fluid analysis, or intraoperatively by a neurosurgeon.

Participants were excluded in case of aneurysms related to trauma, arteriovenous malformations, fusiform aneurysms, or non-definitive aneurysms, aneurysms that were treated before the presentation, or trauma SAH. Moreover, we also excluded patients whose household registration was not in Sichuan province or whose personal identification number was not found in the electronic medical record system, because we used personal identification number to identify mortality by searching the databases of the Household Registration Administration System in Sichuan province.

Demographics Characteristics

The primary exposure was COPD. Diagnosis of COPD was based on medical reports. Demographic and clinical data included age, sex, hypertension, diabetes mellitus, coronary heart disease, smoking (current, ever, never), alcohol use, size of aneurysm, location of aneurysm, external ventricular drain, and treatment of aneurysm. Hunt & Hess grade and Fisher grade were also obtained on admission.

Outcomes

The primary outcome was long-term mortality, which was defined as the mortality at the longest follow-up. The time of death was determined by searching the data bases of the Household Registration Administration System. In China, every resident has a unique identification number. If one dies, a death certificate should be reported to the household registration offices in the bureau of public security within 30 days as required by law. As the death certificate database is accurate and complete, the rate of loss to follow-up of our cohort was negligible.

Secondary outcomes included mortality in hospital, 1 year, and 2 years, neurological complications, infectious complications, acute kidney injury, length of hospital stay, and poor functional outcome at the time of discharge. Infectious outcomes were pneumonia, intracranial infection, urinary tract infection, and bloodstream infection. Neurological complications were hydrocephalus, delayed neurological ischemic deficits, rebleeding, and seizures.

Pneumonia is defined as a state of lung tissue inflammation of infectious etiology with the radiographic demonstration of parenchymal disease. Bloodstream infection was defined as positive blood culture necessitating treatment with antibiotics. Urinary tract infection was a positive urine culture or positive leukocyte esterase and positive nitrite on a urinalysis that necessitates treatment with antibiotics. Intracranial infection was defined as a positive cerebrospinal fluid culture requiring treatment with antibiotics. Poor functional outcome was defined as modified Rankin Scale (mRS) 4-6. Re-bleeding was defined as acute worsening in neurologic status along with an increase in hemorrhage volume which was confirmed in a repeat CT or MRI scan. Delayed ischemic neurological deficits was defined as angiographic vasospasm associated with a decline in neurological status lasting >2 h and with other causes being ruled out. Infections were diagnosed by treating physicians.

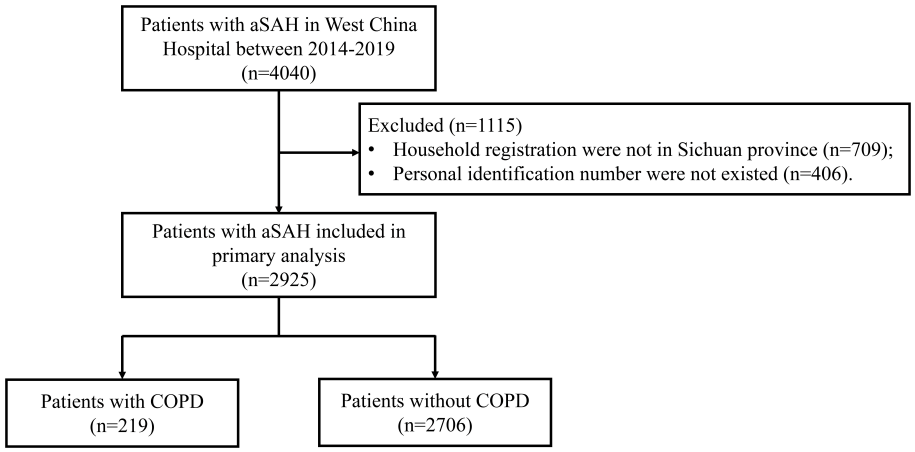

FIGURE 1 | Flow chart of enrollment.

Statistical Analysis

We used SPSS, version 24 (SPSS Inc) and R software version R3.3.2 (Matching and Frailty pack packages, R Foundation for Statistical Computing) for statistical analyses.

From our experience and from previous reports, age, sex, hypertension, diabetes mellitus, chronic renal failure, coronary heart disease, smoking, alcohol use, Hunt and Hess grade and Fisher grade were considered important confounders. Propensity score matching (17) was used to minimize bias from confounding variables when comparing patients with COPD and patients without COPD in the cohort study. The propensity score for each patient was calculated through the logistic regression modeling. Exact matching was performed in patients with and without COPD in a 1:5 ratio, with a caliper size of 0.2. We then compared the characteristics of patients with and without COPD using absolute standardized differences, and a difference more than 0.1 is considered meaningful.

We also adjusted potential confounding factors using logistic regression. Each variable was screened by univariable logistic regression model for each outcome. Variables with a p-value $<$ 0.10 were entered into the multivariable logistic regression model which was created using backward elimination.

The Kaplan–Meier curve was generated for mortality. The relationships between COPD and long-term mortality were further assessed with pre-specified Cox regression models with adjustment for confounder using backward elimination.

For proportional outcomes comparing patients with COPD and patients without COPD after PSM, the paired t-test was used for continuous variables, and univariable logistic regression was used for binary variables. Two-sided $P < 0.05$ was considered statistically significant.

We used the E-value to assesses how large the effect from unmeasured confounding would be to negate the study results (18). E-values were computed with an online E-value calculator (https://mmathur.shinyapps.io/evalue/) (19).

RESULTS

We screened 4,040 consecutive individuals with aSAH in West China hospital during the study period. After excluding 709 patients whose household registration were not in Sichuan province and 406 patients whose personal identification number were not existed in electronic medical record system, a total of 2,925 patients were included in this study (**Figure 1**). In patients with aSAH, 219 (7.5%) patients had COPD. Patient demographics stratified by COPD are shown in **Table 1**. Before matching, there were more old patients in the COPD group than in the non-COPD group. Compared with patients without COPD, patients with COPD more frequently had diabetes, and more patients with COPD are smokers. Patients with COPD have higher Hunt & Hess grade. There was a total of 166:830 matched pairs (1:5). After matching, the variables were balanced between patients with COPD and patients without COPD.

The univariable logistic regression and multivariable logistic regression for the association between COPD and long-term mortality was shown in **Supplementary Table 1**. In univariate analysis, COPD was associated with increased odds of long-term mortality (OR 2.01, 95% CI 1.49–2.69). After adjusted for variables of age, hypertension, diabetes, size of aneurysm, external ventricular drain, and treatment of aneurysm in multivariable logistic regression, the association between COPD and long-term mortality was not changed (OR 2.01, 95% CI 1.49–2.69). Even after propensity score matching, our findings remained robust: COPD was associated with higher mortality (OR 1.63, 95% CI 1.02–2.62; **Table 2**). Propensity score matching analysis also showed similar associations between COPD and other mortality, such as in-hospital, 1 and 2 years.

Patients were followed-up for a median of 3.8 years, and during follow-up 633 patients (21.6%) died. The impact of COPD on mortality throughout follow-up period was shown in the Kaplan–Meier plot (**Figure 2**). Long-term mortality was higher in patients with COPD compared to patients without COPD in

TABLE 1 | Baseline characteristics of the patients by COPD.

Characteristics	Before matching			After matching		
	Non-COPD (n = 2,706)	COPD (n = 219)	SMD	Non-COPD (n = 830)	COPD (n = 166)	SMD
Mean age (SD), year	54.9 (11.7)	67.0 (9.1)	1.16	64.8 (8.9)	64.8 (8.8)	0.01
Female	1,771 (65.4)	125 (57.1)	0.17	491 (59.2)	97 (58.4)	0.02
Current Smoking	521 (19.3)	50 (22.8)	0.12	172 (20.7)	36 (21.7)	0.02
Alcohol abuse	516 (19.1)	48 (21.9)	0.07	174 (21.0)	31 (18.7)	0.06
Hypertension	683 (25.2)	60 (27.4)	0.05	243 (29.3)	44 (26.5)	0.06
Diabetes	147 (5.4)	20 (9.1)	0.14	68 (8.2)	13 (7.8)	0.01
Anterior circulation aneurysm	2,025 (74.8)	157 (71.7)	0.15	617 (74.3)	123 (74.1)	0.03
Mean size of aneurysm (SD), cm	0.7 (0.5)	0.7 (0.6)	0.03	0.7 (0.6)	0.7 (0.7)	0.04
Hunt and Hess grade						
I	262 (9.7)	16 (7.3)	0.11	69 (8.3)	11 (6.6)	0.01
II	1,392 (51.4)	109 (49.8)		404 (48.7)	85 (51.2)	
III	692 (25.6)	55 (25.1)		231 (27.8)	42 (25.3)	
IV	313 (11.6)	38 (17.4)		111 (13.4)	28 (16.9)	
V	47 (1.7)	1 (0.5)		15 (1.8)	0 (0)	
Fisher grade						
I	122 (4.5)	13 (5.9)	0.01	44 (5.3)	11 (6.6)	0.01
II	430 (15.9)	36 (16.4)		179 (21.6)	34 (20.5)	
III	345 (12.7)	22 (10.0)		121 (14.6)	20 (12.0)	
IV	1,253 (46.3)	106 (48.4)		486 (58.6)	101 (60.8)	
Operation						
Clip	1,710 (63.2)	123 (56.2)	0.21	491 (59.2)	98 (59.0)	0.04
Coil	337 (12.5)	21 (9.6)		85 (10.2)	15 (9.0)	
No treatment	659 (24.4)	75 (34.2)		254 (30.6)	53 (31.9)	
EVD	56 (2.1)	7 (3.2)	0.07	22 (2.7)	5 (3.0)	0.02

COPD, chronic obstructive pulmonary disease; SMD, Standardized mean difference; SD, standard deviation; EVD, External ventricular drain.
Unless otherwise indicated, data are n (%).

the Cox regression models [adjusted hazard ratio (HR) 1.52, 95% CI 1.14–2.02].

Before and after matching, COPD was associated with an increased risk of infectious complications, including pneumonia (OR 3.24, 95% CI 2.30–4.56), urinary tract infection (OR 1.81, 95% CI 1.20–2.73), bloodstream infection (OR 3.83, 95% CI 1.84–7.99), and hospital infection (OR 3.24, 95% CI 2.28–4.61). Before matching, COPD was associated with several neurological complications [hydrocephalus (OR 1.90, 95% CI 1.43–2.52), re-bleeding (OR 1.72, 95% CI 1.24–2.39), and seizures (OR 1.78, 95% CI 1.12–2.84)]. After matching, however, COPD was associated with an increased incidence of seizures, but not hydrocephalus and rebleeding. After matching, the length of hospital stay was significantly longer in patients with COPD ($P < 0.001$).

The E-value for long-term mortality (HR) was 2.01 with a lower limit of 1.42, suggesting that unmeasured confounding was unlikely to explain the findings.

We further assessed interactions by other variables on COPD. Except for subgroup analyses of age, external ventricular drain, operation, and pneumonia, there is no significant effect modification of the change in COPD and long-term mortality on these variables (**Figure 3**).

DISCUSSION

In this cohort study of patients with aSAH, we found that compared to patients without COPD, patients with COPD have increased odds of short-term and long-term death and poor functional outcome at discharge. Moreover, COPD is associated with an increased incidence of seizures and infectious complications, especially pneumonia, which may contribute to the increased mortality observed in aSAH patients with COPD.

Mechanisms

Several mechanisms may explain the association between COPD and poor outcomes. First, COPD causes spillover of multiple pro-inflammatory markers into the circulation, leading to chronic low-grade systemic inflammation, ultimately resulting in unstable plaque formation and prothrombotic events (20). Second, COPD, especially during exacerbation, are hypoxemic and hypercapnic at baseline which may increase their

TABLE 2 | Comparison of unadjusted and risk-adjusted outcomes by COPD.

Outcomes	*n* (%)	Unadjusted		Multivariable regression adjustment		Propensity score adjustment	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Mortality in hospital	148/2,936 (5.0)	2.15 (1.33–3.49)	0.002	1.98 (1.18–3.33)	0.01	1.86 (1.01–3.45)	0.05
Mortality at 1 year	358/2,936 (12.2)	1.74 (1.21–2.49)	0.003	1.41 (0.94–2.13)	0.10	1.59 (1.04–2.43)	0.03
Mortality at 2 years	485/2,823 (16.5)	2.17 (1.59–2.98)	<0.001	1.77 (1.22–2.58)	0.003	1.75 (1.20–2.55)	0.004
Long-term mortality	633/2,936 (21.6)	2.01 (1.49–2.69)	<0.001	1.46 (1.03–2.07)	0.03	1.45 (1.02–2.07)	0.04
mRS 4-6 at discharge	798/2,935 (27.2)	1.79 (1.35–2.38)	<0.001	1.85 (1.30–2.63)	0.001	1.59 (1.12–2.25)	0.01
mRS 4-5 at discharge	653/2,790 (22.2)	1.72 (1.26–2.34)	0.001	1.59 (1.08–2.36)	0.02	1.48 (1.02–2.16)	0.04
Neurological complications							
Hydrocephalus	293/2,936 (10.0)	1.36 (0.89–2.06)	0.15	1.03 (0.65–1.64)	0.89	0.99 (0.59–1.65)	0.97
Rebleeding	163/2,936 (5.6)	1.48 (0.88–2.49)	0.14	1.38 (0.81–2.34)	0.23	1.24 (0.63–2.45)	0.54
DNIDs	551/2,936 (18.8)	1.02 (0.72–1.45)	0.89	1.01 (0.71–1.44)	0.94	0.80 (0.51–1.26)	0.34
Seizures	103/2,936 (3.5)	1.83 (1.01–3.34)	0.05	2.26 (1.18–4.34)	0.01	2.06 (0.97–4.38)	0.06
Infection complications							
Pneumonia	807/2,936 (27.5)	4.32 (3.26–5.73)	<0.001	3.59 (2.63–4.89)	<0.001	3.24 (2.30–4.56)	<0.001
Intracranial infection	326/2,936 (11.1)	1.36 (0.91–2.02)	0.13	1.35 (0.89–2.05)	0.16	1.19 (0.73–1.93)	0.49
Urinary tract infection	429/2,936 (14.6)	1.94 (1.40–2.70)	<0.001	1.74 (1.22–2.47)	0.002	1.81 (1.20–2.73)	0.01
Bloodstream infection	91/2,936 (3.1)	2.99 (1.73–5.17)	<0.001	2.89 (1.67–5.02)	<0.001	3.83 (1.84–7.99)	<0.001
Hospital infection	1,110/2,936 (37.8)	3.90 (2.91–5.24)	<0.001	3.30 (2.41–4.51)	<0.001	3.24 (2.28–4.61)	<0.001

OR, odds ratio; CI, confidence interval; DNIDs, Delayed Neurological Ischemic Deficits.

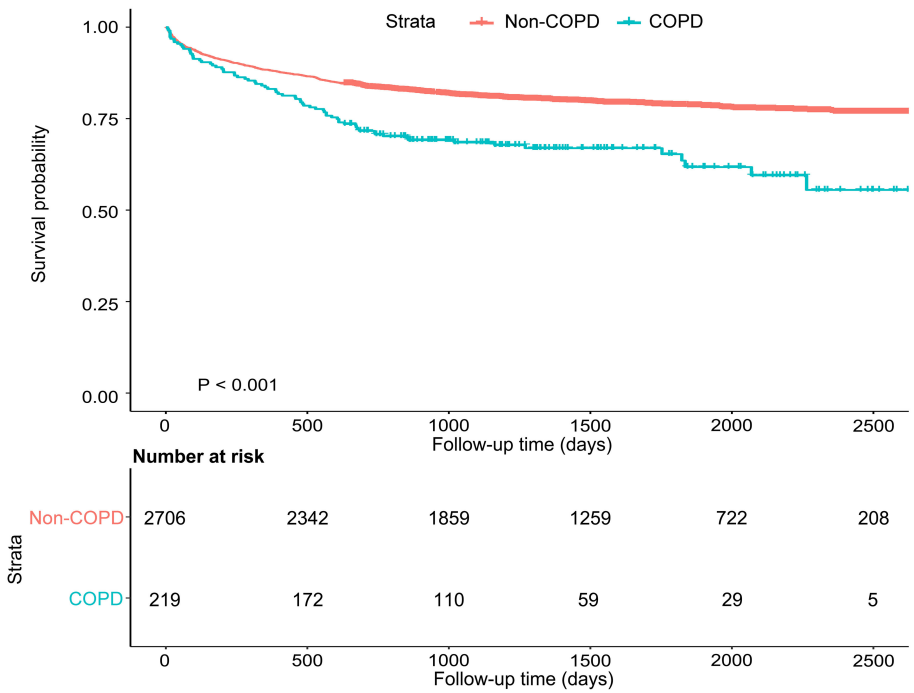

FIGURE 2 | Kaplan–Meier curve of mortality after aSAH among patients with and without COPD.

susceptibility to brain injury. The intraneural hypoxemia can occur in ∼40–50% of patients with mild COPD (21). Third, COPD have associated comorbid conditions after stroke, such as seizure (22). Fourth, COPD are commonly treated with corticosteroids, and hospitalized patients on corticosteroids have a heightened risk of nosocomial infection.

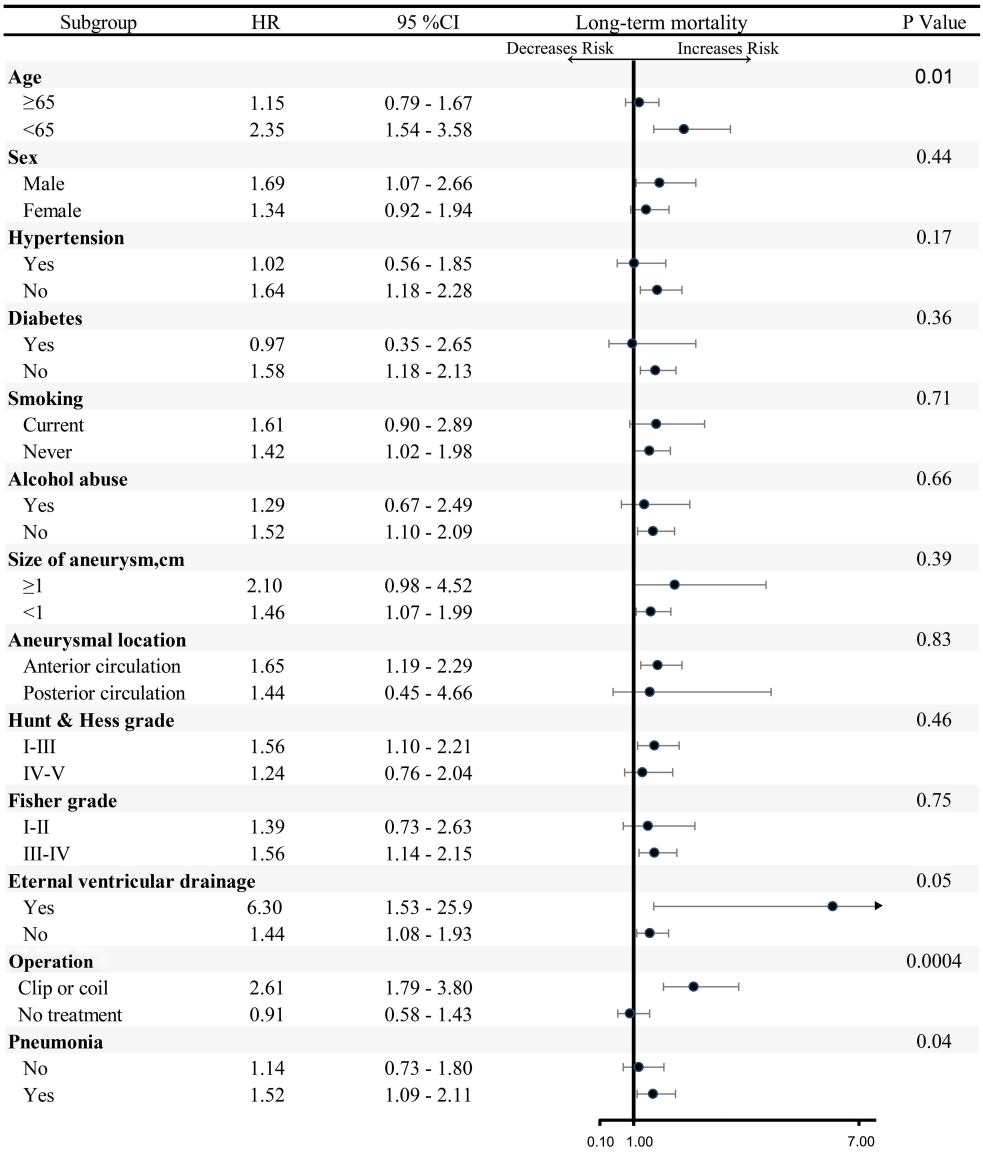

FIGURE 3 | Subgroup analysis of association between COPD and long-term mortality. EVD, External ventricular drain; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

Mortality

For ischemic stroke patients, the association between COPD and the increased in-hospital mortality have been demonstrated both before (OR: 1.30, 95% CI: 1.26–1.35) and after adjusting confounders (OR: 1.08, 95% CI: 1.03–1.13) (10). Recently, the study by de Miguel-Díez et al. further confirmed this conclusion (23). However, for patients with aSAH, only one study related to this topic assessed the association between mortality and COPD in stroke patients (10). COPD was associated with increased odds of in-hospital mortality (OR 1.29, 95% CI 1.16–1.42) in univariate analysis; however, the association was not significant after adjusting confounders (adjusted OR 0.98, 95% CI 0.85–1.13) (10). The previous study was limited by short-term follow-up and the epidemiologic study design that was unadjusted for important confounders (e.g., hemorrhage severity), which led to the uncertainty of their conclusions.

Functional Outcome

This study found an association of COPD with poor functional outcomes in patients with aSAH. While such an association has not been previously assessed in patients with aSAH, a study found that COPD increased the incidence of discharge to nursing homes and rehabilitation facilities after surgery (24), and another study found that the discharge destination is a surrogate for mRS functional outcome in stroke survivors (25). More research is

needed to confirm the association of COPD with poor functional outcomes in patients with aSAH.

Infection Complications

In this study, COPD was associated with an increased frequency of a variety of infection complications. In a cohort study by Lee et al., COPD is an independent risk factor for pneumonia and septic shock after total shoulder arthroplasty (26). Yakubek et al. published a study found that in patients undergoing total hip arthroplasty, patients with COPD are more likely to experience pneumonia and deep surgical site infection (24).

Two large randomized clinical trials conducted in patients hospitalized for stroke found that prophylactic antibiotics did not reduce the incidence of pneumonia (12, 13). A possible explanation for the lack of benefit is that the included patients have a general risk for pneumonia but not high risk, with 7–16% patients developing pneumonia in the control group. In the present study, half of the patients with COPD have pneumonia. The use of prophylactic antibiotics in patients with COPD may reduce the risk of progression to clinically overt pneumonia better than in general patients.

Strengths and Limitations

One of the major strengths of our study is the high-quality, standardized, single-institution database, the large sample size, and the use of PSM to adjust for confounders. We determined all-cause mortality based on the household registration in systems, which is accurate and complete, without lost to follow-up.

However, the limitations of this study must also be considered. First, based on the retrospective study, the interpretation of the specific causal relationship for COPD on mortality was is limited. Secondly, pulmonary function testing was not recorded in our database. We cannot assess the association between severity of COPD and outcomes, limiting the strength of our conclusions. Moreover, the results of this study are contingent on the accuracy and reliability of COPD status data, which were based on patient self-report and family members of incapacitated patients. It is possible that some patients in the control group also had COPD, leading to reporting and recall biases; however, these biases may serve to increase the confidence in our conclusion.

CONCLUSIONS

In aSAH patients, COPD was associated with a significant increase in short-term and long-term mortality. COPD increased the risk of infectious complications, especially pneumonia. Since these complications can potentially be prevented by antibiotics drugs, our findings are of clinical relevance and can open up new lines of inquiry. Certainly, future RCTs are needed to explore whether the use of prophylactic antibiotic therapy could improve the outcomes among these patients.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of West China Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FF and WL: study concept and design. YZ, LY, and WY: acquisition, analysis, or interpretation of data. YZ and WY: statistical analysis. YZ and LY: drafting of the manuscript. All authors: critical revision of the manuscript for important intellectual content.

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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.2021.723115/full#supplementary-material

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Screening Computed Tomography Angiography to Identify Patients at Low Risk for Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage

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Introduction: Delayed cerebral ischemia (DCI) occurs during a risk period of 3–21 days following aneurysmal subarachnoid hemorrhage (aSAH) and is associated with worse outcomes. The identification of patients at low risk for DCI might permit triage to less intense monitoring and management. While large-vessel vasospasm (LVV) is a distinct clinical entity from DCI, the presence of moderate-to-severe LVV is associated with a higher risk of DCI. Our hypothesis was that the absence of moderate-to-severe LVV on screening computed tomographic angiography (CTA) performed within the first few days of the DCI risk period will accurately identify patients at low risk for subsequent DCI.

Methods: This was a retrospective cohort study. Our institutional SAH outcomes registry was queried for all aSAH patients admitted in 2016–2019 who underwent screening CTA brain between days 4 and 8 following ictus. We excluded patients diagnosed with DCI prior to the first CTA performed during this time period. All variables are prospectively entered into the registry, and outcomes including DCI and LVV are prospectively adjudicated. We evaluated the predictive value and accuracy of moderate-to-severe LVV on CTA performed 4–8 days following ictus for the prediction of subsequent DCI.

Results: A total of 243 aSAH patients were admitted during the study timeframe. Of the 54 patients meeting the eligibility criteria, 11 (20%) had moderate-to-severe LVV on the screening CTA study performed during the risk period. Seven of the 11 (64%) patients with moderate-to-severe LVV on the days 4–8 screening CTA vs. six of 43 (14%) patients without, subsequently developed DCI. On multivariate analysis, the presence of LVV on days 4–8 screening CTA was an independent predictor of DCI (odds ratio 10.26, 95% CI 1.69–62.24, $p = 0.011$). NPV for the subsequent development of DCI was 86% (95% CI 77–92%). Sensitivity was 54% (25–81%), specificity 90% (77–97%), and positive predictive value 64% (38–83%).

Conclusions: The presence of moderate-to-severe LVV on screening CTA performed

between days 4 and 8 following aSAH was an independent predictor of DCI, but achieved only moderate diagnostic accuracy, with NPV 86% and sensitivity 54%. Complementary risk-stratification strategies are likely necessary.

Keywords: subarachnoid hemorrhage, cerebral vasospasm, computed tomography angiography, cerebral ischemia, intracranial aneurysm

INTRODUCTION

While mortality from aneurysmal subarachnoid hemorrhage (aSAH) has improved over the past few decades, morbidity remains high (1). Delayed cerebral ischemia, defined as the development of otherwise unexplained neurologic deterioration during the appropriate time period or radiographic evidence of cerebral infarction, is an important cause of poor outcomes following aSAH (1, 2). DCI typically occurs during a risk period of 3–21 days following aSAH. Up to 30% of aSAH patients may suffer DCI (3). While large-vessel vasospasm (LVV) was once considered the sole cause, DCI is now thought to be a complex entity, with inflammation playing a major role in the pathophysiology (2, 3).

While LVV may not be the sole cause of DCI, and in itself does not predict long-term outcomes, a strong correlation does exist between LVV and DCI. Several studies suggest that while DCI may occur in vascular territories without evidence of moderate-to-severe LVV, it is relatively uncommon in patients without significant LVV anywhere. This association between LVV and DCI is often leveraged to stratify DCI risk in asymptomatic patients, with patients at high risk receiving more intense monitoring in the Intensive Care Unit (ICU), and those at lower risk, without other indications for ICU care, potentially managed in lower intensity settings, such as moderate care (3). Such risk stratification may permit more cost-effective care and optimize ICU capacity for critically-ill patients. Some centers therefore perform screening CTA between days 4 and 8 to risk-stratify aSAH patients. While this practice is popular at several centers, and CTA is highly accurate for the detection of vasospasm outside the distal vasculature (4), the value of CTA performed on asymptomatic patients during the 4–8-day period has not been studied.

Our objective therefore was to evaluate predictive value and diagnostic accuracy of CTA performed on asymptomatic patients during the 4–8-day period to identify patients at low subsequent risk of DCI.

MATERIALS AND METHODS

This was a retrospective observational study, using prospectively collected data from a single center disease-specific registry. The Institutional Review Board (IRB) determined that this study is exempt from IRB regulation (HUM00037496). All adult (age 18 or older) patients with angiographically-confirmed aSAH admitted between January 2016 and June 2019 who underwent CTA 4–8 days following ictus were included. We excluded patients with a clinical diagnosis of DCI prior to the first CTA performed during this period. The data source was the University of Michigan Subarachnoid Hemorrhage (SAH) outcomes database (UMSAHOD). All patients with SAH (aSAH and angiogram-negative SAH) admitted to the University of Michigan are entered into this database. All data are prospectively entered, including demographics, comorbidities, baseline clinical variables including clinical grade, radiological findings, grade on admission, aneurysm location, treatment method, in-hospital events/complications, and outcomes. In-hospital events such as DCI and LVV are prospectively adjudicated in monthly or bi-monthly meetings of neurocritical care faculty investigators, at which at least two faculty members are present to adjudicate key variables including LVV as well as outcomes such as DCI. Documentation of DCI in the UMSAHOD is based on a neurocritical care faculty investigators' review of the entire medical record for the admission, for the presence of otherwise unexplained clinical deterioration during the appropriate period of risk (days 3–21 following ictus) or the appearance of delayed infarction on imaging. Documentation of moderate or severe LVV in the UMSAHOD is based on subjective review of the CTA by neurocritical care faculty investigators. While CONSCIOUS-1 criteria are broadly applied based on a subjective estimate of reduction in vessel caliber, direct measurement with calipers is not routinely performed (5). The presence of moderate-to-severe vasospasm in any one of the following segments was necessary to diagnose LVV: intracranial internal carotid artery, middle cerebral artery M1 or M2 segments, anterior cerebral artery A1 or A2 segments, posterior cerebral artery P1 or P2 segments, basilar artery, or intracranial vertebral artery.

Management of Aneurysmal Subarachnoid Hemorrhage and Delayed Cerebral Ischemia

Following the diagnosis of aSAH, every attempt was made to secure the aneurysm *via* endovascular coiling or microsurgical clipping within 24 h of hospital admission. All patients were admitted to the neurointensive care unit. Nimodipine was administered for 21 days. Transcranial Doppler evaluation was performed daily for 14 days, starting at the day of admission. Fluid administration was targeted to euvolemia. Neurological decline attributable to DCI was typically evaluated using a combination of CTA, CT perfusion (CTP), and digital subtraction angiography. In the absence of clinical decline, performance of screening CTA for risk-stratification was at the discretion of the attending neurointensivist or neurosurgeon. Suspected DCI was treated with a combination of hemodynamic augmentation in all cases, and endovascular therapy in some patients with moderate-to-severe LVV.

Statistical Analysis

Descriptive analysis was performed using proportion and percentage for categorical variables, and median with interquartile range for continuous variables. Associations between categorical variables and outcomes of interest were tested for statistical significance using the Chi-square or Fisher exact test as appropriate. Associations between continuous variables and outcomes of interest were tested for statistical significance using the Mann–Whitney *U*-test. In order to study the predictive value of screening CTA, we performed multivariate analysis using binary logistic regression with the occurrence of DCI as the dependent variable. Covariates in the logistic regression model were selected based on prior evidence of association with DCI and biological plausibility (6). These included age, gender, Hunt, and Hess grade, modified Fisher grade, treatment modality (clipping, coiling, or neither), and the presence of LVV on day 4–8 screening CTA. The diagnostic accuracy of days 4–8 screening CTA to identify patients who develop DCI was studied, including sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Diagnostic test positivity was defined as the prospective determination of the presence of moderate or severe LVV on CTA performed during this period by a neurointensivist as documented in the UMSAHOD. The gold standard (disease positivity) was the prospective determination of the occurrence of DCI following screening CTA based on review of all admission records as documented prospectively in the UMSAHOD.

RESULTS

A total of 243 aSAH patients were admitted during the study period (2016–2019). Of these, 76 (31%) underwent CTA during the 4–8-day window following ictus. Of these, 22 were excluded for occurrence of DCI prior to the CTA study. Patient baseline characteristics are in **Table 1**. Patient selection flow is outlined in **Figure 1**. Of the 54 patients meeting eligibility criteria, 11 (20%) had moderate-to-severe LVV on a screening CTA study performed during the risk period, and a total of 13 (24%) developed DCI. Seven of 11 (64%) patients with moderate-to-severe LVV on the days 4–8 screening CTA vs. six of 43 (14%) patients without, subsequently developed DCI ($p = 0.002$). On multivariate analysis, the presence of LVV on days 4–8 screening CTA was an independent predictor of DCI (odds ratio 10.26, 95% CI 1.69–62.24, $p = 0.011$). No other variable attained statistical significance once LVV was added to the model. The NPV of CTA performed during days 4–8 for the subsequent development of DCI was 86% (95% CI 77–92%). Sensitivity was 54% (25–81%), specificity 90% (77–97%), and PPV 64% (38–83%).

DISCUSSION

In our study, the presence of LVV on screening CTA performed on days 4–8 following aSAH was an independent predictor of DCI, but attained only moderate diagnostic accuracy in this role. While the NPV was 86%, sensitivity was only 54%. Therefore, based on the findings of our study, while only 14% of patients with mild or no LVV on days 4–8 screening CTA will develop DCI, about 4–5 of every 10 patients who subsequently develop DCI will be misclassified. These findings suggest that while screening CTA may be a useful tool for risk stratification, it cannot be relied upon in isolation. These findings are important because the use of screening CTA for risk-stratification during the DCI risk period is quite common in clinical practice (3). An important rationale for this practice is that the identification of aSAH patients at low risk for DCI may permit more targeted utilization of resources, especially ICU capacity. It has been estimated in one region that the length of stay for SAH patients may be $4,400 per day (7).

Our study suggests that while LVV and DCI are closely related, this widely utilized strategy focused on the detection of LVV will miss a potentially clinically relevant minority of aSAH patients who develop DCI. Several studies have examined the relationship between LVV and DCI. A *post-hoc* analysis of the CONSCIOUS-1 trial revealed that cerebral infarction rarely occurs (3%) in patients with mild or no LVV, while the presence of LVV was a strong independent predictor of infarction (8). In one study of aSAH patients evaluated with CTA and CTP, the presence of severe LVV was associated with a significant reduction in perfusion in the corresponding vascular territory, although this association was not as strong for moderate vasospasm (9). The flow territory that was least perfused corresponded to the vessel with the most severe vasospasm in only 65% of patients with moderate-to-severe LVV. A study that evaluated 25 aSAH patients with the gold standard diagnostic tools of DSA for LVV and ^{15}O Positron Emission Tomography (PET) for ischemia found that the cerebral blood flow was lower and oxygen extraction fraction higher in brain regions supplied by vessels with significant LVV. However, hypoperfusion was also seen in 24% of patients without LVV (10).

A study that examined the association between LVV and delayed infarction on imaging found that 31% of patients with moderate-to-severe LVV and only 4% of patients with mild or no LVV suffered cerebral infarction, although 28% of the infarcts occurred outside the territory of vessels with moderate-to-severe LVV (11).

DCI remains a significant treatable contributor to morbidity in aSAH patients. While the pathophysiology of DCI continues to be under investigation, evaluation of vascular caliber remains important due to its simplicity and moderate strength in determining the risk of DCI. Transcranial Doppler (TCD) is most commonly used to identify developing LVV (12). However, TCD is highly operator dependent, can only evaluate the most proximal vessel segments, is prone to errors related to angle of insonation, and demonstrates inconsistent accuracy (13, 14). In addition, several patients lack acoustic windows (15). CTA is an attractive modality due to its wide availability and non-invasive nature. The major disadvantages are exposure to radiocontrast and radiation, and, as a consequence, the inability to perform daily assessment. Evaluation of CTA for determining the presence of vasospasm in comparison with the gold standard of digital subtraction angiography (DSA) has revealed high sensitivity and specificity. For central vasospasm, sensitivity and specificity are about 91–92% and 73–90%, respectively. For peripheral

TABLE 1 | Patient baseline characteristics.

Variable	All subjects $N = 54$	DCI absent $N = 41$	DCI present $N = 13$	*P*-value (univariate)
Age in years, median (IQR)	62 (53–73)	63 (53–73)	56 (45–69)	0.15
Gender - Female	41 (76%)	30 (73%)	11 (85%)	0.40
Hunt and Hess grade, median (IQR)	3 (2–4)	3 (2–4)	4 (2–4)	0.16
Modified Fisher grade, median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	0.21
Treatment modality				0.86
-Clipping	15 (28%)	11 (27%)	4 (31%)	
-Coiling	31 (57%)	23 (56%)	8 (62%)	
-Neither	8 (15%)	7 (17%)	1 (7%)	
LVV on CTA	11 (20%)	4 (10%)	7 (54%)	0.001

DCI, delayed cerebral ischemia.
IQR, interquartile range.
LVV, large-vessel vasospasm.
CTA, computed tomographic angiography.

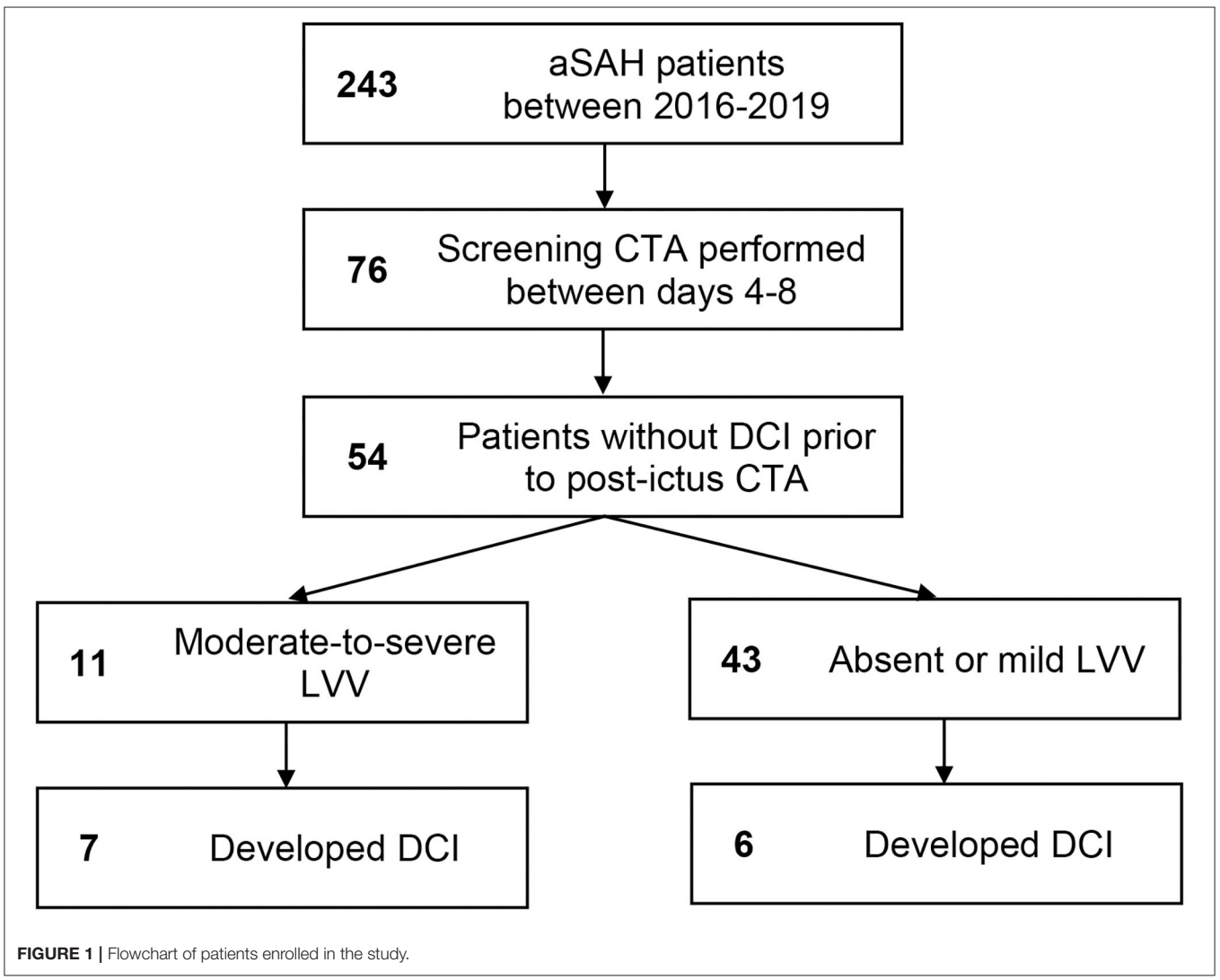

FIGURE 1 | Flowchart of patients enrolled in the study.

vasospasm, these are slightly lower, with a sensitivity and specificity of 82–90% and 50–69%, respectively (16). Our study suggests that an optimal multimodal approach may combine evaluation of vascular caliber with other modalities. Non-invasive modalities shown to predict or identify the presence of DCI include CTP (16), continuous electroencephalography

with measurement of the alpha-delta ratio or percentage alpha variability (17), and monitoring of the TCD pulsatility index (18). Invasive monitoring with cerebral oximetry (19), cerebral microdialysis (20), and thermal diffusion flowmetry may also be useful for the early detection of DCI (21). Of note, most of these modalities achieve early detection of DCI, rather than identification of patients at low risk who may be triaged to a lower intensity of care.

Our study has several limitations. It is retrospective, done at a single center, and the sample size is small, although all data including test positivity (LVV on CTA) and disease positivity (occurrence of DCI) were prospectively identified and documented. Screening CTA for risk-stratification was not performed consistently and was at the discretion of the attending physician. Patients who underwent CTA are likely to have been perceived as being at higher risk for DCI by the clinical team, thereby altering the pretest probability of disease. While screening CTP was sometimes performed, the sample size of such patients was insufficient for meaningful analysis of predictive ability and diagnostic accuracy at the time of completion of this manuscript. The presence of moderate-to-severe LVV was adjudicated subjectively—CONSCIOUS-1 criteria were followed using visual estimates rather than measurement with calipers. The diagnosis of DCI, although prospective, was inherently subjective. UMSAHOD investigators adjudicating the clinical diagnosis of DCI were not blinded to the CTA results. Our focus was on the prediction of DCI, rather than long term outcomes; prior studies have addressed the association between LVV, DCI, and long-term outcomes.

In conclusion, the presence of moderate-to-severe LVV on screening CTA performed between days 4 and 8 following aSAH was an independent predictor of DCI, but achieved only moderate diagnostic accuracy, with NPV 86% and sensitivity 54%. Complementary risk-stratification strategies are likely necessary.

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 human participants were reviewed and approved by University of Michigan Institutional Review Board (IRBMED). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AN, CW, AP, KS, and VR: contributed to conception and design of the study. CW, KS, and VR: organized the database. VR: performed the statistical analysis. AN and VR: wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Association Between Glycemic Gap and In-hospital Outcomes in Aneurysmal Subarachnoid Hemorrhage

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Introduction: Glycemic gap (GG), as determined by the difference between glucose and the hemoglobin A1c (HbA1c)-derived estimated average glucose (eAG), is associated with poor outcomes in various clinical settings. There is a paucity of data describing GG and outcomes after aneurysmal subarachnoid hemorrhage (aSAH). Our main objectives were to evaluate the association of admission glycemic gap (aGG) with in-hospital mortality and with poor composite outcome and to compare aGG's predictive value to admission serum glucose. Secondary outcomes were the associations between aGG and neurologic complications including vasospasm and delayed cerebral ischemia following aSAH.

Methods: We retrospectively reviewed 119 adult patients with aSAH admitted to a single tertiary care neuroscience ICU. Spearman method was used for correlation for non-normality of data. Area under the curve (AUC) for Receiver Operating Characteristic (ROC) curve was used to estimate prediction accuracy of aGG and admission glucose on outcome measures. Multivariable analyses were conducted to assess the value of aGG in predicting in-hospital poor composite outcome and death.

Results: Elevated aGG at or above 30 mg/dL was identified in 79 (66.4%) of patients. Vasospasm was not associated with the elevated aGG. Admission GG correlated with admission serum glucose ($r = 0.94$, $p < 0.01$), lactate ($r = 0.41$, $p < 0.01$), procalcitonin ($r = 0.38$, $p < 0.01$), and Hunt and Hess score ($r = 0.51$, $p < 0.01$), but not with HbA1c ($r = 0.02$, $p = 0.82$). Compared to admission glucose, aGG had a statistically significantly improved accuracy in predicting inpatient mortality (AUC mean ± SEM: 0.77 ± 0.05 vs. 0.72 ± 0.06, $p = 0.03$) and trended toward statistically improved accuracy in predicting poor composite outcome (AUC: 0.69 ± 0.05 vs. 0.66 ± 0.05, $p = 0.07$). When controlling for aSAH severity, aGG was not independently associated with delayed cerebral ischemia, poor composite outcome, and in-hospital mortality.

Conclusion: Admission GG was not independently associated with in-hospital mortality or poor outcome in a population of aSAH. An aGG ≥30 mg/dL was common in our population, and further study is needed to fully understand the clinical importance of this biomarker.

Keywords: aneurysmal subarachnoid hemorrhage, hyperglycemia, glycemic gap, outcomes, mortality

INTRODUCTION

Hyperglycemia portends a poor outcome in aneurysmal subarachnoid hemorrhage (aSAH) (1–9). Given its clinical importance, this may be one of several key physiologic derangements that should be targeted to improve patient outcomes. Suggested mechanisms of secondary brain injury promoted by hyperglycemia include cerebral vasospasm, delayed cerebral ischemia (DCI), promotion of an oxidative state, intravascular coagulation abnormalities, cerebral edema promoted by matrix metalloproteinase activity, and metabolic dysfunction (1, 4, 9–11). Serum glucose level alone, however, does not account for a patient's baseline average glucose level.

Glycemic gap (GG) is a measure of an acute derangement in glucose level in response to an active disease state, calculated by the difference between raw capillary glucose level and the estimated average glucose (eAG) derived from serum hemoglobin A1c (HbA1c) level. Recent studies describe its utility in predicting ICU mortality and adverse outcomes among diabetics (12–15); however, these studies included only a minority of patients with a primary neurologic disease. A retrospective study by Yang et al. on acute ischemic stroke patients with diabetes showed that admission glycemic gap (aGG) was superior to admission glucose and HbA1c in predicting worse NIHSS and functional outcome at discharge (16). Another study on aSAH patients used admission glucose to HbA1c ratio to demonstrate that stress-induced hyperglycemia occurred in nearly half of patients and predicted placement of an external ventricular drain (EVD) (17). The utility of GG in aSAH otherwise has not been fully established, especially in its association with hospital course and short-term outcome.

The main study objectives are to evaluate the association of aGG with in-hospital mortality and poor outcome, and to compare the entity's predictive value to that of admission serum glucose in a population of adult patients with aSAH treated at a single center. We hypothesized that elevated aGG is associated with negative patient outcomes and had better predictive accuracy than admission serum glucose level. If true, this would support the use of aGG as an important predictor of outcome in clinical practice and future translational research.

METHODS

Population and Enrollment

During a period from 2012 to 2018, adult patients admitted to the neurocritical care unit at the academic tertiary care medical center of The University of Southern California with a primary admitting diagnosis of non-traumatic subarachnoid hemorrhage. Patients were excluded from the analysis if (a) subarachnoid hemorrhage was due to a non-aneurysmal cause (e.g., primary intracerebral hemorrhage, dural fistula, trauma), (b) initial clinical exam suggested brain death (bilateral mydriasis with no reactivity to light), or (c) HbA1c was not available. A total of 119 individuals aged ≥18 with a primary diagnosis of aSAH met inclusion and exclusion criteria. Of the 119 patients included in the analysis, 12 had no identified aneurysm on Computed Tomography angiography (CTA) or digital subtraction angiogram (DSA) but distribution of bleed was suggestive of aSAH rather than perimesencephalic SAH.

Data Collection and Outcome Measures

The institutional review board of The University of Southern California approved the study procedures (HS-16-00265). Patient consent was waived due to the retrospective nature of the study. Data were gathered from the Electronic Medical Record (EMR) and available medical records from transferring hospitals. We extracted information on demographics, presentation, admission serum studies, clinical and radiographic characteristics of aSAH, and hospital course including short-term outcomes. Vasospasm was diagnosed with a combination of transcranial Doppler ultrasound (anterior circulation mean flow velocity > 120 cm/s with a Lindegaard Ratio >3, vertebral or basilar artery mean flow velocity > 80 cm/s), or findings from CTA or DSA. DCI was defined as persistent focal neurologic deficit attributed to vasospasm, or delayed infarct seen on CT or MRI not attributed to the initial bleed or subsequent procedures. Ventilator-free days is an established measure of acute respiratory failure that provides a greater statistical power to treatment effects (18). The entity was defined to be 0 if the patient died before 28 days, the number of days on mechanical ventilation subtracted from 28 if successfully weaned from mechanical ventilation within 28 days, and 0 if the patient required mechanical ventilation for 28 days or more. For those who were discharged within 28 days of admission, it was assumed that they remained free of ventilators after discharge. The patients who did not require an EVD placement during hospitalization were recorded as having the EVD day of 0.

The estimated average glucose (eAG) in the past 3 months was calculated by the standard equation: [(28.7×HbA1c)-46.7] (mg/dL). Admission glycemic gap was defined as eAG subtracted from admission serum glucose (mg/dL). For dichotomization based on aGG, the cutoff value of ≥30 mg/dL was defined as "elevated." This cutoff aGG was selected by manually evaluating ROC sensitivity and specificity cutoff values by increments of 10 for in-hospital mortality. This analysis led to selection of 30 mg/dL, which had the sensitivity of 0.90 (95% CI 0.79, 1.0)

and specificity of 0.41 (95% CI 0.31, 0.51), demonstrating a high rate of inclusion with reasonable specificity. The primary outcome was the association of admission glucose and aGG with in-hospital mortality and poor composite outcome. Poor composite outcome was defined as any incidence of percutaneous gastrostomy, tracheostomy, discharge to a nursing facility, or hospital death, whereas good composite outcome was absence of these outcomes. This measure serves to identify patients who will require continued nursing care for activities of daily living. This definition has been similarly used in aSAH populations as the Nationwide Inpatient Sample Subarachnoid Hemorrhage Outcome Measure (NIS-SOM) using ICD-9 code-based national administrative data (19). Secondary outcomes included the association of aGG with neurologic complications of DCI and vasospasm.

Statistical Analysis

Data distribution was examined by histogram and D'Agostino's K-squared test. Spearman method was used for correlation for non-normality of data. Wilcoxon Rank-sum test was used for non-parametric comparisons. If data were normally distributed, mean values with standard deviation (SD) were reported; otherwise, median values with interquartile range (IQR) were reported. Fisher's exact test was used for any subset sample size of below 5. ANOVA was performed for assessment of a global difference in aGG among diabetics (HbA1c of greater than or equal to 6.5), pre-diabetics (HbA1c of 5.7–6.4), and non-diabetics (HbA1c of 5.6 or less). A *post-hoc* contrast test was done to compare aGG in diabetics against pre-diabetics and non-diabetics combined. Area under the curve (AUC) for Receiver Operating Characteristic (ROC) curve was used to estimate prediction accuracy of admission glucose and aGG (**Figure 2**). A *z*-test was used to compare the AUC between admission glucose and aGG. As previously described, the diagnostic cut-point of aGG at 30 mg/dL was determined by manual assessment of sensitivity and specificity at each 10-unit increment of aGG. Multivariable Poisson regression was used to calculate the relative risk (RR) between the dichotomized GG and inpatient clinical outcomes. Pearson and deviance statistics were used to assess model overdispersion. When model overdispersion was found, a negative binomial model was used instead. We performed a multivariable analysis controlling for known predictors of outcome in aSAH—Hunt and Hess scale score, modified Fisher scale score, and GCS. PASS 2021 (NCSS, LLC) was used for a *post-hoc* power analysis to evaluate the association between aGG and primary outcomes of interest when adjusted for co-variates. All other data analyses were conducted using SAS (version 9.4; SAS Institute Inc, Cary, NC). Statistical testing was performed at an α level of 0.05.

RESULTS

We identified a total of 119 adult patients with a primary diagnosis of aSAH who met inclusion and exclusion criteria and were included in the analysis. Patient race/ethnicity was as follows: White ($n = 23$), Hispanic ($n = 56$), and others/unknown ($n = 40$). The cohort's mean age was 59 $\pm$ 14 years, in whom 33% were men. The overall median Hunt and Hess and modified Fisher grades were 3 and 4, respectively. The overall median aGG was 48 (IQR 20, 89) mg/dL. **Table 1** summarizes demographic and clinical admission factors between patients with high ($\geq$30 mg/dL) vs. low (<30 mg/dL) aGG. Our aGG cutoff value of $\geq$30 mg/dL had the sensitivity of 0.90 (95% CI 0.79, 1.0) and specificity of 0.41 (95% CI 0.31, 0.51) for mortality. For poor composite outcome at the same cutoff value of 30 mg/dL, the sensitivity and specificity were 0.79 (95% CI 0.68, 0.90) and 0.45 (95% CI 0.33, 0.58), respectively. Seventy-nine (66.4%) patients had an elevated aGG of $\geq$30 mg/dL with the median level of 63 (IQR 48, 108) mg/dL, significantly higher than the lower aGG group with the median level of 10 (IQR $-$0.5, 20) mg/dL. There was a significantly higher occurrence of comorbid history of diabetes mellitus in the elevated aGG group. Age, sex, race/ethnicity, body mass index (BMI), and prior history of other cardiovascular comorbidities were similar between groups. Median HbA1c did not differ significantly between high vs. low aGG groups. Although ANOVA showed a global difference in the means of aGG among diabetics (86.9 $\pm$ 12.9), pre-diabetics (49.2 $\pm$ 7.0) and non-diabetics (55.1 $\pm$ 6.9) ($p = 0.04$), comparison between the two aGG groups did not indicate heterogeneous distribution ($p = 0.12$). A *post-hoc* contrast test showed a higher aGG in diabetics compared to pre-diabetics and non-diabetics combined ($p = 0.01$). Patients with elevated aGG had a significantly increased admission serum glucose, white blood cell (WBC) count, anion gap, as well as lower bicarbonate. There were similar occurrences of fever and infection on admission.

Spearman correlation analysis (**Table 2**) demonstrated that aGG as a continuous variable was strongly correlated with admission glucose ($r = 0.94$, $p < 0.01$) but not with HbA1c ($r = 0.02$, $p = 0.82$). There were positive correlations between aGG and Hunt and Hess scale ($r = 0.51$, $p < 0.01$), modified Fisher scale ($r = 0.37$, $p < 0.01$), lactate ($r = 0.41$, $p < 0.01$), procalcitonin ($r = 0.38$, $p < 0.01$), and WBC on admission ($r = 0.45$, $p < 0.01$). Admission GG was negatively associated with GCS ($r = -0.50$, $p < 0.01$). No correlations were found with regards to age ($r = -0.04$, $p = 0.66$) and BMI ($r = 0.09$, $p = 0.32$). Higher aGG was also inversely correlated with ventilator-free days ($r = -0.40$, $p < 0.01$) and positively correlated with EVD days ($r = 0.24$, $p < 0.01$). Scatterplots demonstrating Spearman correlation between aGG and admission glucose and HbA1c are depicted in **Figure 1**.

Table 3 summarizes hospital outcomes by aGG groups. Patients with elevated aGG $\geq$30 mg/dL had a greater use of EVDs, but similar length of ICU and hospital stay. While vasospasm was not associated with increased aGG, DCI occurred more commonly among those with higher aGG. Hospital mortality and poor composite outcome both occurred more frequently in those with elevated aGG. As shown in the ROC curves in **Figure 2**, aGG had a significantly better prediction accuracy than admission glucose in predicting death (AUC mean $\pm$ SEM: 0.77 $\pm$ 0.05 vs. 0.72 $\pm$ 0.06, $p = 0.03$) and a non-significant trend for better accuracy in predicting poor outcome (AUC mean $\pm$ SEM: 0.69 $\pm$ 0.05 vs. 0.66 $\pm$ 0.05, $p = 0.07$). When adjusted for the disease severity measures, aGG was independently associated with EVD days, but not with length of hospitalization, DCI,

TABLE 1 | Demographic and clinical admission factors between patients with high vs. low admission glycemic gap.

Variable	aGG ≥ 30 mg/dL ($n = 79$)	aGG < 30 mg/dL ($n = 40$)	Overall cohort ($n = 119$)	p-value[†]
Age, years (mean ± SD)	58.01 ± 13.04	60.03 ± 14.90	58.69 ± 13.66	0.45
Sex				0.23
Male, *n* (%)	23 (29.1%)	16 (40.0%)	39 (32.8%)	
Female	56 (70.9%)	24 (60.0%)	80 (67.2%)	
Race/ethnicity				0.74
White, *n* (%)	14 (17.7%)	9 (22.5%)	23 (19.3%)	
Hispanic	39 (49.4%)	17 (42.5%)	56 (47.1%)	
Others/unknown[a]	26 (32.9%)	14 (35.0%)	40 (33.6%)	
BMI[b], kg/m^2 (median, IQR)	27.46 (23.73, 30.08)	25.96 (23.16, 30.78)	27.22 (23.38, 30.48)	0.47[#]
Diabetes Mellitus based on admission HbA1c[c]				0.13*
Diabetic, *n* (%)	13 (16.5%)	2 (5.0%)	15 (12.6%)	
Pre-diabetic	30 (38.0%)	21 (52.5%)	51 (42.9%)	
Neither	36 (45.6%)	17 (42.5%)	53 (44.5%)	
History of diabetes mellitus				**0.04***
Yes, *n* (%)	18 (22.8%)	3 (7.5%)	21 (17.7%)	
No	61 (77.2%)	37 (92.5%)	98 (82.4%)	
Coronary artery disease				0.38*
Yes, *n* (%)	3 (3.8%)	3 (7.5%)	6 (5.0%)	
No	76 (96.2%)	37 (92.5%)	113 (95.0%)	
Hypertension				0.07
Yes, *n* (%)	51 (64.6%)	19 (47.5%)	70 (58.8%)	
No	28 (35.4%)	21 (52.5%)	49 (41.2%)	
Chronic renal disease				0.07*
Yes, *n* (%)	6 (7.6%)	0 (0%)	6 (5.0%)	
No	73 (92.4%)	40 (100.0%)	113 (95.0%)	
HFrEF				0.48*
Yes, *n* (%)	2 (2.5%)	2 (5.0%)	4 (3.4%)	
No	77 (97.5%)	38 (95.0%)	115 (96.6%)	
Glasgow Coma Scale (median, IQR)	10 (6, 14)	14.5 (10, 15)	11 (7, 15)	**<0.01**[#]
Hunt and Hess scale				**<0.01**
1–3 (good), *n* (%)	19 (24.1%)	24 (60.0%)	43 (36.1%)	
4–5 (poor)	60 (76.0%)	16 (40.0%)	76 (63.9%)	
Modified Fisher scale				**<0.01**
0–2 (good), *n* (%)	5 (6.3%)	9 (22.5%)	14 (11.8%)	
3–4 (poor)	74 (93.7%)	31 (77.5%)	105 (88.2%)	
Admission glycemic gap, mg/dL (median, IQR)	63 (48, 108)	10 (−0.5, 20)	48 (20, 89)	**<0.01**[#]
Serum glucose[d], mg/dL (median, IQR)	191 (165, 224)	124.5 (115.5, 138)	165 (136, 211)	**<0.01**[#]
HbA1c[e], % (median, IQR)	5.8 (5.5, 6.2)	5.7 (5.5, 6.05)	5.7 (5.5, 6.1)	0.89[#]
Lactate[f], mmol/L (median, IQR)	2.7 (1.9, 4.25)	1.65 (1.2, 2.9)	2.45 (1.5, 3.8)	**<0.01**[#]
Procalcitonin[g], ng/mL (median, IQR)	0.13 (0.1, 0.22)	0.1 (0.07, 0.14)	0.1 (0.1, 0.2)	0.12[#]
Infection[h]				0.1
No abx used, no infection, *n* (%)	8 (10.1%)	10 (25.0%)	18 (15.1%)	
Abx used, no documented infection	38 (48.1%)	16 (40.0%)	54 (45.4%)	
Abx used, documented infection	33 (41.8%)	14 (35.0%)	47 (39.5%)	
Fever				0.71*
Yes, *n* (%)	3 (3.8%)	1 (2.5%)	4 (3.4%)	
No	76 (96.2%)	39 (97.5%)	115 (96.6%)	
Location of aneurysm[i]				0.72
Anterior circulation, *n* (%)	50 (63.3%)	26 (65.0%)	76 (63.9%)	

(Continued)

TABLE 1 | Continued

Variable	aGG ≥ 30 mg/dL ($n = 79$)	aGG < 30 mg/dL ($n = 40$)	Overall cohort ($n = 119$)	p-value[†]
Posterior circulation	22 (27.9%)	9 (22.5%)	31 (26.1%)	
No clear source	7 (8.9%)	5 (12.5%)	12 (10.1%)	
WBC, 10^3 cells/μL (median, IQR)	15.57 (10.53, 19.36)	10.28 (8.35, 13.96)	13.8 (9.2, 18.7)	**<0.01**[#]
Sodium, mmol/L (mean ± SD)	138.52 ± 3.66	138.83 ± 3.84	138.62 ± 3.71	0.67
Bicarbonate, mmol/L (median, IQR)	22 (20, 24)	26 (23.5, 27)	23 (20, 27)	**<0.01**[#]
Anion gap, mmol/L (median, IQR)	15 (13, 17)	12 (10, 15)	14 (12, 16)	**<0.01**[#]
Creatinine[j], mg/dL (median, IQR)	0.80 (0.62, 0.93)	0.70 (0.64, 0.90)	0.79 (0.62, 0.91)	0.25[#]

[†] *Statistically significant values are given in bold ($p < 0.05$).*
[a] *The patients were unable to or did not provide an answer.*
[b] *Admission BMI was not available in three patients.*
[c] *Diabetes is defined as Admission HbA1c of greater than or equal to 6.5, pre-diabetes is defined as HbA1c of 5.7–6.4.*
[d] *Conversion factor: multiply by 0.0555 to convert glucose from mg/dL to mmol/L.*
[e] *Conversion factor: multiply by 28.7 and subtract by 46.7 to convert National Glycohemoglobin Standardization Program HbA1c (%) to estimated average serum glucose (mg/dL). Multiply by 0.0555 to convert from mg/dL to mmol/L.*
[f] *Admission lactate level was obtained in 108 patients.*
[g] *Admission procalcitonin level was obtained in 57 patients.*
[h] *Documented infection was determined by obtained cultures and imaging (i.e., chest-ray). Some patients with no documented infection were empirically treated because of suspicion of infection and/or prophylactically for procedures (i.e., external ventricular drain).*
[i] *No definitive bleeding source found in 12 patients.*
[j] *Conversion factor: multiply by 76.25 to convert creatinine from mg/dL to μmol/L.*
[#] *Wilcoxon Rank-sum test.*
**Fisher's exact test.*
SD, standard deviation; BMI, Body Mass Index; IQR, interquartile range; HbA1c, Hemoglobin A1c; HFrEF, heart failure with reduced ejection fraction; WBC, white blood cell count.

and vasospasm (**Table 4**). When unadjusted, the RRs for poor composite outcome and in-hospital mortality were 1.90 (95% CI 1.00, 3.59) and 4.39 (95% CI 1.33, 14.50), respectively, in those with aGG of ≥30 mg/dL. In the multivariable analyses, neither of the outcome measures were statistically significant, with the RRs of 1.07 (95% CI 0.55, 2.09) and 2.10 (95% CI 0.60, 7.30) for poor composite outcome and in-hospital mortality, respectively.

Post-hoc Power Analysis

The *post-hoc* power analysis showed the power of Poisson regression depended on the effect size of rate ratio and the overall association between aGG and covariates. With an over association of $r = 0.5$ between aGG and covariates (modified Fisher, Hunt and Hess, and GCS on admission), estimated from a logistic regression, an effect size of RR = 3.37 is required to reach 80% power. The Hunt and Hess grade especially had a strong association with both aGG and in-hospital mortality.

DISCUSSION

Glycemic gap is a standardized way to measure acute stress-induced hyperglycemia relative to baseline glycemic status. Obtaining aGG only requires a peripheral blood draw, and its analysis does not involve detailed clinical or radiologic evaluations. Our study describes the correlation between aGG and short-term outcomes in an adult population of aSAH. An elevated aGG ≥30 mg/dL was common in our cohort, occurring in 66.4% of all patients. This elevated status was associated with markers of disease severity and in-hospital outcomes, strengthening the concept that the entity is an indicator of physiologic stress response to aSAH. According to ROC curve analysis, aGG outperformed admission glucose in predicting in-hospital mortality and was similarly accurate in discerning poor composite outcome.

We were unable to demonstrate that aGG independently predicts in-hospital mortality and poor composite outcome in aSAH after controlling for Hunt and Hess scale, modified Fisher scale, and GCS. The unadjusted relative risks for poor composite outcome and in-hospital mortality halved when adjusted for the three clinical/radiographic severity measures associated with complicated hospital course and outcome in SAH. Despite not reaching statistical significance, the rate ratio of 2.10 (95% CI 0.60, 7.30) for in-hospital mortality in patients with aGG ≥30 mg/dL in our multivariable analysis suggests that our study is underpowered and that further study may be needed to determine the true association between aGG and the outcome. As expected, Hunt and Hess scale had a strong association with both aGG and with in-hospital mortality and was likely the primary driver in the elevated aGG group. Interestingly, there was no similar hint that aGG independently predicts poor composite outcome (RR = 1.07, 95% CI 0.55, 2.09), possibly because aGG specifically identifies acute pathophysiologic processes leading to the extreme outcome of death. Poor composite outcome, in comparison, encompasses non-fatal outcomes, and aGG may lose its association with less severe health consequence. Our multivariable analysis also suggests that aGG is independently associated with longer EVD duration. The ratio of days for EVD and for hospitalization changed minimally with adjustment, indicating that these in-hospital outcomes were not significantly mediated by the adjusted factors. Larger, prospective studies are needed to further elucidate the importance of aGG in patients with aSAH.

TABLE 2 | Spearman correlation between admission glycemic gap and patient characteristics and outcomes.

Variable	Spearman correlation coefficient (r)[†]	p-value[†]
Age, years	−0.04	0.66
BMI (kg/m^2)[a]	0.09	0.32
Glasgow Coma Scale	−0.50	**<0.01**
Hunt and Hess scale	0.51	**<0.01**
Modified Fisher scale	0.37	**<0.01**
Serum glucose, mg/dL[b]	0.94	**<0.01**
HbA1c, %[c]	0.02	0.82
Lactate, mmol/L[d]	0.41	**<0.01**
Procalcitonin, ng/mL[e]	0.38	**<0.01**
WBC, 10^3 cells/μL	0.45	**<0.01**
Sodium, mmol/L	−0.03	0.77
Bicarbonate, mmol/L	−0.33	**<0.01**
Anion gap, mmol/L	0.39	**<0.01**
Creatinine, mg/dL[f]	0.14	0.14
Ventilator-free days	−0.40	**<0.01**
EVD days	0.24	**<0.01**
Hospital days	0	0.99
ICU days	0.04	0.67

[†]Coefficient (r) values > 0 indicate a positive association; values < 0 indicate a negative association. Statistically significant values are given in bold (p < 0.05).
[a]Admission BMI was not available in three patients.
[b]Conversion factor: multiply by 0.0555 to convert glucose from mg/dL to mmol/L.
[c]Conversion factor: multiply by 28.7 and subtract by 46.7 to convert National Glycohemoglobin Standardization Program HbA1c (%) to estimated average serum glucose (mg/dL). Multiply by 0.0555 to convert from mg/dL to mmol/L.
[d]Admission lactate level was obtained in 108 patients.
[e]Admission procalcitonin level was obtained in 57 patients.
[f]Conversion factor: multiply by 76.25 to convert creatinine from mg/dL to μmol/L.
BMI, Body Mass Index; HbA1c, Hemoglobin A1c; WBC, white blood cell count; EVD, external ventricular drain; ICU, intensive care unit.

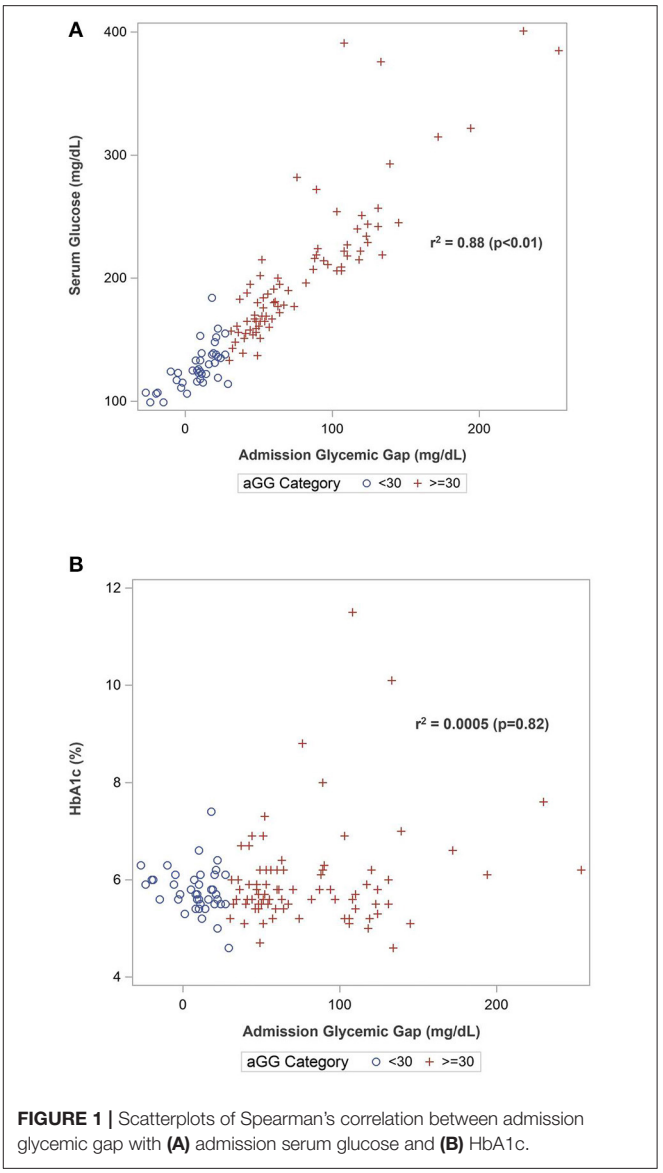


FIGURE 1 | Scatterplots of Spearman's correlation between admission glycemic gap with **(A)** admission serum glucose and **(B)** HbA1c.

Based on the ROC curve analysis, aGG may be a superior predictor for in-hospital mortality in aSAH patients compared to admission glucose. Our cutoff value of 30 mg/dL was deemed optimal considering the clinical context under which this entity is used—to capture most deaths with a reasonable false positive rate. This is close to the cutoff of 26 mg/dL, derived through a ROC analysis in another study on aneurysmal and non-aneurysmal SAH (17). In comparison, one previous study in a medical ICU with 12.4% of the cohort having a primary neurologic condition, an aGG cutoff of 80 mg/dL was proposed in discerning mortality in diabetics (14). Considering the predictive role of aGG in inclusion of poor outcomes, the authors believed that the higher aGG cutoff of 80 mg/dL would be less ideal with a lower sensitivity; however, it would expectedly confer a higher specificity. More study is needed to evaluate whether a universally effective aGG cutoff for mortality exists for diabetics and non-diabetics.

From our univariate analysis, elevated aGG was associated with known patient history of diabetes mellitus, but not with HbA1c level on admission. One plausible explanation is that the chronic systemic inflammation, insulin resistance, and vasculopathy in diabetics can add to the vulnerability of patients during the acute illness to experience hyperglycemia. Further investigation, especially with a larger diabetic group, can help further elucidate the implication of HbA1c in diabetics, including in those with well-controlled, poorly controlled, or newly diagnosed disease.

Admission GG was also associated with higher WBC, lower bicarbonate, and higher lactate level, indicative of acute physiological stress reaction. Acute glucose derangement has been seen in aSAH in the setting of lactic acidemia (20), sepsis (3), coagulopathy (10), symptomatic cerebral vasospasm (21), and DCI (4). Our study shows that those with aGG ≥30 mg/dL had a higher proportion of DCI from Chi-squared test **(Table 3)** but no difference in vasospasm. One possible explanation is that there is an underlying microvasculature process leading to cerebral ischemia. Such a hypothesis has been suggested for

TABLE 3 | In-hospital outcomes between patients with elevated vs. non-elevated admission glycemic gap.

Variable	aGG ≥ 30 mg/dL (*n* = 79)	aGG < 30 mg/dL (*n* = 40)	Overall cohort (*n* = 119)	*p*-value[†]
Insulin drip				**<0.01**[*]
Yes, *n* (%)	21 (26.6%)	2 (5.0%)	23 (19.3%)	
No	58 (73.4%)	38 (95.0%)	96 (80.7%)	
Aneurysmal procedure				0.93[*]
Clip/wrap, *n* (%)	30 (38.0%)	16 (40.0%)	46 (38.7%)	
Coil	29 (36.7%)	15 (37.5%)	44 (37.0%)	
Others	1 (1.3%)	1 (2.5%)	2 (1.7%)	
None	19 (24.1%)	8 (20.0%)	27 (22.7%)	
Vasospasm				0.17
Yes, *n* (%)	42 (53.2%)	16 (40.0%)	58 (48.7%)	
No	37 (46.8%)	24 (60.0%)	61 (51.3%)	
DCI				**<0.01**
Yes, *n* (%)	30 (38.0%)	5 (12.5%)	35 (29.4%)	
No	49 (62.0%)	35 (87.5%)	84 (70.6%)	
Ventilator-free days (median, IQR)	12 (0, 27)	27 (20, 29)	21 (0, 28)	**<0.01**[#]
EVD placed?				<0.01
Yes, *n* (%)	73 (92.4%)	25 (62.5%)	98 (82.4%)	
No	6 (7.6%)	15 (37.5%)	21 (17.7%)	
EVD days (median, IQR)	12 (6, 17)	6 (0, 14)	10 (3, 16)	**<0.01**[#]
Hospital days (median, IQR)	16 (10, 24)	15 (13, 19.5)	15 (12, 22)	0.63[#]
ICU days (median, IQR)	14 (9, 20)	13 (10, 16)	14 (10, 18)	0.27[#]
Percutaneous Endoscopic Gastrostomy placed?				0.72
Yes, *n* (%)	16 (20.3%)	7 (17.5%)	23 (19.3%)	
No	63 (79.8%)	33 (82.5%)	96 (80.7%)	
Tracheostomy placed?				0.14[*]
Yes, *n* (%)	14 (17.7%)	3 (7.7%)	17 (14.4%)	
No	65 (82.3%)	36 (92.3%)	101 (85.6%)	
Disposition				**<0.01**[*]
Death (%)	26 (32.9%)	3 (7.5%)	29 (24.4%)	
Home	26 (32.9%)	23 (57.5%)	49 (41.2%)	
Acute rehab	7 (8.9%)	6 (15.0%)	13 (10.9%)	
Other hospital	11 (13.9%)	2 (5.0%)	13 (10.9%)	
Nursing facility	9 (11.4%)	5 (12.5%)	14 (11.8%)	
Drug rehab	0 (0%)	1 (2.5%)	1 (0.8%)	
Poor composite outcome[a]				**<0.01**
Yes, *n* (%)	45 (57.0%)	12 (30.0%)	57 (47.9%)	
No	34 (43.0%)	28 (70.0%)	62 (52.1%)	

[†] *Statistically significant values are given in bold ($p < 0.05$).*

[a] *Poor composite outcome is defined as incidence of percutaneous endoscopic gastrostomy, tracheostomy, discharge to a nursing facility, and/or hospital death.*

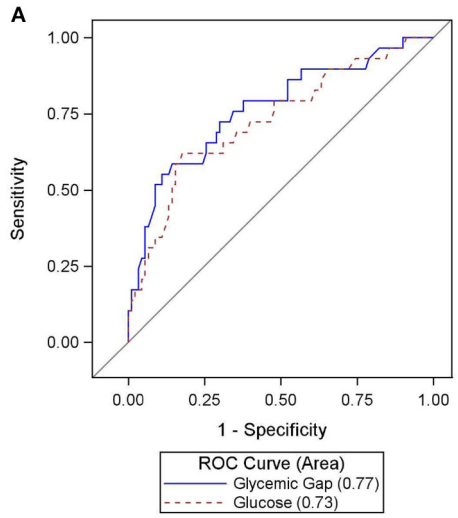
[#] *Wilcoxon Rank-sum test.*

[*] *Fisher's exact test.*

DCI, delayed cerebral ischemia; IQR, interquartile range; EVD, external ventricular drain; ICU, intensive care unit.

patients with sepsis due to infectious etiologies (22) and could be a pathophysiological process for mitochondrial dysfunction in acute aSAH (23). Admission GG also may not be directly biologically causative of poor outcome after aSAH, but our results are hypothesis-generating.

Additionally, we found that more poor grade patients had aGG ≥30 mg/dL. One could postulate that such an association is a marker of disease severity (i.e., stress hyperglycemia). One could also theorize that the microcirculation as well as hyperacute vasospasm are also involved in the acute setting of poor grade patients. A previous case series demonstrated that hyperacute vasospasm could play a role in the outcome and mortality of poor grade aSAH patients (24). As was discussed in the previous paragraph, a combination of microcirculatory dysfunction and hyperacute vasospasm could play a role in defining patients that become poor grade aSAH. This two-hit



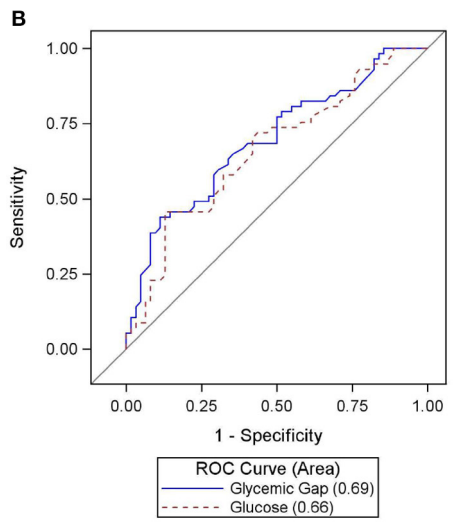


FIGURE 2 | (A) Accuracy of admission glucose vs. admission glycemic gap in predicting in-hospital mortality. **(B)** Accuracy of admission glucose vs. admission glycemic gap in predicting poor composite outcome.

TABLE 4 | Relative difference of major in-hospital outcomes based on admission glycemic gap ≥ 30 mg/dL, adjusted with co-variates.

In-hospital outcomes		Covariate adjustment	
		Unadjusted	**Adjusted for HH, mF, GCS on admission**
EVD days	Ratio* (95% CI)	1.69 (1.16, 2.48)	1.51 (1.04, 2.21)
	p-value†	**<0.01**	**0.03**
Hospital days	Ratio* (95% CI)	1.07 (0.85, 1.36)	1.05 (0.82, 1.35)
	p-value	0.55	0.68
Vasospasm	Ratio* (95% CI)	1.09 (0.80, 1.50)	1.12 (0.79, 1.57)
	p-value	0.58	0.52
DCI	Ratio* (95% CI)	1.23 (0.87, 1.74)	1.24 (0.85, 1.80)
	p-value	0.25	0.27
Poor composite outcome#	Ratio* (95% CI)	1.90 (1.00, 3.59)	1.07 (0.55, 2.09)
	p-value	0.05	0.85
In-hospital mortality	Ratio* (95% CI)	4.39 (1.33, 14.50)	2.10 (0.60, 7.30)
	p-value	**0.02**	0.24

**Ratio of days for EVD days and hospital days, rate ratio or RR for vasospasm, DCI, poor composite outcome, and in-hospital mortality.*

†Statistically significant values are given in bold ($p < 0.05$).

#Poor composite outcome is defined as incidence of percutaneous endoscopic gastrostomy, tracheostomy, discharge to a nursing facility, and/or hospital death.

HH, Hunt and Hess scale; mF, modified Fisher scale; GCS, Glasgow Coma Scale; EVD, external ventricular drain; CI, confidence interval; DCI, delayed cerebral ischemia.

hypothesis could further explain mitochondrial dysfunction in poor grade aSAH.

Our assessment of the prognostic value with aGG should be interpreted with caution. Our study supported a statistically significant trend of increased risk of DCI with elevated glycemic gap with Chi-squared test (**Table 3**). However, when tested the rate ratio using negative binomial model with and without covariates adjustment (**Table 4**), the association only remained a trend without statistical significance. Chi-squared test, similarly to odds ratio in a logistic regression model, can exaggerate an association when the outcome rate is high (25), as in our DCI occurrence of 29.4%. Therefore, the statistical significance diminished when tested with negative binomial model (**Table 4**). Since our sample size of 119 is not considered small, we can conclude that there is no large effect size for the association between DCI and aGG. A statistically significant rate ratio could be detected with a larger sample size. Furthermore, an aGG cutoff of at or above 30 mg/dL showed a non-significant trend of increased mortality with the RR of 2.10, and a greater sample size may have detected an independent difference. A threshold value of 30 mg/dL might serve as a clinically useful, general rule to help identify aSAH patients at highest risk for poor outcomes; however, the aGG value should be interpreted on an individual basis.

Our study is limited by the retrospective, observational design, which is subject to missing or misclassified data and unmeasured confounding. We cannot exclude a possibility that those with HbA1c ordered were more likely to be diabetic or have a higher disease severity, creating a potential selection bias; however, we routinely order HbA1c on patients admitted to our neuro ICU. We are also unable to confirm whether our patients received pre-treatment for hyperglycemia or routine insulin for diabetes mellitus prior to recorded glucose, which may have influenced admission glucose and calculated aGG levels. Variables such as socioeconomic or insurance status, or withdrawal of life-sustaining care may influence inpatient mortality and post-hospital disposition but were not captured in this analysis. Additionally, outcomes post-discharge could not be assessed; therefore, it is unknown if aGG has any predictive power on long-term functional outcomes. Our definition of poor outcome, used in other secondary database analysis (19, 26), identified patients requiring nursing care for activities of daily living in the short-term, but it may not accurately predict long-term dependence. Lastly, correlative relationships do not imply causation, and

further randomized clinical trials would be needed to determine if active aGG control will lead to improved outcomes.

Our study confirms correlation between aGG and glucose, as well as between elevated aGG and several admission and inpatient factors known to be associated with hyperglycemia. We demonstrated that aGG was superior to admission glucose in predicting mortality, and that its level below 30 mg/dL served as a useful marker of significantly reduced mortality on our moderate-size cohort of critically ill aSAH patients. Further studies with a large size of diabetic patients are warranted to help better ascertain the mechanistic role of GG in the metabolic and inflammatory processes of aSAH as well as application in prognostication following aSAH with other known markers, as tested with the APACHE-II score in prediction of ICU mortality in general (14). Finally, an equally important area to study is to assess whether pursuing longitudinal glycemic control based on aGG is more effective and feasible.

CONCLUSIONS

An elevated admission glycemic gap is common in aSAH patients and is associated with disease severity. In our study, an aGG $\geq$30 mg/dL was not independently associated with in-hospital mortality and poor outcome after controlling for disease severity, but the study was underpowered to find an independent association. Future study is needed to better understand the clinical significance of this marker and evaluate its use as a predictor of important clinical outcomes in this population.

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 human participants were reviewed and approved by University of Southern California Health Sciences Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PS, PN, SB, and MK-T: acquisition of data, analysis and interpretation of data, and drafting or revising the article. RP: acquisition of data, conception and design, analysis and interpretation of data, and drafting or revising the article. JM and SC: analysis and interpretation of data and drafting or revising the article. BE: conception and design, analysis and interpretation of data, and drafting or revising the article. All authors contributed to the article and approved the submitted version.

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REVIEW
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Hemorrhagic Transformation After Ischemic Stroke: Mechanisms and Management

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Symptomatic hemorrhagic transformation (HT) is one of the complications most likely to lead to death in patients with acute ischemic stroke. HT after acute ischemic stroke is diagnosed when certain areas of cerebral infarction appear as cerebral hemorrhage on radiological images. Its mechanisms are usually explained by disruption of the blood-brain barrier and reperfusion injury that causes leakage of peripheral blood cells. In ischemic infarction, HT may be a natural progression of acute ischemic stroke and can be facilitated or enhanced by reperfusion therapy. Therefore, to balance risks and benefits, HT occurrence in acute stroke settings is an important factor to be considered by physicians to determine whether recanalization therapy should be performed. This review aims to illustrate the pathophysiological mechanisms of HT, outline most HT-related factors after reperfusion therapy, and describe prevention strategies for the occurrence and enlargement of HT, such as blood pressure control. Finally, we propose a promising therapeutic approach based on biological research studies that would help clinicians treat such catastrophic complications.

Keywords: cerebral hemorrhage, stroke, acute, hemorrhagic transformation (HT), risk factors, reperfusion

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INTRODUCTION

Hemorrhagic transformation refers to hemorrhagic infarction that occurs after venous thrombosis or arterial thrombosis and embolism (1, 2). Autopsy studies have reported an HT rate of 18–42% in acute ischemic stroke due to arterial occlusion (1, 3). The frequency of HT has been reported mainly in clinical studies using brain imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), rather than pathological studies (4). Therefore, prior to considering the frequency of occurrence of HT, we need to understand the imaging and clinical definitions of HT. Although rates of HT in ischemic stroke have been reported, more than half of all cerebral infarctions demonstrate certain stages of HT (5).

The radiographic definition of HT is generally classified by the European Cooperative Acute Stroke Study (ECASS) (6). On CT scans, the severity of HT is divided into two stages: hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) with or without mass effect. Each stage is divided into two subtypes (7). Each characteristic is presented in **Table 1** (8).

With recent advances in intravenous (9) or endovascular (10) reperfusion therapies for acute ischemic stroke (11), stroke physicians need to deepen their understanding of cerebral hemorrhagic complications. Although the overall risks of complications have been well-documented in various

TABLE 1 | Characteristics of hemorrhagic transformation (HT) according to European Cooperative Acute Stroke Study (ECASS) 2 (8).

Types of HT	Mass effect	Definition
Hemorrhagic infarction-1 (HI-1)	Absence of mass effect	Small petechial bleeding along the margins of the infarcted area
Hemorrhagic infarction-2 (HI-2)		Confluent petechial bleeding within the infarcted area
Parenchymal hemorrhage-1 (PH-1)	Mildmass effect	Hematoma in <30% of the infarcted area
Parenchymal hemorrhage-2 (PH-2)	Definite mass effect	Hematoma in more than 30% of the infarcted area

randomized controlled trials (RCTs) of reperfusion therapies (12), the mechanisms underlying cerebral hemorrhage or hematoma after stroke in individual patients remain poorly understood. Intracranial bleeding after acute ischemic stroke has a significant impact on patient outcomes (13, 14), and controlling the risk of bleeding plays an important role in determining whether to proceed with recanalization (15). Large parenchymal hematomas and symptomatic intracerebral hemorrhage (sICH) are the most feared, tend to have a high mortality rate, and appear in up to 6% of patients after intravenous thrombolysis (16). In addition, infarction evolution with HT can lead to significant neurological deterioration (17–19). The frequency of HT is associated with different factors, such as epidemiological factors (e.g., age, pre-stroke treatment, and conditions), characteristics of the infarct (size of ischemic core and timing of follow-up), reperfusion techniques in the acute phase (intravenous thrombolysis, mechanical thrombectomy, or combined), radiological diagnosis (CT or MRI techniques), and use of antithrombotics after the acute phase (20–22).

CLINICAL PRESENTATIONS, HISTOPATHOLOGY, AND RADIOLOGIC FEATURES

Various criteria have been applied to define whether a hemorrhagic infarction is symptomatic; however, only parenchymal hematomas have been reported to be consistently linked to worsening and long-term deterioration (23). Many cases of HT, including most petechial hemorrhages, are asymptomatic (24). Only sICH (parenchymal hematoma) appears to be clinically evident and often exhibits rapid neurological deterioration (25). In untreated patients, HT rarely occurs during the first 6 h. It usually appears in the first few days, most within 4 days of infarction (26, 27). Patients who have undergone acute treatment with thrombolysis or thrombectomy usually experience bleeding 24 h after stroke onset (early HT) (28).

Pathologists have traditionally called petechial HT "red softening." Petechial HT is considered to be due to (a) insufficient perfusion from adjacent collateral vessels or (b) reperfusion of infarcted tissues with weakened vessels (extravasation) (29). The former explains why HT occurs in patients with permanently occluded vessels (30), while the latter explains why the proportion of patients with HT is higher in those who receive reperfusion therapy than in those who do not receive reperfusion therapy (31).

Figure 1 shows the relationship between HT probability and reperfusion (R) after ischemic stroke. The radiologic features differ from those of petechial hemorrhagic infarction and parenchymal hemorrhage (19). Petechial hemorrhagic infarction usually appears as tiny punctate regions in the hemorrhage and is often not individually resolved (32). In parenchymal hematomas or hemorrhage, radiological features on both CT and MRI, which combine the features of ischemic infarction and cerebral hemorrhage, overlap (33).

MECHANISMS OF HT AFTER ISCHEMIC STROKE

The blood–brain barrier (BBB) is a physiological barrier between the brain parenchyma and brain circulation that nourishes brain tissue, filters various substances from the brain to the blood, and protects the brain (34, 35). The BBB is composed of endothelial cells, basement membrane, pericytes, and astrocytes, collectively referred to as the neurovascular unit and linked to circulating peripheral blood cells (36, 37). Early disruption of the BBB plays a pivotal role in HT formation during acute ischemic stroke (38). Leukocyte types and various molecules are associated with HT after ischemic stroke (39). Neutrophils and brain tissue are major sources of matrix-metalloproteinase-9 (MMP-9) within the first 18–24 h after stroke (28, 40). Intravenous infusion of exogenous tissue plasminogen activator (tPA) can increase MMP-9 levels by activating neutrophils (41), and endogenous tPA can increase MMP-3 levels by acting on endothelial cell lipoprotein receptor protein (LRP) (42), and can increase MMP-2 levels by activating platelet-derived growth factor-CC as a trigger *via* astrocyte platelet-derived growth factor receptor A (43). **Figure 2** shows a possible mechanism for early vs. delayed HT.

Theoretically, cerebral infarction does not occur until the cerebral blood flow reaches a minimum threshold, where oxygen and glucose cannot be sufficiently guaranteed (44). As in other organs, infarcted cerebral tissue tends to bleed, and cerebral hemorrhage can lead to severe neurological deterioration (22). Mechanisms related to HT can be considered from various perspectives, such as histological changes, vascular occlusion, collateral circulation, BBB disruption, and infarct size (45, 46).

Acute cerebral ischemia leads to considerable damage to capillary cells, which causes an increase in vascular permeability and extravasation of blood in the brain parenchyma (47, 48). The two main factors described in this process are oxidative stress and reperfusion injury, which cause damage to blood vessels through various injury mechanisms, such as inflammation, leukocyte infiltration, vascular activation, and extracellular proteolysis (49, 50). The consequences are destruction of the basal lamina and endothelial tight junctions (51). Among the molecular processes involved, MMP-9 has been shown to play an important role in the destruction of basal lamina type IV collagen (52, 53). Destruction

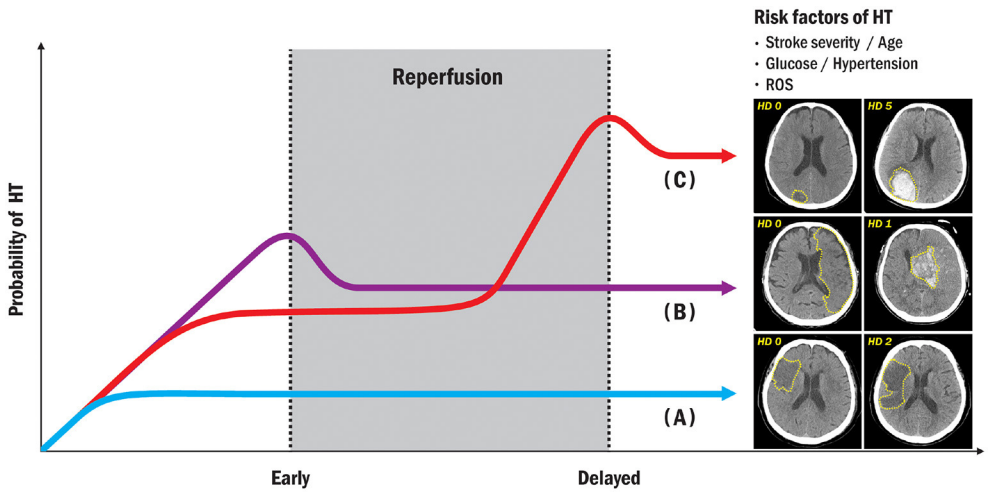

FIGURE 1 | Illustration showing correlation between HT and reperfusion time after ischemic stroke. Under the risk factors commonly associated with HT; **(A)** no HT (no bleeding regardless of reperfusion); **(B)** early HT (definite bleeding usually 6–24 h after stroke); **(C)** delayed HT (definite bleeding usually more than 24 h after ischemic stroke). HT, hemorrhagic transformation; ROS, reactive oxygen species.

of the basal lamina leads to leakage of macromolecules into interstitial fluids in the central nervous system (54). In contrast to cytotoxic edema (cell death from ionic pump failure), the resulting ionic gradient causes interstitial edema, known as "vasogenic edema" (55). Vasogenic edema can lead to lesions in adjacent tissues. Therefore, this mechanism can worsen, causing malignant infarction, resulting in fatal consequences and high risk of HT (56).

Reperfusion can trigger harmful cascades, such as oxidative stress, suppression of protein synthesis, platelet activation, activation of the complement system, leukocyte infiltration, basal lamina disruption, and eventual cerebral cell death in the central nervous system (57–60). Reperfusion injury alone seems to be enough to cause fatal hematoma, but all ischemic strokes with tissue reperfusion do not cause hematoma (29). Fragments of thrombus with a large thrombotic burden can contribute to bleeding complications in the delayed phase (> 24 h) after acute stroke. Fragmentation of a large thrombus can lead to distal migration and damage to the vascular bed (61).

In summary, the development of HT after stroke involves multiple interconnected pathological processes from peripheral blood cells to neurovascular units, such as hyperactive ischemic cascades with increased MMP levels, excessive levels of ROS, coagulopathy, BBB breakdown, and reperfusion injury.

FACTORS ASSOCIATED WITH HT AFTER ISCHEMIC STROKE

Although the usefulness of these HT-related factors may be limited in clinical practice, some factors predict HT. Given the fibrinolytic or antithrombotic therapy in acute ischemic stroke settings, imaging techniques, and predictive biomarkers can help screen specific patients at increased risk of HT as a group of particular interest (62–64). Advances in the use of neuroimaging and composite scores can lead to more personalized approaches for HT prediction, but various factors should be considered when drawing conclusions that may affect the timing of HT detection (16, 28). This point can be influenced by the accuracy of imaging modalities used, such as CT or MRI with or without gradient-echo or susceptibility-weighted sequences (65), which are more sensitive to the detection of blood products (64). Factors associated with HT after ischemic stroke are shown in detail in **Table 2**.

REVERSAL OF COAGULOPATHY WITH VARIOUS AGENTS

Although coagulopathy correction remains the mainstay of treatment after tPA infusion, no specific agent has been found to be most effective in dealing with fatal HT expansion, which includes sICH (86). In patients with sICH, which occurs within 36 h after tPA infusion, there are several suggestions that can be considered depending on the mechanisms of action of reversal agents (87). The details are listed in **Table 3**.

PREVENTION OF HT EXPANSION

Hematoma expansion or sICH is a major predictor of death and disability in patients with acute stroke with HT (88). Therefore, in addition to aggressive reversal of coagulopathy, other strategies to prevent hematoma expansion may be needed as therapeutic targets in sICH.

Elevation and variability in blood pressure have been linked to the risk of hematoma enlargement in patients with spontaneous ICH in observational studies (89). In

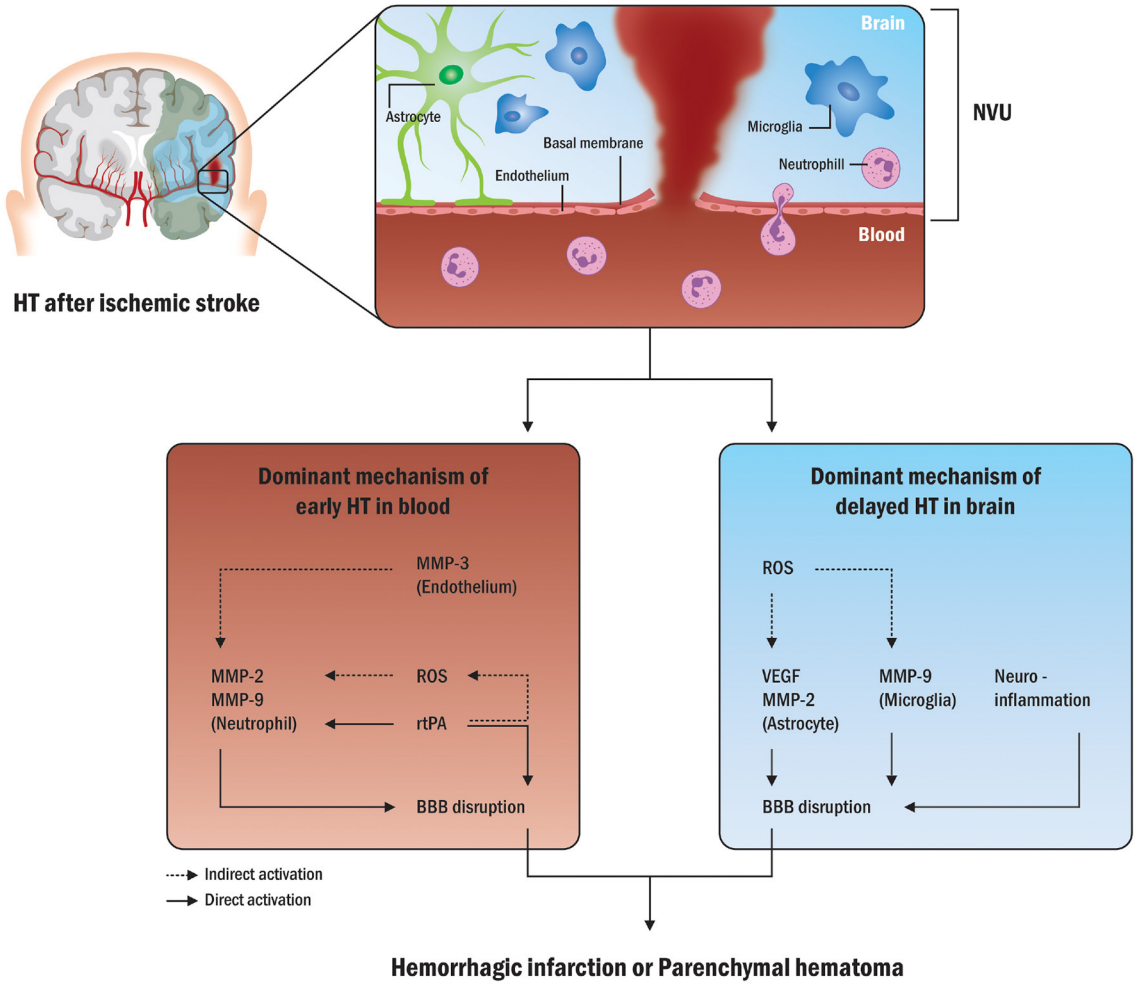

FIGURE 2 | Possible mechanisms in early and delayed HT. The disruption of the BBB is a common pathway in HT formation following acute ischemic stroke. Various molecules from neutrophils and peripheral blood in possible processes in early HT are mainly associated with HT after ischemic stroke. Exogenous tPA can also increase MMP-9 levels by activating neutrophils and increasing MMP-2 levels. Conversely, in possible processes for delayed HT, the brain tissue is a major source of MMP-9 within the first 18–24 h following stroke, and endogenous tPA can act on endothelial cells to increase MMP-2 release from astrocytes as well as MMP-9 release from microglia. HT, hemorrhagic transformation; NVU, neurovascular unit; MMP, matrix-metalloproteinase; ROS, reactive oxygen species; tPA, tissue plasminogen activator; BBB, blood-brain barrier; VEGF, vascular endothelial growth factor.

patients with spontaneous intracerebral hemorrhage, studies have shown that intensive control of systolic blood pressure is relatively safe to lower to 140 mmHg, but this that measure had no apparent effect compared with the systolic blood pressure target of 180 mmHg (90). Although the optimal target for blood pressure control in sICH is still unclear, the treatment goal is to supply adequate blood flow to the ischemic area, reduce the pressure on the brain with autoregulation impairment, and eventually reduce the risk of hematoma expansion (91). However, the effects of BP on hematoma enlargement are for primary intracranial hemorrhage and are independent of those in patients with HT after ischemic stroke. Nonetheless, the recent Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial has shown that intensive blood pressure control potentially reduces the risk of major intracranial hemorrhage in patients with acute ischemic stroke receiving intravenous thrombolytic therapy (92).

Patients with acute ischemic stroke may be at risk of additional ischemia, especially in a low blood pressure environment, if occluded vessels are not reopened following thrombolytic therapy or mechanical thrombectomy. Although several studies have linked poor neurological outcomes to decreased mean arterial pressure (93), Rasmussen et al. only included patients whose blood pressure was measured during endovascular procedures or intravenous alteplase infusion procedures, and the results were stratified according to the presence of sICH (94).

TABLE 2 | Various associated factors with HT.

Associated factors	High risk	Low risk
Clinical features		
Age (21)	Old	Young
Sex (21)	Male	Female
Weight (66)	Obese	Normal weight
Temperature (67)	Fever	Normothermia
Glucose (68)	Hyperglycemia	Normoglycemia
Blood pressure (68)	Hypertensive	Normotensive
Variability of blood pressure (69)	Yes	No
Stroke severity (21)	Severe stroke (≥22 on NIHSS)	Mild stroke (1–5 on NIHSS)
Size/type of infarct (21)	Large/embolic territorial (MCA, ACA, PCA, cerebellar)	Small/lacunar or small vesseldisease
Atrial fibrillation (21)	Yes	No
Congestive heart failure (22)	Yes	No
Renal impairment (70)	Yes	No
Previous stroke (21)	Yes	No
Diabetes (21)	Yes	No
Platelet count (16)	Low	No
Previous antiplatelet treatment (68)	Yes	No
OTT (66)	Late (≥ 180 min)	Early (< 180 min)
ERT (71)	Late (> 6 h)	Early (≤ 6 h)
Biochemical factors		
MMP-9/c-Fn (70)	High	Low
Fibrinogen (16)	Low	High
Ferritin (28)	High	Low
S100B (72)	High	Low
TAFI (73)	High	Low
PAI-1 (73)	Low	High
VAP-1/SSAO activity (70)	High	Low
APC (28)	High	Low
PDGF-CC (74)	High	Low
Genetics		
Leukocyte mRNA (MCFD2, VEGI/AREG, MARCH7, SMAD4) (75)	Low/High	High/Low
A2M (76)	High	Low
Factor FXII (76)	Low	High
Factor FXIII V34L (77)	High	Low
Imaging findings		
Early signs of ischemia (21)	Yes	No
Focal hypodensity, edema, mass effect on baseline (20)	Yes	No
Leukoaraiosis (22)	Yes	No
BBB permeability (16)	Yes	No
Areas of hypoperfusion on CTP (78)	Yes	No
HARM (79)	Yes	No
MRI enhancement pattern (63)	Yes	No
Collateral flow (29)	Low	High
ADC value (80)	Low	High
Cerebral blood flow or volume (28)	High	Low
Infarct volume on DWI (25)	Large	Small
Composite rating scores		
HAT (0-5 points) (81)	High	Low
MSS (0-4 points) (82)	High	Low
SITS-SICH (0-12 points) (66)	High	Low
SEDAN (0-5 points) (83)	High	Low
GRASPS GWTG (0–101 points) (70)	High	Low
SPAN-100 (0–1 points) (84)	High	Low
THRIVE (0–9 points) (85)	High	Low

NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; OTT, onset to treatment; ERT, endovascular recanalization therapy; MMP-9, matrix metalloproteinase-9; c-Fn, cellular fibronectin; S100B, S100 calcium-binding protein B; TAFI, thrombin activatable fibrinolysis inhibitor; PAI-1, plasminogen activator inhibitor; VAP-1, vascular adhesion protein-1; SSAO, semicarbazide-sensitive amine oxidase; APC, activated protein c; PDGF-CC, platelet-derived growth factor-cc; mRNA, messenger ribonucleic acid; MCFD2, multiple coagulation factor deficiency protein 2; VEGI, vascular endothelial growth factor; AREG, Amphiregulin; MARCH7, membrane-associated RING-CH-type finger 7; SMAD4, smad family member 4; A2M, alpha-2-macroglobulin; BBB, blood-brain-barrier; CTP, computed tomography perfusion; HARM, hyperintense acute injury marker; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; HAT, hemorrhage after thrombolysis; MSS, multicenter stroke survey; SITS-SICH, safe implementation of treatments in stroke symptomatic intracerebral hemorrhage; SEDAN, blood sugar, early infarct signs, hyperdense cerebral artery sign, age, NIHSS; GRASPS GWTG, glucose at presentation, race, age, sex, systolic blood pressure at presentation, and severity of stroke at presentation (NIHSS)-Get with the Guidelines; SPAN-100, stroke prognostication using age and NIHSS; THRIVE, totaled health risks in vascular events.

One study related to thrombolysis and blood pressure showed that decreased systolic blood pressure was associated with improved neurological outcomes and lower rates of sICH (86, 95). In the European Cooperative Acute Stroke Study II (ECASS II) clinical trial, higher systolic blood pressure was associated with worse functional outcomes and sICH (93). However, there was no clear evidence that lower blood pressure led to worse functional outcomes (87). In the presence of lethal HT after tPA infusion (especially parenchymal hemorrhage type 2), few data on blood pressure treatment are available, especially when compared with other types of HT. In tPA-related HT, healthcare providers should determine the target blood pressure and consider the severity of sICH, risk of bleeding enlargement, and risk of impending ischemia (96). Theoretically, with incomplete recanalization, higher blood pressure targets may be needed to maintain adequate collateral blood flow to the ischemic bed and reduce the risk of infarct growth among patients with HI-1 and HI-2 (97). Under complete recanalization, strict blood pressure control measures may be reasonable (98).

Stricter blood pressure control may be more beneficial and less harmful for patients with parenchymal hematoma at higher risk of hematoma enlargement. Hematomas with smaller volumes

TABLE 3 | Potential reversal agents for treatment of HT.

Reversal agent	Suggested dose	A promising treatment group	Adverse effects
Cryo-precipitate	10 U	All sICH patients	Lack of pathogen inactivation, risk of transfusion related lung injury, and delay in obtaining the solution
Platelets	6–8 U	MostsICH patients (except for patients with thrombocytopenia, which platelet count <100,000/μL)	Lack of pathogen inactivation, risk of transfusion-related lung injury
PCC	20–40 mL	sICH patients on warfarin treatment before alteplase administration (adjunct treatment to cryo-precipitate)	Risk of thrombotic complication
FFP	12 mL/kg	sICH patients on warfarin treatment before alteplase administration but cannot treat PCC (adjunct treatment to cryoprecipitate)	Risk of thrombotic complications, and volume overload
Vitamin K	5–10 mg	sICH patients on warfarin treatment before alteplase administration	Risk of anaphylaxis
Antifibrinolytic agent	Amicar: 1–4 g/h TXA: 10 mg/kg	All sICH patients (especially, those who decline blood products)	Risk of thrombotic complications
rFVIIa	20–160 μg/kg	Unclear	Risk of thrombotic complication

sICH, symptomatic intracerebral hemorrhage; PCC, prothrombin complex concentrates; FFP, fresh frozen plasma; Amicar, aminocaproic acid; TXA, tranexamic acid; rFVIIa, recombinant factor VIIa.

are generally left untreated (99), and deep-seated (thalamus or brainstem) hemorrhages are usually not evacuated.

In summary, healthcare providers should determine blood pressure targets by weighing the risk of worsening ischemia based on the severity of hemorrhage and its risk of expansion. Patients with incomplete recanalization may need higher blood pressure targets to maintain sufficient blood flow to the ischemic bed and reduce the risk of infarct growth. Conversely, patients with complete recanalization may need strict blood pressure control to avoid impending HT.

BLOOD PRESSURE MANAGEMENT AFTER THROMBECTOMY FOR PREVENTING HT

Observational studies have shown an increased risk of HT in patients with high blood pressure and high variability in blood pressure, suggesting a close relationship between hemodynamics and HT (69). High variability in blood pressure has been considered a strong risk factor for cerebral edema and post-stroke HT, as rapid changes in blood pressure can easily rupture already damaged blood vessels due to ischemic insult (100, 101). Current guidelines recommend maintaining blood pressure below a fixed threshold of 180/105 mmHg for at least 24 h, regardless of thrombolytic or endovascular intervention (96, 102). A recent US study reported that a peak systolic BP of 158 mmHg in the first 24 h after endovascular therapy best dichotomized good and bad outcomes (103). A prospective randomized trial reported neutral results when determining whether a target systolic blood pressure (SBP) < 130 mmHg after endovascular reperfusion can reduce the risk of intracranial hemorrhage (104). Therefore, lowering the post-reperfusion BP target can be considered to prevent reperfusion injury and promote tissue restoration in ischemic penumbra (98).

Cerebral autoregulation is the intrinsic dilative-constrictive capacity of the cerebral vasculature that preserves stable blood flow in the face of systemic blood pressure changes (105, 106). Autoregulatory capacity in acute stroke is crucial for maintaining stable blood flow to the ischemic penumbra and avoiding excessive hyperperfusion (107).

Petersen et al. reported more longitudinal autoregulation modes, indicating dynamic autoregulatory failures up to 1 week after emergent large vessel occlusion (ELVO) strokes (108). **Figure 3** shows the presence of HT within or above the autoregulatory limits due to fluctuations in blood pressure. This investigation showed that the autoregulatory parameter in the ipsilateral cerebral hemisphere was lower than that in the opposite hemisphere, indicating a decrease in the ability to buffer blood pressure fluctuations (91). In patients with stroke with cerebral autoregulation impairment, restoration tends to be delayed for up to 3 months, emphasizing the clinical relevance of autoregulation in stroke research (109, 110).

In summary, continuous optimization of blood pressure would be a good method for patients tailored to their own physiology, where hemodynamic management represents an appropriate and neuroprotective avenue for critically ill patients. Exceeding the upper limits of autoregulation may predispose patients to reperfusion injury, and maintaining blood pressure within autoregulatory limits may avoid bleeding complications while achieving favorable outcomes. Furthermore, trajectory analysis has the potential to provide more individualized hemodynamic management during and after thrombectomy procedures in intensive care settings.

MEDICAL TREATMENT AND NEUROSURGICAL CONSIDERATIONS

Hemorrhagic transformation after ischemic stroke can be suspected based on clinical presentation (neurological worsening in National Institutes of Health Stroke Scale, NIHSS, score) and radiological findings within 48 h on CT or MRI (111, 112). First, hemodynamic stabilization should be performed, followed by

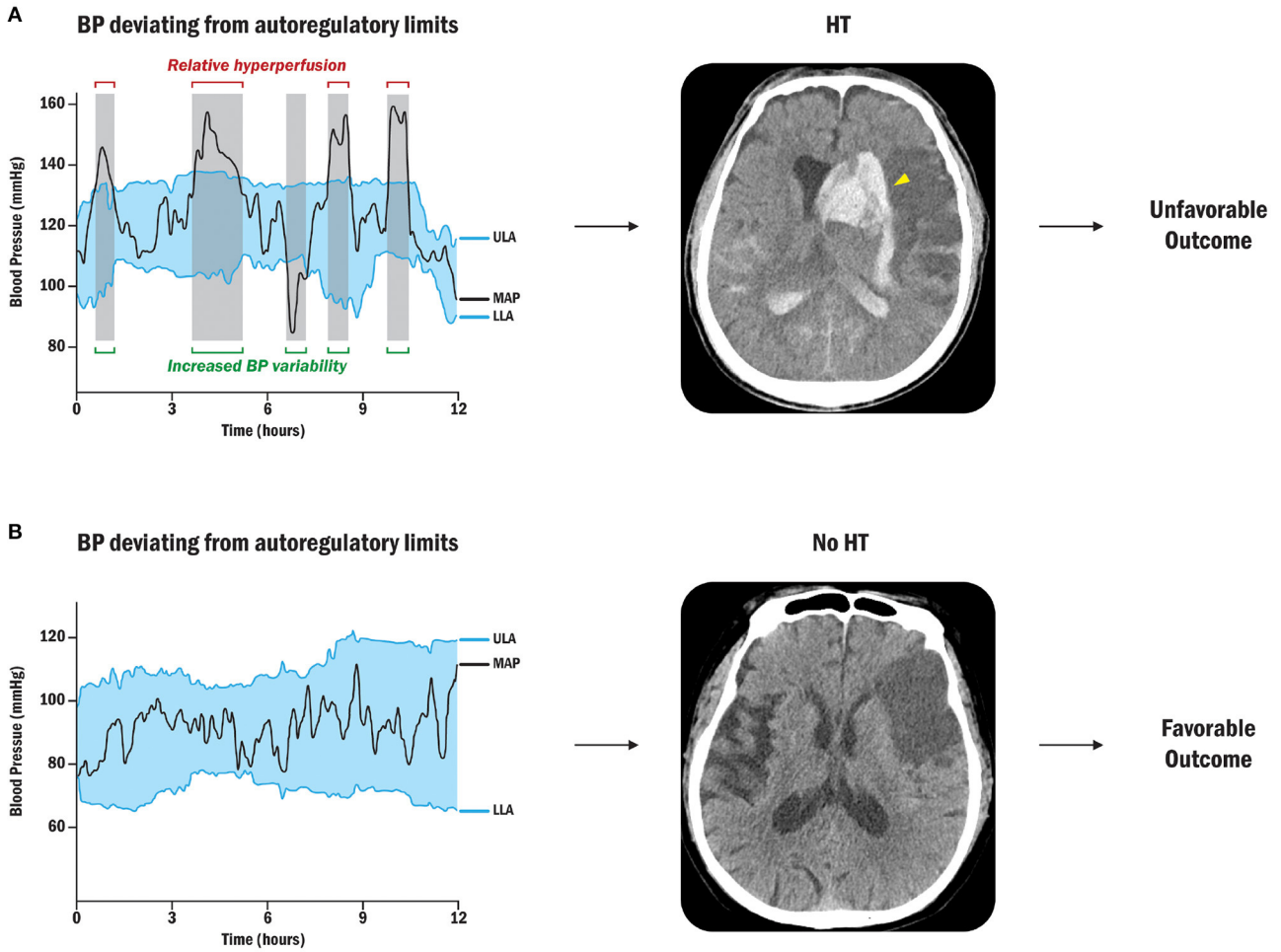

FIGURE 3 | Sequential BP changes, cerebral autoregulation, and HT (91). **(A)** Patient with BP deviation from autoregulatory limits: Relative hyperperfusion above the upper limit of autoregulation may lead to HT and unfavorable outcomes. The yellow arrowhead points out the radiological HT after cerebral ischemic stroke. **(B)** Patient with acceptable BP fluctuations: Strictly controlled blood pressure within personalized limits of autoregulation can prevent secondary brain injury by protecting against HT after stroke. BP, blood pressure; ULA, upper limit of autoregulation; MAP, mean arterial pressure; LLA, lower limit of autoregulation.

transfer to a neuro-intensive care unit if available (113). To evaluate the mechanisms of HT, HT-associated factors, such as clinical features, biochemical factors, genetics, imaging findings, and composite rating scores, should be analyzed. Temperature and glycemic controls should then be performed, such as mechanical prophylaxis for deep vein thrombosis (86). Second, blood pressure control and correction of coagulopathies should be mainstays of HT treatment (114). Finally, neurosurgical considerations are needed as soon as possible if hazardous HT is suspected (115). A plausible algorithm for appropriate clinical approaches to HT after ischemic stroke is depicted in **Figure 4**.

It is challenging to construct evidence-based treatment algorithms for surgical interventions because of the lack of expected data to guide the therapeutic timing and surgical techniques to be implemented (116). Nonetheless, neurosurgical treatment can be considered in patients with sICH where outcomes can be improved despite ischemic injury. Indeed, the risks and benefits of rapid surgical decompression vs. iatrogenic injury must be carefully weighed in the setting of possible tPA-associated coagulopathy.

Neurosurgical treatment can also be considered in patients with supratentorial ICH who exhibit neurological deterioration, coma, significant midline shift, or elevated intracranial pressure refractory to medical treatment. The goal is to decompress the brain and reduce the impact of mass effect, malignant edema, and toxic blood byproducts (117). Open craniotomy can eliminate the compressive effect of a hematoma higher than 30 cm^3 in volume from lobar, cerebellar, or surgically accessible basal ganglia hematomas (118, 119). However, this requires an incision through the cortex and white matter tracts along the path to the lesion. The clinical effectiveness of these interventions remains controversial (120, 121). Minimally invasive craniotomy and stereotactic hematoma evacuation are currently under investigation for spontaneous ICH and post-thrombolytic hemorrhage.

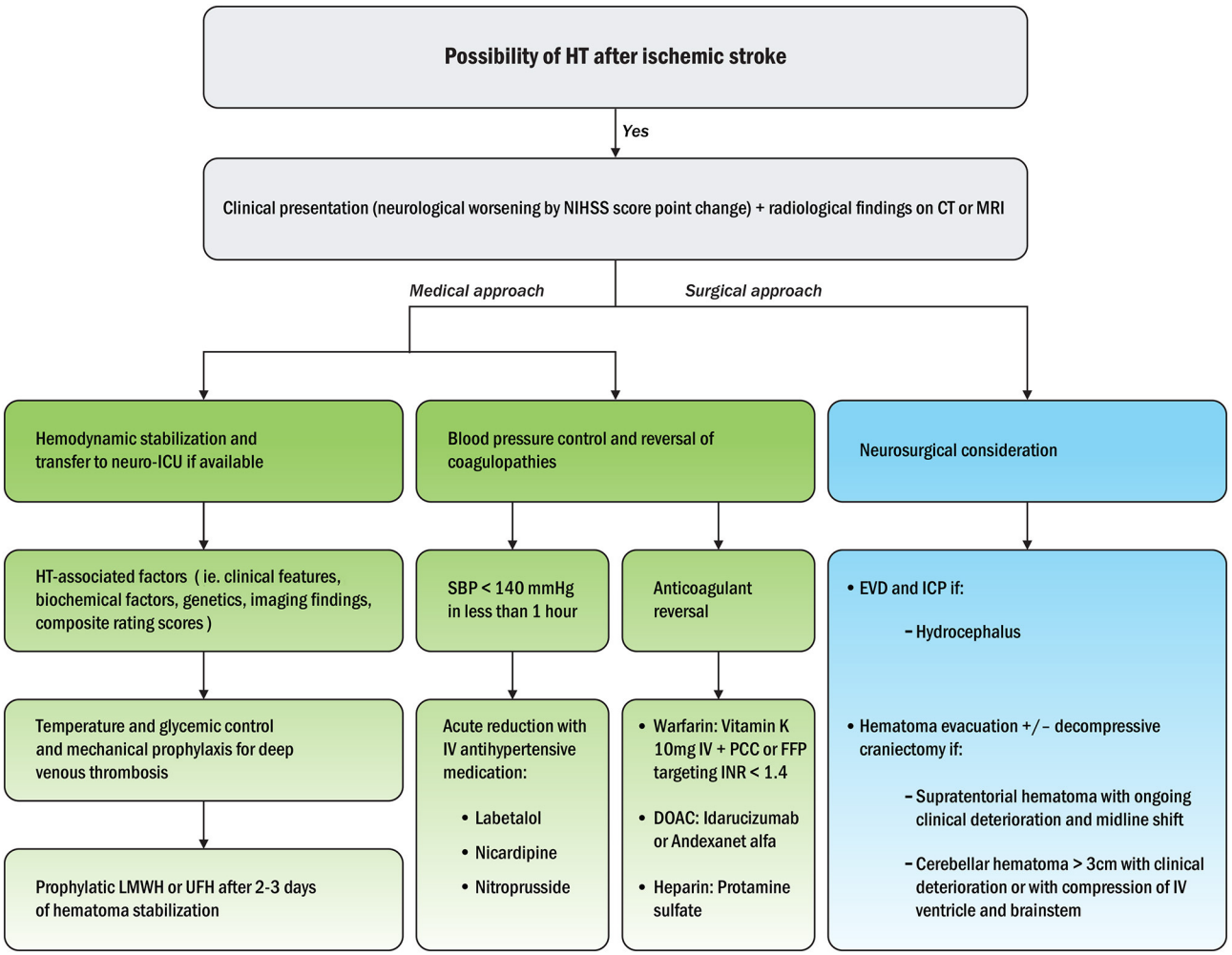

FIGURE 4 | Treatment algorithm for appropriate medical and surgical approaches to HT after ischemic stroke (115). NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; MRI, magnetic resonance imaging; ICU, intensive care unit; LMWH, low molecular weight heparin; UFH, unfractionated heparin; SBP, systolic blood pressure; IV, intravenous; PCC, prothrombin complex concentrates; FFP, fresh frozen plasma; INR, international normalized ratio; DOAC, direct oral anticoagulants; EVD, external ventricular drainage; ICP, intracranial pressure.

POTENTIAL THERAPEUTIC INTERVENTIONS ALONG WITH BIOLOGICAL RESEARCH ON HT

Since HT in acute ischemic stroke is radiologically diagnosed, the timing of HT detection is affected by the accuracy of imaging modalities, such as CT or MRI, with or without gradient-echo or susceptibility-weighted imaging sequences that are more sensitive to blood products (122).

Strong evidence exists that matrix metalloproteinases, especially MMP-9, play a pivotal role in the pathogenesis of the abnormal permeability of the BBB, an important culprit of HT (42, 52, 53). The use of drugs to block the release of MMP-9 is challenging. The phosphodiesterase-III inhibitor cilostazol prevented the development of HT, reduced brain edema, prevented endothelial injury *via* reduction of MMP-9 activity, and prevented the BBB from opening in an experimental model (123–125). Another drug, the broad-spectrum MMP inhibitor BB-94, reduced the risk and severity of HT in rats with homologous clot-induced middle cerebral artery occlusion compared with rats treated with intravenous tPA alone (41). The MMP-9 inhibitor minocycline reduced the risk of HT after tPA in animal models (126, 127), and the Minocycline to Improve Neurologic Outcome in Stroke (MINOS) human trials showed a decrease in plasma MMP-9 levels in patients treated with intravenous tPA (128, 129). Targeted temperature management may be an important step to mitigate HT after recanalization in patients with clinically malignant ELVO, as it reduces the metabolic rate and excessive free radical levels, protects the BBB by reducing MMP-2 or MMP-9 expression, and inhibits immune system responses (130, 131). Nevertheless, effective management of lethal HT requires further experimental studies and trials based on core molecular mechanisms.

CONCLUSION

Symptomatic intracerebral hemorrhage is a life-threatening complication requiring emergent medical and surgical treatment in patients with acute ischemic stroke. Therefore, we need to understand possible mechanisms and treat this potentially serious complication with systematic algorithms in future stroke therapy.

AUTHOR CONTRIBUTIONS

JH performed roles of the conception of this review and wrote the manuscript, interpretation of data, and revising it critically for important intellectual content. DK performed roles of interpretation of data and drafting the article. MK performed roles of the acquisition of data. All authors contributed to the article and approved the submitted version.

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Prognostic Significance of Prolonged Corrected QT Interval in Acute Ischemic Stroke

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Background and Purpose: The aim of this study was to determine the relationship between the heart rate-corrected QT (QTc) interval and the risk of incident long-term mortality in patients with acute ischemic stroke (AIS), considering the impact of sex differences on clinical characteristics, outcomes, and QTc intervals.

Methods: We analyzed prospectively registered data included patients with AIS who visited the emergency room within 24 h of stroke onset and underwent routine cardiac testing, such as measurements of cardiac enzymes and 12-lead ECG. QTc interval was corrected for heart rate using Fridericia's formula and was stratified by sex-specific quartiles. Cox proportional hazards models were used to examine the association between baseline QTc interval and incident all-cause death.

Results: A total of 1,668 patients with 1,018 (61.0%) men and mean age 66.0 ± 12.4 years were deemed eligible. Based on the categorized quartiles of the QTc interval, cardiovascular risk profile, and stroke severity increased with prolonged QTc interval, and the risk of long-term mortality increased over a median follow-up of 33 months. Cox proportional hazard model analysis showed that the highest quartile of QTc interval (≥479 msec in men and ≥498 msec in women; hazard ratio [HR]: 1.49, 95% confidence interval [CI]: 1.07–2.08) was associated with all-cause death. Furthermore, dichotomized QTc interval prolongation, defined by the highest septile of the QTc interval (≥501 ms in men and ≥517 m in women: HR: 1.33, 95% CI: 1.00–1.80) was significantly associated with all-cause mortality after adjusting for all clinically relevant variables, such as stroke severity.

Conclusions: Prolonged QTc interval was associated with increased risk of long-term mortality, in parallel with the increasing trend of prevalence of cardiovascular risk profiles and stroke severity, across sex differences in AIS patients.

Keywords: QTc interval, ischemic stroke, mortality, electrocardiography, comorbidities

INTRODUCTION

The QT interval on surface ECG represents ventricular repolarization time, and prolongation of the heart rate-corrected QT (QTc) interval is associated with functional re-entry, torsade de pointes, and sudden death (1). Aside from its direct association with the risk of fatal arrhythmia, prolonged QTc interval is associated with increased risks of mortality and incident cardiocerebrovascular disease in both high-risk individuals (2, 3) and the general population (4–6).

Although prolonged QTc interval is prevalent and one of the most common ECG abnormalities in patients with acute ischemic stroke (AIS) (7, 8), the clinical utility of QTc interval duration in AIS remains limited due to complex mechanism. Apart from neurally mediated autonomic dysregulation leading to prolong the QTc interval (9, 10), other factors prevalent in patients with stroke may contribute to QTc interval prolongation (11); these include atherosclerotic risk factors, cardiac diseases, electrolyte imbalance, and certain drugs. Furthermore, sex differences should be considered as one of the most decisive factors determining abnormal QTc interval prolongation (12), but also, as a potential confounder leading to a disproportionate distribution of QTc prolonging factors, such as age, atherosclerotic risk factors, cardiovascular and cerebrovascular risk profiles, and even medications (13).

The present study was designed to determine the relationship between QTc interval and the risk of incident long-term mortality in patients with AIS while considering the impact of sex differences on clinical characteristics, outcomes, and QTc intervals.

MATERIALS AND METHODS

Study Population

We analyzed prospectively registered data included patients with AIS who visited the emergency room within 24 h of symptom onset and were admitted to the Asan Medical Center between May 2007 and December 2011. While in the emergency room, all patients underwent routine cardiac testing, such as measurements of cardiac enzymes and 12-lead ECG investigations were performed on admission according to the stroke protocols in our center, which abide by the 2007 guidelines (14). Patients underwent additional cardiac evaluations by a cardiologist if they were suspected to suffer from acute coronary syndrome during the evaluation at the emergency department. Then, patients were excluded if (1) they were diagnosed with the concomitant acute coronary syndrome (15) at admission, or (2) their brain images or ECGs were of poor quality, or (3) they had a complete bundle branch block (QRS interval > 120 ms), ventricular rhythm, or pacemaker-paced rhythm. The study protocol was approved by the Institutional Review Board of the Asan Medical Center, which waived the requirement for informed consent because of the registered data analysis design of this study.

Patient and Public Involvement in the Study

Patients and the public were not involved and were not applicable in this study.

Electrocardiogram Analysis and QT Interval Duration

All patients underwent a 12-lead ECG (GE Healthcare, Waukesha, WI) at admission, with the results processed using the Marquette 12SL ECG Analysis Program. The resultant 12-lead ECG waveforms were uploaded in digital form and interpreted by a cardiologist according to a modified version of the Minnesota code (16). The QT interval was defined as the time duration between the earliest QRS onset to the latest T-wave offset in the 12 ECG leads. For calculation of QTc interval, Fridericia's formula was used because it has been regarded as being appropriate for calculating QTc interval in patients with tachycardia or bradycardia (17), or AF due to the beat-to-beat variability in the RR interval (18, 19). QTc intervals were calculated by a specialized cardiologist and stratified by quartiles for each sex.

Data Acquisition

Clinical data were obtained from the patients' electronic medical records. These included demographic characteristics, conventional risk factors for stroke, comorbidities such as a previous history of stroke and cardiac comorbidities. The latter included ischemic heart disease (IHD), defined as a medical history of IHD or evidence of prior IHD on admission by 12-lead ECG; atrial fibrillation (AF), defined as a history of AF, evidence of AF on admission by 12-lead ECG, and newly diagnosed AF after admission; ventricular hypertrophy (VH), defined as a medical history of hypertrophic cardiomyopathy or evidence of VH on admission by 12-lead ECG; and congestive heart failure (CHF), defined as a history of cardinal manifestations and treatment for heart failure. Other factors recorded included chronic kidney disease (CKD), defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 on admission; and active cancer, defined as cancer within 6 months prior to enrollment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer (20). Neurological status was determined using the National Institutes of Health Stroke Scale (NIHSS) (21), which assessed stroke severity and the specific locations of insular cortical lesions.

Collection of Mortality Data

Follow-up information for patients was obtained using the national death certificate data from the Korean National Statistical Office until 31 December 2012. The nationwide official data for death certificates produced by the Korean National Statistical Office are updated annually. Deaths were classified according to the *International Classification of Diseases, Tenth Revision* (22). Causes of death were classified as stroke (ICD codes: I60–I69), cardiac causes (ICD codes: I20–I25 or I30–I52), malignancies (ICD codes: C00-C96), and other causes.

Statistical Analysis

Baseline characteristics were compared according to the distribution of QTc intervals, which were categorized by quartiles

for each sex. Continuous variables were expressed as means ± SDs or medians (interquartile ranges [IQR]) and compared by ANOVA tests. Categorical variables were expressed as numbers (%) and compared by Chi-square tests.

Multivariate Cox proportional hazards models were used to determining the relationship between the quartiles of sex-specific QTc intervals and all-cause death in all patients and each sex. Hazard ratios (HRs) are reported with 95% CIs. Model 1 included adjustments for age, sex, conventional risk factors for stroke, comorbidities, and all laboratory results, whereas Model 2 included all the variables in Model 1, as well as NIHSS scores for estimating the HR of quartiles and dichotomized QTc interval prolongation. Variables were included in a stepwise method based on our previous studies, with a consideration of the strong impact of neurologic deficits on long-term mortality as well as QTc-interval prolongation (23, 24). The timing of events according to QTc interval was assessed by the Kaplan–Meier method, with curves compared by log-rank tests. In addition, the prognostic value of dichotomized QTc interval prolongation, defined by cut-offs according to the highest median, tertile, quartile, quintile, sextile, septile, octile, and decile of sex-specific QTc intervals, was compared with the generally adopted cut-offs for community-based QTc interval prolongation (i.e., ≥450 ms in men and ≥460 ms in women) (25) to determine the optimal prognostic cut-off value for QTc interval prolongation. The discriminatory power of the models was estimated using Harrell's C-statistics. All reported p-values were two-sided, with $p < 0.05$ considered statistically significant. All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

We included 1,668 patients in this study (**Figure 1**), 1,018 (61.0%) men and 650 (39.0%) women, of mean age 66.0 ± 12.4 years (range, 24–96 years). Their mean QTc interval was 462.3 ± 43.9 ms (range, 343–809 ms), and the sex-specific mean QTc intervals were 455.2 ± 41.8 ms (range, 311–654 ms) in men and 473.3 ± 44.7 ms (range, 357–809 ms) in women (**Supplementary Figure 1**).

Table 1 summarizes the baseline characteristics in patients stratified by the quartiles of sex-specific QTc intervals. Patients in higher quartiles of QTc interval were tended to be older, and were more likely to have rapid heart rates and a lower proportion of people with a sinus rhythm on baseline ECG, hypertension, and comorbidities, such as AF, CHF, and CKD; and had higher white blood cell (WBC) counts and glucose and possibly C-reactive protein (CRP) concentrations than patients with lower quartiles of QTc interval. In addition, patients in higher quartiles

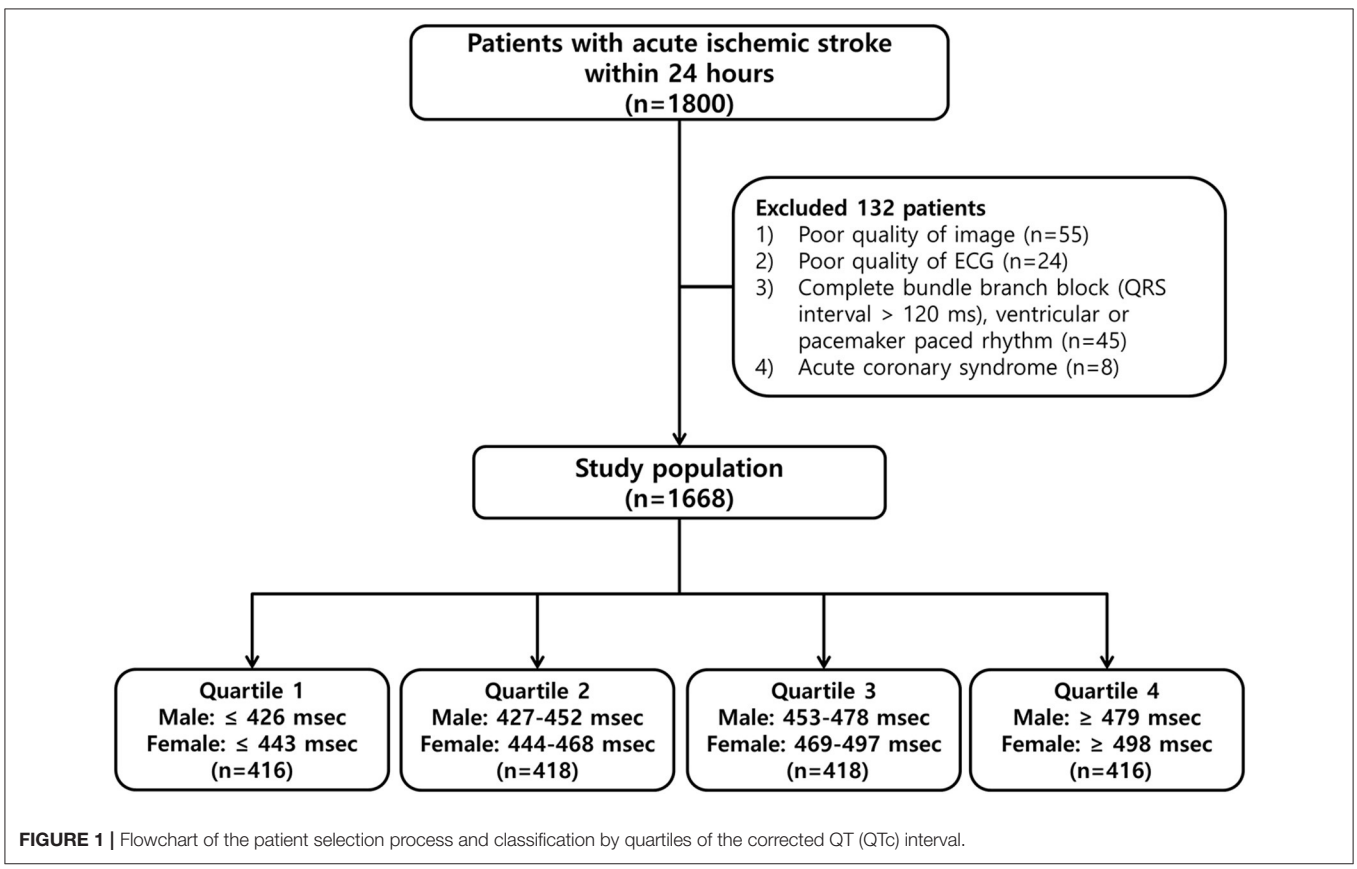

FIGURE 1 | Flowchart of the patient selection process and classification by quartiles of the corrected QT (QTc) interval.

TABLE 1 | Characteristics according to the corrected QT (QTc) intervals.

Variable	Quartiles of QTc interval*				*P*-value†
	Q1 ($n = 416$)	Q2 ($n = 418$)	Q3 ($n = 418$)	Q4 ($n = 416$)	
Age (years)	64.9 ± 12.2	65.8 ± 12.4	66.8 ± 12.4	66.7 ± 12.5	0.10
Male	254 (61.1)	255 (61.0)	255 (61.0)	254 (61.1)	1.00
Baseline ECG information					
Heart rate	66.3 ± 13.2	73.9 ± 13.5	79.2 ± 14.8	91.2 ± 19.7	<0.01
Normal sinus rhythm	300 (72.1)	312 (74.6)	268 (64.1)	227 (54.6)	<0.01
Risk factors					
Hypertension	243 (58.4)	257 (61.5)	281 (67.2)	280 (67.3)	0.02
Diabetes mellitus	92 (22.1)	102 (24.4)	106 (25.4)	117 (28.1)	0.25
Hyperlipidemia	90 (21.6)	95 (22.7)	101 (24.2)	92 (22.1)	0.84
Current smoking	125 (30.0)	132 (31.6)	134 (32.1)	123 (29.6)	0.84
Comorbidities					
Prior stroke	96 (23.1)	107 (25.6)	118 (28.2)	112 (26.9)	0.37
IHD	51 (12.3)	61 (14.6)	58 (13.9)	59 (14.2)	0.78
AF	106 (25.5)	86 (20.6)	122 (29.2)	158 (38.0)	< 0.01
VH	107 (25.7)	98 (23.4)	99 (23.7)	125 (30.0)	0.11
CHF	29 (7.0)	29 (6.9)	48 (11.5)	67 (16.1)	< 0.01
CKD	33 (7.9)	56 (13.4)	61 (14.6)	73 (17.5)	< 0.01
Comorbid cancer	19 (4.6)	27 (6.5)	23 (5.5)	19 (4.6)	0.56
Laboratory results					
WBC (10^3/uL)	7.8 ± 2.6	7.9 ± 2.8	8.3 ± 2.6	8.9 ± 3.3	< 0.01
PLT (10^3/uL)	220.8 ± 60.6	222.8 ± 68.6	218.8 ± 64.0	226.8 ± 75.6	0.39
Hb (g/dL)	13.9 ± 1.8	13.8 ± 1.9	13.9 ± 1.9	13.9 ± 2.2	0.96
Glucose (mg/dL)	136.4 ± 53.4	144.6 ± 55.6	151.0 ± 65.0	149.4 ± 50.9	< 0.01
Albumin (g/dL)	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.5	0.67
HDL (mg/dL)	42.7 ± 12.1	43.0 ± 11.6	43.1 ± 12.0	43.3 ± 11.9	0.89
LDL (mg/dL)	111.2 ± 36.8	108.0 ± 34.0	109.2 ± 32.7	105.1 ± 34.3	0.10
Homocysteine (mmol/mL)	14.5 ± 7.4	14.9 ± 7.5	15.4 ± 7.3	14.3 ± 5.8	0.14
CRP (mg/dL)	0.5 ± 1.6	0.7 ± 2.1	0.7 ± 2.0	0.9 ± 2.7	0.07
Characteristics of stroke					
NIHSS score	3 [1–7]	4 [2–8]	5 [2–10]	5 [3–12]	< 0.01

**QTc cut-off points between quartiles 1 and 2, 2 and 3, and 3 and 4 were 427, 453, and 479 ms, respectively, for men and 444, 469, and 498 ms, respectively, for women.*
Variables are presented as mean ± SD, median [interquartile range], or number (%).
AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; Hb, hemoglobin; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PLT, platelet; VH, ventricular hypertrophy; WBC, white blood cell.
† p-values were calculated by Pearson chi-square test or ANOVA test, as appropriate.

of QTc interval had higher NIHSS scores than patients with lower quartiles of QTc interval.

To assess the relationship of QTc interval to the overall burden of cardiac and neurologic conditions, the cardiac burden was defined as the mean number of cardiac comorbidities, such as IHD, AF, VH, and CHF; and the neurological burden was defined as mean NIHSS score, representing stroke severity. Overall, cardiac and neurologic burdens gradually increased with prolonged QTc intervals (**Figure 2**).

QTc Interval for Prediction of Long-Term Mortality

Over a median follow-up period of 33 months (IQR, 20–48 months), 323 (19.4%) patients died. A total of 153 deaths were stroke-related (9.2%), 32 were cardiac-related (1.9%), and there were other causes (8.3%; **Supplementary Table 1**), with a higher mortality rate in women (149 of 650 women [22.9%]) than men (174 of 1,018 men [17.1%]; **Supplementary Figure 2**). Kaplan–Meier analysis of long-term survival showed that prolonged QTc interval was dose-dependently associated with a gradually increased risk of mortality over 6 years, especially in men but not in women (**Figure 3**).

The crude incidence of all-cause death in the entire patient cohort increased linearly according to the increased quartiles of QTc interval. Adjusted multivariable analysis using the Cox-regression model with stepwise selection of all clinically relevant variables before adjustment for neurological severity showed that the risk of death, relative to the lowest quartile of QTc interval tended to be higher in the second and third quartiles, and significantly higher in the fourth (HR: 1.49, 95% CI: 1.07–2.08)

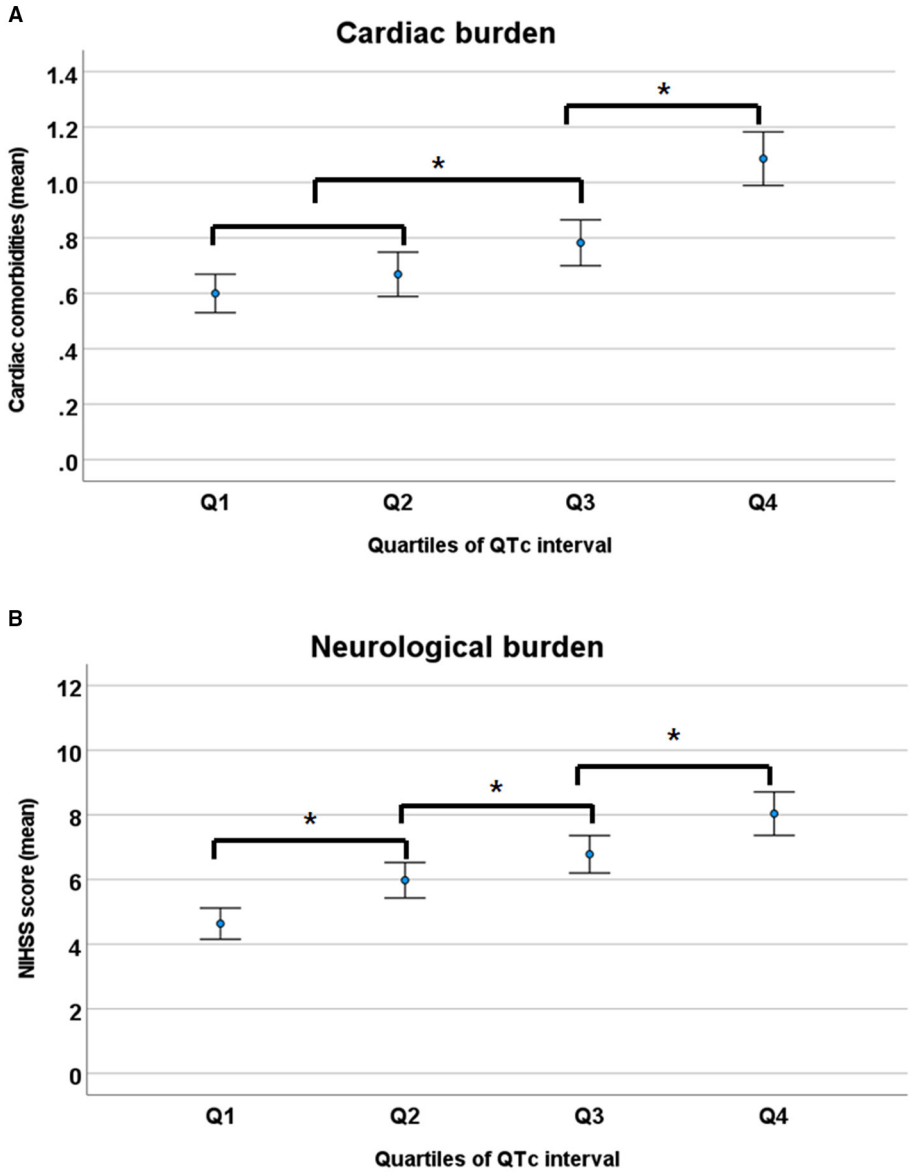

FIGURE 2 | Cardiac **(A)** and neurological burden **(B)** according to the quartiles of QTc intervals. NIHSS, National Institutes of Health Stroke Scale. *$p < 0.05$ by ANOVA with Duncan *post-hoc* test.

quartile ($p = 0.0422$ for trend), before adjusting for neurological factors (**Table 2**).

To assess the cut-off value for the QTc interval prolongation that was predictive of long-term mortality, the QTc intervals were dichotomized using various cut-off values from the highest median to the decile values. The prognostic value of the highest sceptile of QTc interval prolongation (defined as $\geq$ 501 ms in men and $\geq$ 517 ms in women, HR: 1.33, 95% CI: 1.00–1.62) was significantly associated with the risk of overall mortality after adjusting for all clinically relevant variables, such as neurological factors with the highest c-index (0.848; **Supplementary Table 2**).

Age and Sex Difference in QTc Interval of Stroke Patients

For the assessment of the relationship between sex and age distribution, and their impact on QTc interval, overall mean age was significantly higher in women than in men (69.3 $\pm$ 12.6 vs. 64.0 $\pm$ 11.8 years, $p < 0.01$ by Student *t*-test), with a positively skewed trend to increasing age, especially in women. In addition, women patients had a higher cardiac and neurological burden (mean number of cardiac comorbidities [0.84 $\pm$ 0.92 vs. 0.74 $\pm$ 0.86, $p = 0.03$] and mean NIHSS score [7.1 $\pm$ 6.4 vs. 5.9 $\pm$ 6.0, $p < 0.01$]) than men patients. When categorized by age group, QTc

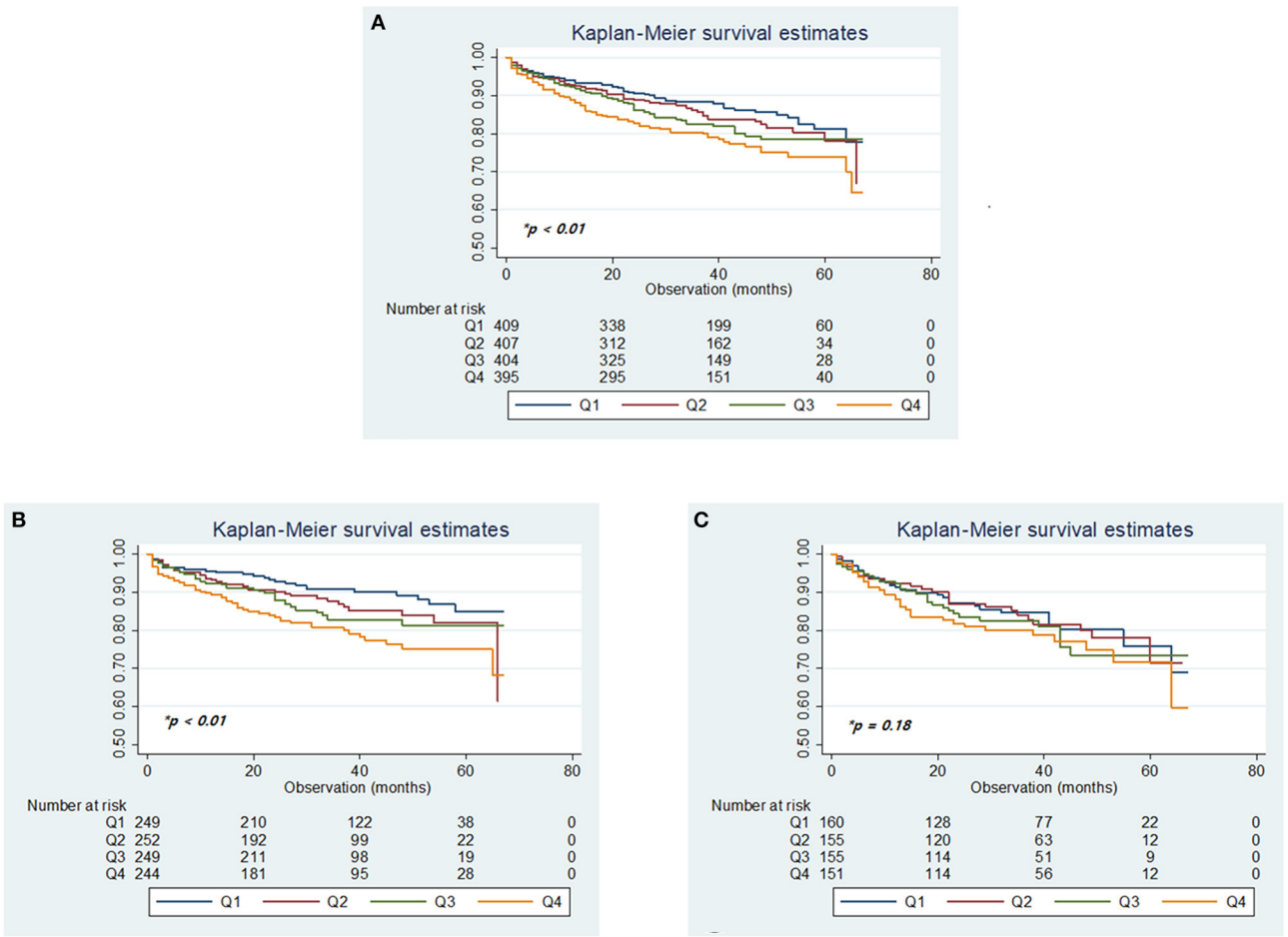

FIGURE 3 | Kaplan–Meier plots of overall survival according to the quartiles of QTc intervals in the total cohort **(A)**, in men **(B)**, and women **(C)**. *p-values determined using the log-rank test.

interval and the burden of cardiac and neurological conditions gradually increased with age. However, the sex-related gap of QTc interval in each age group remained consistent, although it tended to narrow gradually with age, despite the absence of significant sex difference in cardiac and neurological burdens (**Figure 4**).

DISCUSSION

This study found that the baseline QTc interval in patients with AIS was associated with the cumulative burden of cardiac comorbidities and the severity of the stroke, as well as with long-term mortality. The median QTc interval in the total cohort of 1,668 patients with a mean age of 66.0 ± 12.4 years and men predominance (61.1%) was 460.5 ms (IQR 434, 487 ms) and was normally distributed. Despite the heterogeneity in patient characteristics and the cut-off values for defining QTc interval prolongation, these results were in good agreement with a systematic review of ECG changes in patients with acute stroke (7): QTc was prolonged in at least 25% of stroke patients, such as those with hemorrhagic and ischemic stroke, and has been reported in 23–45% of patients with AIS, constituting the most frequent single ECG abnormality.

In this study, the highest quartile of the QTc interval prolongation was associated with the long-term mortality and the highest septile of QTc interval as dichotomized QTc interval prolongation was significantly associated with the long-term mortality even across stroke severity, performing better performance than other cut-off values. A meta-analysis that included multiple studies found that QTc interval > 450 ms was significantly associated with all-cause and coronary heart disease mortality in general populations despite methodological heterogeneity across studies (26). Moreover, a prolonged QT interval in patients with acute stroke was associated with a significantly greater risk of all-cause mortality within 3 months (27). The prognostic significance of prolonged QTc interval may be attributable to an increased risk of fatal or non-fatal sustained arrhythmia, as well as representing the dysregulation of the autonomic nervous system that contributes to long-term atherosclerotic changes in multiple vessels (23, 28). However,

TABLE 2 | Annual incidence rate and unadjusted and adjusted hazard ratios for quartiles of sex-specific QTc intervals predicting clinical outcomes during the 6-year follow-up period.

Quartiles*			Unadjusted		Adjusted**		Adjusted†	
	Number of events	Incidence, %/year	HR	95% CI	HR	95% CI	HR	95% CI
Total cohort								
Q1	63/416 (15.1)	4.7	Reference		Reference		Reference	
Q2	72/418 (17.2)	6.1	1.22	0.87–1.71	1.16	0.82–1.65	1.17	0.82–1.66
Q3	82/418 (19.6)	7.2	1.43	1.03–1.98	1.01	0.71–1.44	0.91	0.64–1.31
Q4	106/416 (25.5)	9.7	1.89	1.39–2.59	1.49	1.07–2.08	1.18	0.84–1.66
P for trend[a]			< 0.01		0.04		0.60	
Male patients								
Q1	31/254 (12.2)	3.8	Reference		Reference		Reference	
Q2	37/255 (14.5)	5.2	1.27	0.79–2.05	1.19	0.72–1.96	1.15	0.70–1.92
Q3	45/255 (17.6)	6.2	1.54	0.98–2.44	1.16	0.70–1.90	1.06	0.64–1.76
Q4	61/254 (24.0)	8.9	2.18	1.42–3.36	1.60	0.99–2.57	1.16	0.71–1.90
P for trend[a]			< 0.01		0.06		0.65	
Female patients								
Q1	32/162 (19.8)	6.4	Reference		Reference		Reference	
Q2	35/163 (21.5)	7.7	1.18	0.73–1.91	1.14	0.69–1.90	1.23	0.74–2.04
Q3	37/163 (22.7)	9.1	1.33	0.83–2.14	0.86	0.50–1.47	0.81	0.48–1.38
Q4	45/162 (27.8)	11.1	1.63	1.03–2.56	1.39	0.85–2.28	1.18	0.71–1.96
P for trend[a]			0.03		0.34		0.82	

**QTc cut-off points between quartiles 1 and 2, 2 and 3, and 3 and 4 were 427, 453, and 479 msec, respectively, for men and 444, 469, and 498 msec, respectively, for women. CI, confidence interval; HR, hazard ratio.*

***Model 1, adjusted for age, sex, conventional risk factors, comorbidities, and all laboratory results.*

† Model 2, adjusted for all variables in model 1 plus the NIHSS score.

[a] P for trend values were calculated by treating quartiles of sex-specific QTc as continuous variables.

studies that included a large number of individuals undergoing medical screening found that QTc in the general population conforms to a normal Gaussian normal distribution and suggest the abnormal QTc values longer than the 97.5th percentile (i.e., >440–450 ms in men and >460 ms in women) (29). In the present study, the mean QTc interval was almost 50 ms longer than the range of QTc intervals in normal populations, a difference that may be attributed to the older age and greater burden of cardiac comorbidities and neurological stress as well as medications contributing QTc interval prolongation in stroke patients than in normal populations. Thus, an appropriate cut-off value defining QTc prolongation in stroke patients should, therefore, be higher than in a normal population.

The present study also found that the quartiles of QTc interval were related to the burdens of cardiac and neurological conditions and the crude incidence of all-cause death, regardless of sex. QTc interval prolongation represents a delay in ventricular repolarization and is associated with various etiologies, such as VH, IHD, certain drugs, dyselectrolytemia, hypertension, diabetes, and stroke (30). QTc interval prolongation also indicates a dysregulated autonomic nervous system, which leads to long-term atherosclerotic changes in systematic vessels and increases the risks of cerebro-cardiovascular diseases and mortality (31). Similarly, abrupt induction of autonomic dysregulation resulting from over-activity of the sympathetic nervous system during acute stroke may prolong QTc interval in patients with AIS (32). Alternatively, direct neuronal effects mediated by the central nervous system *via* neuron endings on the heart or coexisting cardiac abnormalities may also play a role (16, 23). Thus, a prolonged QTc interval may reflect both the direct and indirect cerebral effects on preexisting cardiac comorbidities and can be regarded as a surrogate for cardiovascular and cerebrovascular risk profiles in patients with AIS. Furthermore, our study revealed no significant difference in the proportion of medications affecting the QTc interval among the different quartiles of the QTc interval (**Table 3**), which can reduce the risk of heterogeneity of our results.

The disproportionate age distribution observed in our patients was affected by sex differences, as well as affecting QTc interval and clinical characteristics in patients with stroke. The present study found that women patients were older, had a higher cardiac and neurological burden than men patients, with QTc interval being more prolonged in women than men pa gap of 20 ms in QTc interval. This finding was in agreement with the previous studies showing sex gaps of 6–10 ms in older age groups and 12–15 ms in younger adults (17), with the gap narrowing after age 40 years (29). However, we observed no sex difference in cardiac and neurological burdens across age groups. These findings confirm that QTc interval can be regarded as a surrogate for cardiovascular and cerebrovascular

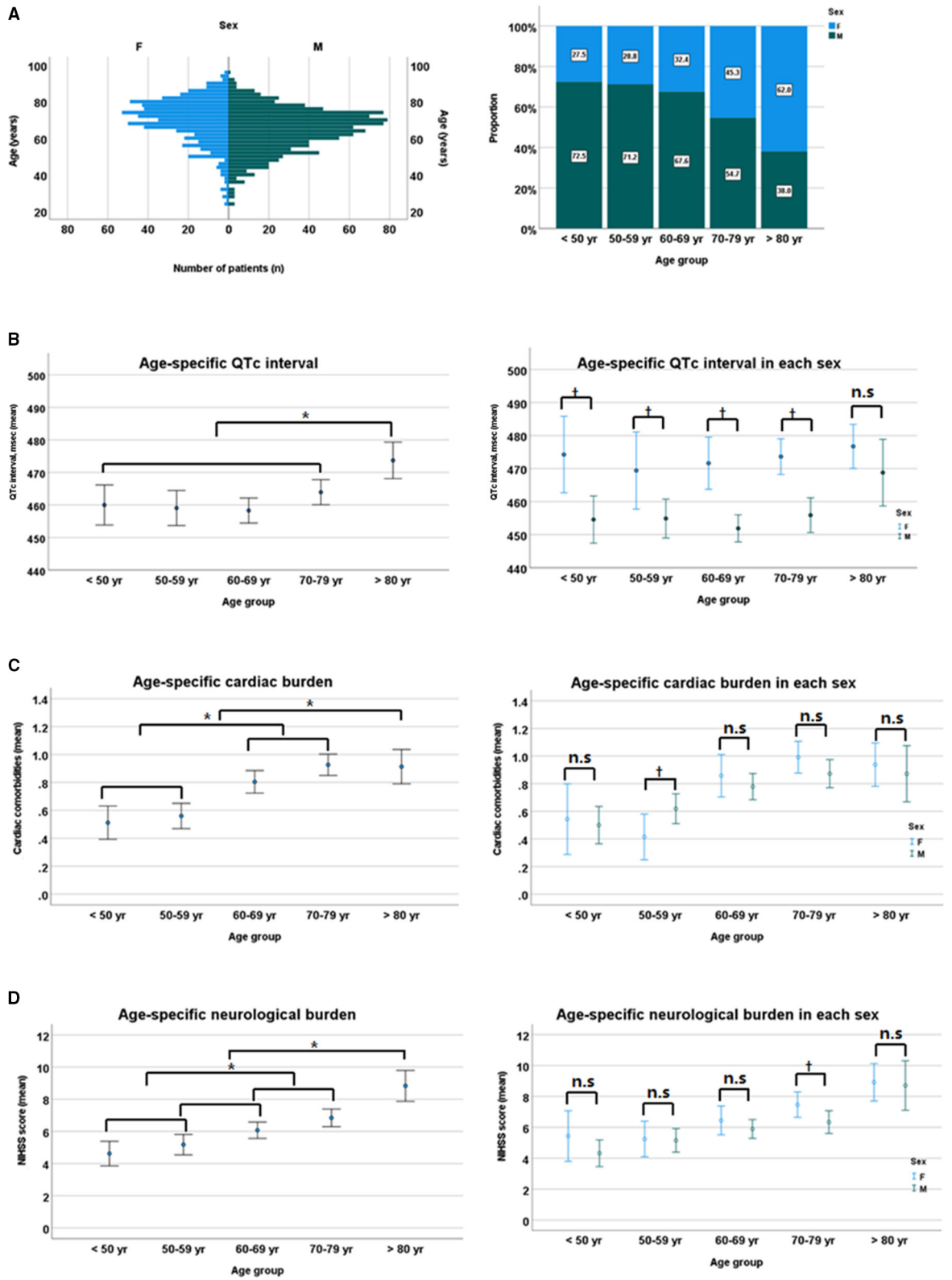

FIGURE 4 | Sex-specific age distribution **(A)**, sex differences in QTc intervals **(B)**, cardiac burden **(C)**, and neurological burden **(D)**. NIHSS, National Institutes of Health Stroke Scale. *$p < 0.05$ by ANOVA with Duncan *post-hoc* test according to age group. †$p < 0.05$ by Student *t*-test between sexes in each age group. n.s, non specific.

TABLE 3 | Medications affecting QTc interval according to the quartiles of the QTc interval.

Variable	Quartiles of QTc interval				*P*-value[†]
	Q1 ($n = 416$)	Q2 ($n = 418$)	Q3 ($n = 418$)	Q4 ($n = 416$)	
QTc interval prolongation					
ACEIs or ARBs	119 (28.6)	130 (31.1)	134 (32.1)	118 (28.4)	0.57
Calcium channel blockers	111 (26.7)	109 (26.1)	112 (26.8)	126 (30.3)	0.51
Beta blockers	76 (18.3)	63 (15.1)	73 (17.5)	72 (17.3)	0.65
Digoxin	12 (2.9)	12 (2.9)	13 (3.1)	14 (3.4)	0.97
Other QTc interval prolonging drugs*	57 (13.7)	54 (12.9)	65 (15.6)	62 (14.9)	0.70
Anti-QTc interval prolongation (33)					
Statin	69 (16.6)	83 (19.9)	85 (20.3)	86 (20.7)	0.42

Variables are presented as number (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[*] QTc interval prolonging drugs determined by the Anatomical Therapeutic Chemical (ATC) code include cilostazol (B01AC23), domperidone (A03FA03), flecainide (C01BC04), amiodarone (C01BD01), sotalol (C07AA07), nicardipine (C08CA04), solifenacin (G04BD08), azithromycin (J01FA10), ofloxacin (J01MA01), ciprofloxacin (J01MA02), tamoxifen (L02BA01), tacrolimus (L04AD02), tizanidine (M03BX02), amantadine (N04BB01), quetiapine (N05AH04), lithium (N05AN01), risperidone (N05AX08), fluoxetine (N06AB03), citalopram (N06AB04), sertraline (N06AB06), escitalopram (N06AB10), galantamine (N06DA04), imipramine (N06AA02, N06AA02), amitriptyline (N06AA09), and diphenhydramine (R06AA02), as listed at www.qtdrugs.org.

[†] p-values were calculated by Pearson chi-square test.

risk profiles, and eventually for long-term mortality, across the sex and age distribution.

Limitations

This study had several limitations. First, the study was performed in a single center, which may reduce its generalizability. In addition, we were unable to determine non-fatal long-term outcomes, such as major adverse cerebro-cardiovascular events (MACCE), because follow-up information about patients was obtained using the national death certificate data from the Korean National Statistical Office. However, this study enrolled all consecutive patients with AIS within 24 h of stroke onset without excluding patients with concomitant cardiac comorbidities or those taking a wide range of medications contributing QTc prolongation. Thus, our results reflect a real-world clinical situation of QTc interval changes in AIS patients. Second, the mechanism underlying QTc interval prolongation remains tentative because ECG was performed at single time points, not overtime. Furthermore, major cardiac and non-cardiac comorbidities were defined as the previous history and/or ECG results at admission, thus possibly underestimating subclinical conditions. In addition, the contribution of each cardiac and non-cardiac condition to QTc interval prolongation is not equally the same, thus a composite term of "cardiac and neurological burdens" is rather an arbitrary one. To overcome these problems, we are currently conducting a prospective trial with serial measurements of troponin and ECG in patients with AIS (Clinical implications of elevated cardiac troponin-I elevation in acute stroke patients; KCT0000682; https://cris.nih.go.kr/cris), which reveal serial changes in QTc intervals and their relationship to major adverse cerebro-cardiovascular events in patients with AIS, as well as the value of troponin (34). Furthermore, this prospective study includes measurements of disease-specific biomarkers such as AF, IHD, and VH, and ECG performed three times during hospitalization to improve the detection rate of cardiac comorbidities. Finally, various medications that contribute to QTc interval should be adjusted, with consideration of the dosage and duration of medication. However, the contribution of representative medications to QTc interval did not differ significantly across the quartiles of QTc intervals in our study.

Conclusions

Prolonged QTc interval was associated with the increased risk of long-term mortality, in parallel with the increasing trend of the prevalence of cardiovascular risk profiles and stroke severity, across sex differences, such as different distributions of age, comorbidities, morality, and QTc intervals in AIS patients.

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 study protocol was approved by the Institutional Review Board of the Asan Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-HA contributed to the study concept, study design, data analysis and interpretation, and drafting and revising the manuscript. J-SL and M-SY contributed to the conception of

the study, data analysis, and statistics. Y-HK, M-GP, and K-PP contributed to the conception of the study, data analysis, and acquisition of clinical data. M-SY, J-HH, and S-YK contributed to the conception of the study, data analysis, and acquisition of clinical data. D-WK and JK contributed to the conception of the study, data analysis, and acquisition of clinical and imaging data. SK contributed to the study concept, study design, analysis and interpretation of the imaging and clinical data, drafting and revising the manuscript, and study supervision. All authors contributed to the article and approved the submitted version.

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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.2021.759822/full#supplementary-material

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Atrial Fibrillation Is Not an Independent Determinant of Mortality Among Critically Ill Acute Ischemic Stroke Patients: A Propensity Score-Matched Analysis From the MIMIC-IV Database

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Background/Objective: This study was conducted to investigate the clinical characteristics and outcomes of patients with acute ischemic stroke and atrial fibrillation (AF) in intensive care units (ICUs).

Methods: In the Medical Information Mart for Intensive Care IV database, 1,662 patients with acute ischemic stroke were identified from 2008 to 2019. Of the 1,662 patients, 653 had AF. The clinical characteristics and outcomes of patients with and without AF were compared using propensity score matching (PSM). Furthermore, univariate and multivariate Cox regression analyzes were performed.

Results: Of the 1,662 patients, 39.2% had AF. The prevalence of AF in these patients increased in a stepwise manner with advanced age. Patients with AF were older and had higher Charlson Comorbidity Index, CHA2DS2-VASc Score, HAS-BLED score, and Acute Physiology Score III than those without AF. After PSM, 1,152 patients remained, comprising 576 matched pairs in both groups. In multivariate analysis, AF was not associated with higher ICU mortality [hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.64–1.42] or in-hospital mortality (HR, 1.08; 95% CI, 0.79–1.47). In Kaplan–Meier analysis, no difference in ICU or in-hospital mortality was observed between patients with and without AF.

Conclusions: AF could be associated with poor clinical characteristics and outcomes; however, it does not remain an independent short-term predictor of ICU and in-hospital mortality among patients with acute ischemic stroke after PSM with multivariate analysis.

Keywords: ischemic stroke (IS), atrial fibrillation, intensive care unit (ICU), MIMIC-IV, propensity score matching (PSM)

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INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide (1). Approximately 90% of stroke cases are ischemic stroke, resulting from arterial occlusion (2). The incidence of stroke increases with age, especially in low- and middle-income countries (3). A major cause of ischemic stroke is thrombosis and embolism from atherosclerotic plaque or from the heart. Compared with other mechanisms of ischemic stroke, patients with atrial fibrillation (AF), a specific risk factor for ischemic stroke, have worse clinical and imaging outcomes (4).

AF is the most prevalent chronic cardiac arrhythmia in the elderly with a reported prevalence of 1–2% in the general population (5, 6). Meanwhile, AF is a major cause of cardioembolic stroke, and patients with AF have a 4–5-fold higher risk of ischemic stroke than the general population (7). Presently, once the diagnosis of AF is made, oral anticoagulation treatment, such as apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin, is recommended to reduce the risk of recurrent stroke, regardless of AF pattern according to the American Heart Association/American Stroke Association guidelines for preventing stroke in 2021 (2).

In a study, the long-term burden of AF resulted in complications, such as stroke, heart failure, and death (8). In another study by Saposnik et al., patients with ischemic stroke and AF had a higher risk of death and intracerebral hemorrhage than those without AF (9). However, some studies have shown that AF is not a predictor of mortality after adjustment using multivariable models (10). Older age and high stroke severity are factors explaining the association between AF and poorer outcomes after acute ischemic stroke (11). Additionally, the prevalence of AF increases by up to 25% for individuals aged more than 80 years (2, 12). A similar pattern was observed among critically ill patients in the intensive care unit (ICU) (13). However, whether AF in patients with stroke admitted to the ICU is associated with poor clinical outcomes remains unclear.

The inconsistency might be due to differences in settings or study designs. Besides, no studies have been conducted involving ICU patients, who had a higher prevalence of AF (14). We believe that using propensity score matching (PSM) presents a more authentic result of whether AF is an independent risk factor for mortality. Therefore, we conducted a retrospective study with PSM using detailed clinical data obtained from the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-IV) database to investigate the relationship between AF and the characteristics and clinical outcomes of patients with acute ischemic stroke who were admitted to the ICU.

METHODS

Study Population and Data Source

We conducted a retrospective study based on the MIMIC-IV database (version 1.0) (15). This database is an updated version of MIMIC-III with preexisting Institutional Review Board approval (Massachusetts Institute of Technology, no. 0403000206; Beth Israel Deaconess Medical Center, 2001P001699) (16). Several improvements have been made, including simplifying the structure, adding new data elements, and improving the usability of previous data elements. Currently, the MIMIC-IV contains comprehensive and high-quality and de-identified data of patients admitted to the ICU or emergency department of the Beth Israel Deaconess Medical Center between 2008 and 2019. One author who has finished the Collaborative Institutional Training Initiative examination (certification number: 39050603 for author Jhou) can access the database and was responsible for data extraction.

Study Population and Variable Extraction

The patients were identified in the MIMIC-IV database from 2008 to 2019. The inclusion criteria were as follows: adult patients (age, 18–89 years) with ischemic stroke, defined as ICD-9 codes of 433, 434, 436, 437.0, and 437.1 or ICD-10 codes of I63, I65, and I66. Patients with ischemic stroke who received acute reperfusion therapy, such as intravenous tissue plasminogen activator or endovascular mechanical thrombectomy were also enrolled in our analysis (17). The exclusion criteria were as follows: patients who were admitted to the ICU more than once, only data on the first ICU admission were recorded and used. The patients enrolled in this study were subsequently divided into the AF and non-AF groups.

The following baseline characteristics were identified: hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, peptic ulcer disease, chronic kidney disease, rheumatoid arthritis, dementia, malignancy, Acute Physiology Score III (APS III), CHA2DS2-VASc score, and HAS-BLED score (**Supplementary Tables 1**, **2**) (18). The overall Charlson Comorbidity Index (CCI) encompassed 18 categories of medical conditions, which were identifiable in medical records (**Supplementary Table 3**) (19–21). Secondary prevention agents for ischemic stroke were also recorded and used, including antiplatelet agents (e.g., aspirin, clopidogrel, cilostazol, ticlopidine, ticagrelor, prasugrel, and dipyridamole) and anticoagulation agents (e.g., warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban). Other clinical indicators included mean arterial pressure, heart rate, body temperature, saturation of peripheral oxygen, leukocyte count, hemoglobin, platelet, creatinine, blood urea nitrogen, sodium, potassium, and bilirubin within 24 h of ICU admission. When the aforementioned indicators had multiple results within 24 h, the worst value was recorded and used for the analysis.

Outcome Measures

The major outcomes were ICU mortality and in-hospital mortality. The minor outcomes included the use of percutaneous endoscopic gastrostomy or jejunostomy tube placement and the complications of intracerebral hemorrhage.

Statistical Analysis

Categorical variables were represented as number (percentage) and were compared using the chi-square test and Fisher's exact test. Continuous variables were described as means (standard deviation) and were compared using the independent samples *t*-tests or Wilcoxon rank-sum test

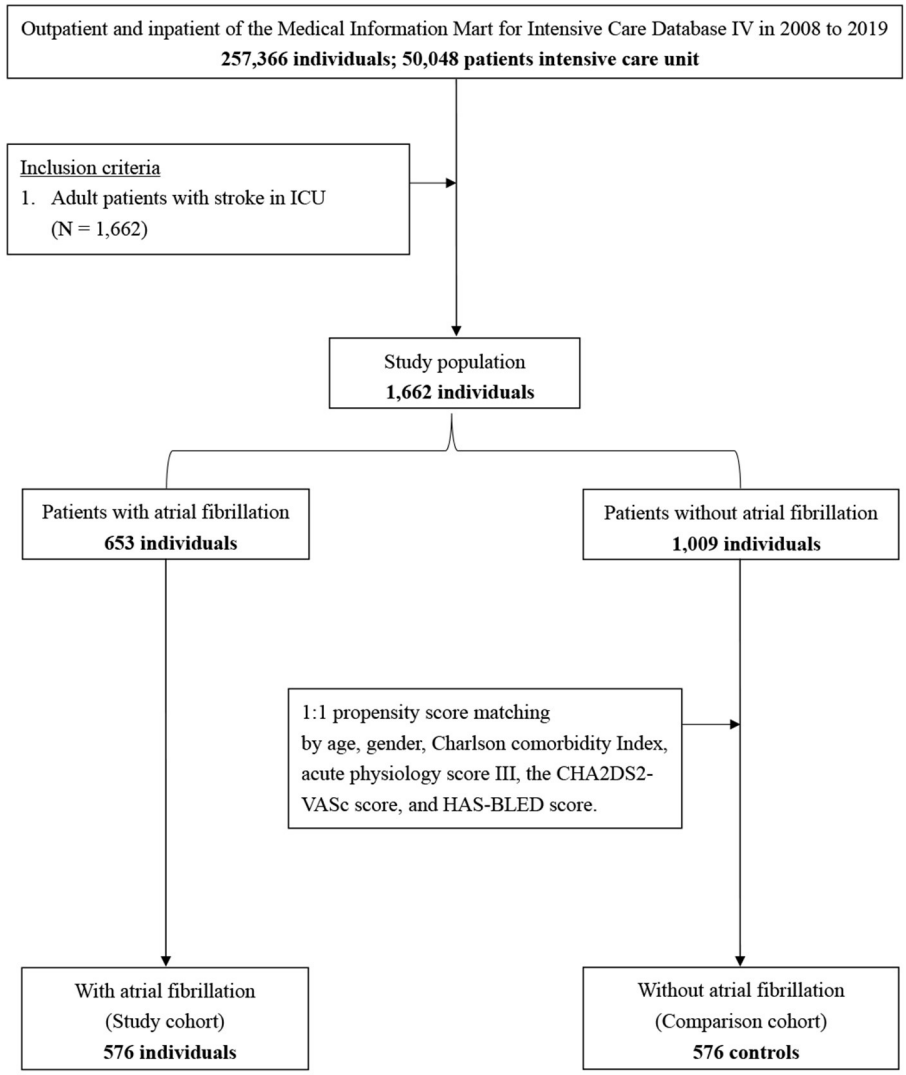

FIGURE 1 | Flowchart of study sample selection from the Medical Information Mart for Intensive Care IV database.

(Mann–Whitney U-test). Missing values of each subjects were not defaulted to negative, and denominators were only reported cases.

Propensity scores were calculated involving the following preoperative variables: age, sex, CCI, APS III, CHA2DS2-VASc score, and HAS-BLED score. A logistic regression model was developed to estimate the patients' propensity scores for the AF group (22). PSM was performed using the Greedy 5-to-1 Digit-Matching algorithm between the AF and non-AF groups (23). In propensity-matched patients, univariate analyzes were conducted using the paired *t*-test or Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Statistical testing was performed to evaluate the effectiveness of PSM. Both primary and secondary outcomes were compared based on the matched data. Sensitivity analysis was performed using the removal of new-onset AF (**Supplementary Table 4**).

For time-to-event outcomes, the major survival outcomes, the times that elapsed until the first event between the two groups were compared using the log-rank test, whereas the Kaplan–Meier method was used to estimate the absolute risk of each event for each group. Univariate and multivariate Cox hazards model analyzes were performed to identify the association between AF and major outcomes, and results were expressed as hazard ratio (HR) with 95% confidence interval (CI). The relationship between AF and minor outcomes was assessed using univariate and multivariate logistic regression analyzes, and results were expressed as odds ratio (OR) with 95% CI.

All comparisons were planned, the tests were 2-sided, and $p < 0.05$ were used to denote statistical significance. Statistical analyzes were performed using Statistical Package for the Social Sciences (version 25.0; IBM Corp., Armonk, NY, USA) and R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 | Characteristics of the study patients.

Characteristics	All patients			Propensity-matched pairs		
	AF group (*n* = 653)	Non-AF group (*n* = 1,009)	*P*-value	AF group (*n* = 576)	Non-AF group (*n* = 576)	*P*-value
Age (years)	75.52 ± 10.59	64.47 ± 14.56	<0.001	74.30 ± 10.58	73.11 ± 10.21	0.052
Gender, *n*			0.002			0.289
Male	312 (47.8%)	562 (55.7%)		283 (49.1%)	301 (52.3%)	
Female	341 (52.2%)	447 (44.3%)		293 (50.9%)	275 (47.7%)	
Race, *n*			0.035			0.012
White	414 (63.4%)	621 (61.5%)		369 (64.1%)	361 (62.7%)	
Black	51 (7.8%)	120 (11.9%)		41 (7.1%)	70 (12.2%)	
Asian	21 (3.2%)	25 (2.5%)		20 (3.5%)	15 (2.6%)	
Other	167 (25.6%)	165 (24.1%)		146 (25.3%)	130 (22.5%)	
MAP (mmHg)	96.27 ± 18.58	94.93 ± 17.83	0.142	96.56 ± 18.53	93.28 ± 18.19	0.003
Temperature (°C)	36.69 ± 0.61	36.78 ± 0.54	0.001	36.69 ± 0.60	36.77 ± 0.57	0.035
Heart rate (beats/minute)	83.94 ± 20.22	78.51 ± 15.82	<0.001	83.66 ± 19.95	78.37 ± 16.24	<0.001
SpO_2 (%)	97.23 ± 2.96	97.33 ± 2.79	0.501	97.27 ± 2.89	97.07 ± 3.14	0.250
Comorbidities, *n*						
CCI	7.66 ± 2.30	6.35 ± 2.64	<0.001	7.54 ± 2.31	7.37 ± 2.45	0.230
Hypertension	484 (74.1%)	722 (71.6%)	0.253	423 (73.4%)	453 (78.6%)	0.038
Hyperlipidemia	166 (25.4%)	200 (19.8%)	0.007	145 (25.2%)	127 (22.0%)	0.212
Diabetes mellitus						
Without chronic complication	175 (26.8%)	272 (27.0%)	0.943	153 (26.6%)	167 (29.0%)	0.357
With chronic complication	44 (6.7%)	86 (8.5%)	0.186	38 (6.6%)	67 (11.6%)	0.003
Coronary artery disease	89 (13.6%)	110 (10.9%)	0.094	82 (14.2%)	77 (13.4%)	0.669
Congestive heart failure	202 (30.9%)	117 (11.6%)	<0.001	167 (29.0%)	75 (13.0%)	<0.001
PVD	68 (10.4%)	122 (12.1%)	0.294	59 (10.2%)	65 (11.3%)	0.568
COPD	120 (18.4%)	158 (15.7%)	0.147	109 (18.9%)	103 (17.9%)	0.648
Liver disease						
Mild	21 (3.2%)	24 (2.4%)	0.304	19 (3.3%)	8 (1.4%)	0.032
Moderate to severe	3 (0.5%)	5 (0.5%)	1.000[#]	3 (0.5%)	3 (0.5%)	1.000[#]
Peptic ulcer disease	10 (1.5%)	7 (0.7%)	0.097	7 (1.2%)	5 (0.9%)	0.562
Chronic kidney disease	120 (18.4%)	118 (11.7%)	<0.001	93 (16.1%)	96 (16.7%)	0.811
Rheumatoid disease	13 (2.0%)	27 (2.7%)	0.373	11 (1.9%)	20 (3.5%)	0.101
Dementia	37 (5.7%)	34 (3.4%)	0.024	28 (4.9%)	32 (5.6%)	0.596
Malignancy	41 (6.3%)	66 (6.5%)	0.831	37 (6.4%)	47 (8.2%)	0.257
Laboratory parameters						
WBC (10^9/L)	10.14 ± 3.78	10.13 ± 4.59	0.938	10.15 ± 3.82	10.21 ± 4.77	0.821
Hgb (g/dL)	12.23 ± 2.23	12.38 ± 2.08	0.187	12.30 ± 2.20	12.13 ± 2.07	0.172
Platelet (10^9/L)	222.96 ± 86.57	235.45 ± 91.12	0.006	222.13 ± 82.68	228.18 ± 82.30	0.225
Creatinine (mEq/L)	1.11 ± 0.96	1.03 ± 0.82	0.062	1.09 ± 0.98	1.10 ± 0.96	0.863
BUN (mg/dL)	21.07 ± 12.52	17.80 ± 11.57	<0.001	20.36 ± 12.19	20.42 ± 13.48	0.941
Sodium (mmol/L)	139.31 ± 4.25	139.34 ± 3.63	0.895	139.25 ± 4.10	139.35 ± 3.92	0.672
Potassium (mmol/L)	4.10 ± 0.60	4.03 ± 0.54	0.008	4.09 ± 0.58	4.06 ± 0.57	0.270
Bilirubin (mg/dL)	0.71 ± 0.51	0.60 ± 0.67	0.010	0.70 ± 0.50	0.61 ± 0.45	0.016
Drugs, *n*						
Anti-platelet agents	469 (71.8%)	876 (86.8%)	<0.001	413 (71.7%)	499 (86.6%)	<0.001
Anti-coagulation agents						
Warfarin	168 (16.7%)	168 (16.7%)	<0.001	193 (33.5%)	68 (11.8%)	<0.001
NOAC	78 (11.9%)	17 (1.7%)	<0.001	75 (13.0%)	6 (1.0%)	<0.001
tPA or EVT	123 (27.3%)	140 (20.7%)	0.009	160 (27.8%)	116 (20.1%)	0.002
CHA2DS2-VASc score	5.49 ± 1.37	4.60 ± 1.51	<0.001	5.38 ± 1.36	5.27 ± 1.38	0.169
HAS-BLED score	4.02 ± 0.93	3.53 ± 0.92	<0.001	3.95 ± 0.93	3.93 ± 0.80	0.634

(Continued)

TABLE 1 | Continued

Characteristics	All patients			Propensity-matched pairs		
	AF group ($n = 653$)	Non-AF group ($n = 1,009$)	*P*-value	AF group ($n = 576$)	Non-AF group ($n = 576$)	*P*-value
APS III	44.27 ± 20.11	35.77 ± 17.34	<0.001	42.40 ± 19.24	40.79 ± 18.69	0.148
ICU mortality, *n*	75 (11.5%)	65 (6.4%)	<0.001	59 (10.2%)	50 (8.7%)	0.365
ICU length of stay, day	4.90 ± 6.61	3.91 ± 4.55	<0.001	4.82 ± 6.58	3.87 ± 4.74	0.005
In-hospital mortality, *n*	125 (19.1%)	102 (10.1%)	<0.001	95 (16.5%)	85 (14.8%)	0.417
Hospital length of stay, day	9.26 ± 10.06	7.39 ± 8.43	<0.001	9.15 ± 10.08	7.36 ± 8.79	0.001
Intracranial hemorrhage, *n*	110 (16.8%)	86 (8.5%)	<0.001	90 (15.6%)	53 (9.2%)	0.001
PEG/PEJ tube placement, *n*	113 (17.3%)	95 (9.4%)	0.001	99 (17.2%)	57 (9.9%)	<0.001

Propensity score matching by age, sex, Charlson comorbidity Index, acute physiology score III, the CHA2DS2-VASc score, and HAS-BLED score.
APS III, acute physiology score III; BPM, beats per minute; BUN, blood urea nitrogen; CCI, Charlson comorbidity Index; COPD, chronic obstructive pulmonary disease; Hgb, hemoglobin; MAP: mean arterial pressure; NOAC, novel oral anticoagulant; PVD, Peripheral vascular disease; SpO_2, saturation of peripheral oxygen; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; WBC, white blood cell.
[#]*Testing by Fisher exact test or Wilcoxon Test, respectively.*

RESULTS

Patient Characteristics

Of the 257,366 medical records reviewed, 50,048 patients were admitted to the ICU. During the study period, we enrolled 1,662 patients with stroke, including 653 patients with AF and 1,009 patients without AF (**Figure 1**). There were 15 new-onset AF of those without history of AF (1.46%, 15/1,024). The basic demographic characteristics of the patients are shown in **Table 1**. The mean age of the AF and non-AF groups were 75.52 and 64.47 years, respectively. The prevalence of AF increased in a stepwise manner with advancing age, from 7.8% in those aged 50 years or younger to 63.5% in those older than 80 years (**Figure 2**). The AF group had higher CCI (7.66 vs. 6.35; $p < 0.001$), CHA2DS2-VASc score (5.49 vs. 4.60; $p < 0.001$), HAS-BLED score (4.02 vs. 3.53; $p < 0.001$), and APS III (44.27 vs. 35.77; $p < 0.001$) and had more comorbidities, including hyperlipidemia (25.4% vs. 19.8%; $p = 0.007$), congestive heart failure (30.9% vs. 11.6%; $p < 0.001$), chronic kidney disease (18.4% vs. 11.7%; $p < 0.001$), and dementia (5.7% vs. 3.4%; $p = 0.024$) (**Table 1**).

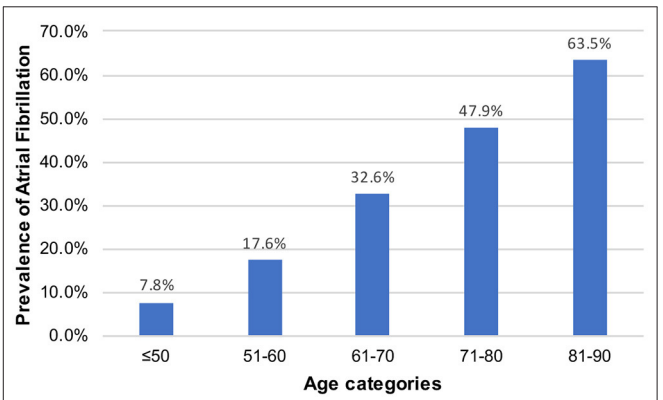

FIGURE 2 | Prevalence of atrial fibrillation.

Post-PSM Characteristics

Propensity scores were calculated involving the following covariates: age, sex, CCI, APS III, CHA2DS2-VASc score, and HAS-BLED score. After 1:1 PSM, 576 pairs in each arm remained. The cohorts were well-balanced based on six covariates between the AF and non-AF groups (**Figure 3**).

Kaplan–Meier Survival Curve of Primary Outcomes Between the AF and Non-AF Groups

The AF group had a higher risk of ICU mortality (11.5% vs. 6.4%; $p < 0.001$) and in-hospital mortality (19.1% vs. 10.1%; $p < 0.001$) than the non-AF group (**Table 1**). The Kaplan–Meier curves for ICU discharge and survival between the AF and non-AF groups are shown in **Figures 4A,B**, and both of these curves were significantly different. However, no difference in hospital discharge and survival was observed between patients with and without AF (**Figures 4C,D**). Survival was followed until hospital discharge, and the longest length of hospital stay was 88 days.

Outcome Measurement

In the cohort before PSM, univariate Cox regression analysis revealed significant difference in ICU mortality (crude HR, 1.43; 95% CI, 1.03–2.00) and in-hospital mortality (crude HR, 1.61; 95% CI, 1.24–2.09); furthermore, patients with AF had a higher risk of intracerebral hemorrhage (crude OR, 2.17; 95% CI, 1.61–2.94) and percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ) placement before PSM (crude OR, 2.01; 95% CI, 1.50–2.70).

After PSM, the results of univariate Cox regression analysis showed that AF was not associated with higher ICU mortality (HR, 0.94; 95% CI, 0.64–1.37) and in-hospital mortality (crude

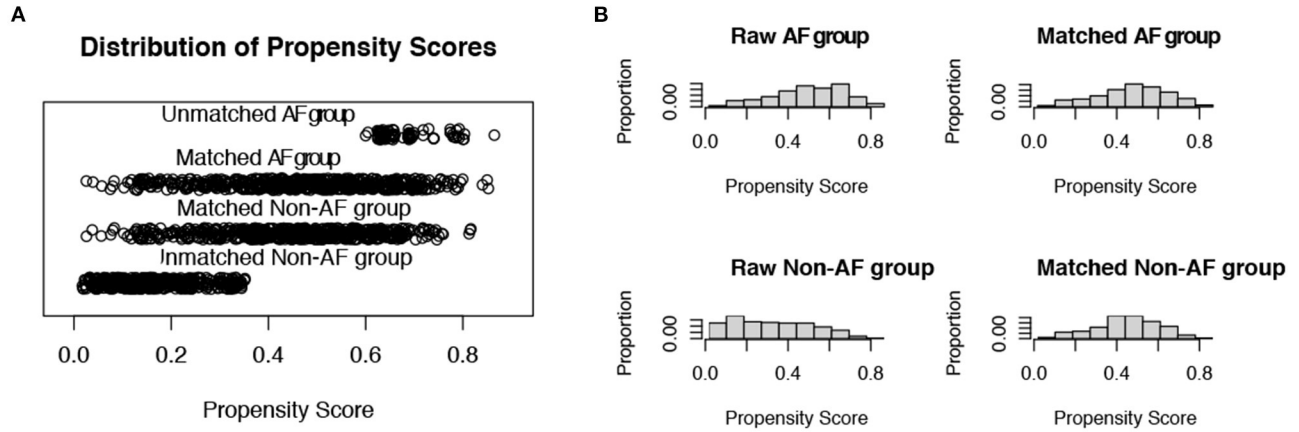

FIGURE 3 | Distribution of propensity scores. **(A)** Jittered plot presenting matched and unmatched subjects, and their distribution of propensity score values; **(B)** Histograms demonstrating the density of propensity score distribution in the atrial fibrillation group and the non-atrial fibrillation group before and after matching. AF, atrial fibrillation.

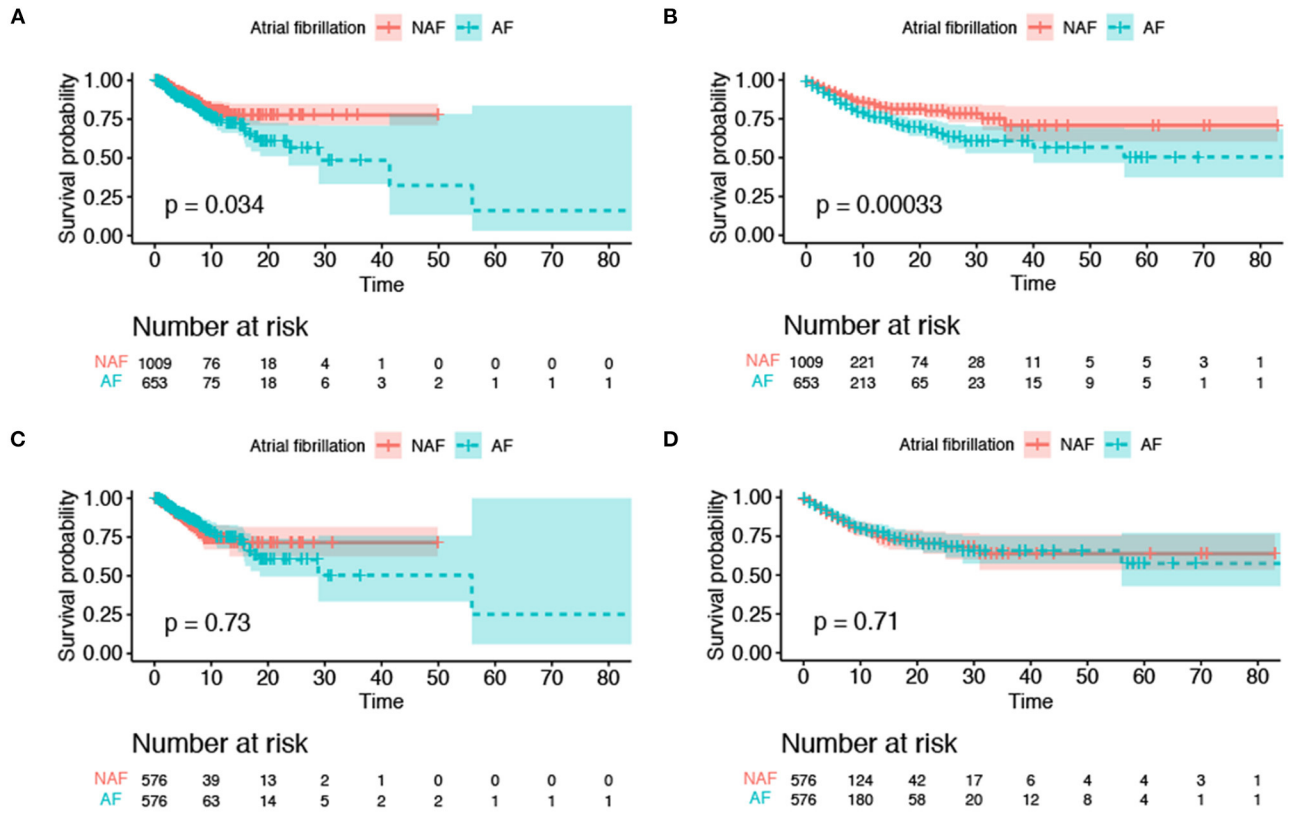

FIGURE 4 | Kaplan–Meier survival curves for survival to intensive care unit discharge and hospital discharge. **(A)** ICU mortality before propensity score matching; **(B)** in-hospital mortality before propensity score matching; **(C)** ICU mortality after propensity score matching; **(D)** in-hospital mortality after propensity score matching. The colored area was the standard deviation. ICU, intensive care unit.

HR, 0.95; 95% CI, 0.71–1.27). In minor outcomes, patients with AF remained a higher risk of intracranial hemorrhage and PEG/PEJ tube placement with crude ORs of 1.83 (95% CI, 1.27–2.62) and 1.89 (95% CI, 1.33–2.68), respectively.

After multivariate analysis, after adjusting for race, hypertension, congestive heart failure, liver disease, diabetes, anti-platelet agents, anti-coagulation agents, intravenous tissue plasminogen activator or endovascular mechanical

TABLE 2 | Association between outcomes and atrial fibrillation among patients with ischemic stroke.

Outcomes	With atrial fibrillation vs. Without atrial fibrillation (Reference)					
	Before PSM—Univariate		After PSM—Univariate		After PSM—Multivariate	
	Crude HR (95% CI)	*P*-value	Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)[#]	*P*-value
ICU Mortality	1.43 (1.03–2.00)	0.035	0.94 (0.64–1.37)	0.733	0.95 (0.64–1.42)	0.806
In-hospital Mortality	1.61 (1.24–2.09)	<0.001	0.95 (0.71–1.27)	0.713	1.08 (0.79–1.47)	0.630

Propensity score matching by age, sex, Charlson comorbidity Index, acute physiology score III, the CHA2DS2-VASc score, and HAS-BLED score.
HR, hazard ratio; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.
[#]All results of OR were adjusted by race, coronary artery disease, congestive heart failure, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, rheumatic arthritis, peptic ulcer disease, liver disease, diabetes, renal disease, paraplegia, malignancy, metastatic solid tumor, anti-platelet agents, anti-coagulation agents.

thrombectomy, no differences in ICU mortality (adjusted HR, 0.95; 95% CI, 0.64–1.42), in-hospital mortality (adjusted HR, 1.08; 95% CI, 0.79–1.47). However, the risk of intracerebral hemorrhage (adjusted OR, 1.96; 95% CI, 1.31–2.92), and PEG or PEJ tube placement before PSM (adjusted OR, 1.76; 95% CI, 1.19–2.60) remained higher among patients with AF than those without AF. The results were shown in **Table 2**. In the sensitivity analyses, we noted the similar findings before and after PSM cohort, as well as adjusted PSM cohort (**Supplementary Table 4**).

DISCUSSION

In this study, we adapted the latest MIMIC-IV database, including medical records of ICU-admitted patients from 2008 to 2019, and used the PSM method for preprocessing data for causal inference. We demonstrated that AF might be a risk factor for ICU or in-hospital mortality among ICU patients with acute ischemic stroke, but it is incoherent through multivariate analysis. Furthermore, secondary outcome analysis demonstrated ICU patients with AF had higher risk of ICH or PEG/PEJ tube placement than those without AF.

Preexisting or new-onset AF is more common among critically ill patients in the ICU (13). The prevalence of AF has been underestimated due to difficulty detecting paroxysmal AF. The mean age of the patients in this study was 68.81 years, which is identical to that (63.9–76.2 years) in a previous study (24–27). The prevalence of AF increases markedly with increasing age (28). In a study from Swedish, the prevalence of AF in patients with ischemic stroke increased with age from 8.6% at <60 years to ≥50% at >90 years (29). This study showed a similar trend, indicating an adequate population representativeness. The prevalence increased in a stepwise manner with advancing age, from 7.8% in those aged 50 years or younger to 63.5% in those older than 80 years. We found an overall AF frequency of 39.3% among patients with ischemic stroke, which is higher than the range of 9.1–31% reported in other studies (10, 11, 30–33), and this may be due to prolonged electrocardiography monitoring and the development of new-onset AF under critical illness (34).

In the past, the prospective follow-up of the Framingham Study cohort failed to observe an association between AF at baseline and the subsequent risk of fatal stroke in 1983 (35). In the previous study conducted by Oxfordshire Community Stroke Project (36), which demonstrated that AF was associated with an increased risk of death within acute phase of stroke in 30 days outcome, however, those excess risk might be explained by the older age or more comorbidities, such as diabetes, in patients with AF. Otherwise, in the long-term prognosis, risk of death from all causes did not show any difference between AF and sinus rhythm group in the multiple regression analyses. Those results would be consistent with our study. Furthermore, investigators of the FINMONICA Stroke Register had analyzed stroke with AF from 1982 to 1992 (37); after simply adjusting with multivariate regression for age, sex, and comorbidities, they have concluded that AF is associated with higher mortality in patients with stroke. This study showed an accordant trend before preprocessing data using the PSM method.

However, the mortality of patients with stroke is influenced by several factors. The older the patients, the higher the prevalence of AF (38, 39). This study showed an identical tendency that the patients in the AF group had more comorbidities and were older than those in the non-AF group. Older patients with stroke have more disabling strokes and higher mortality rate (40, 41). Additionally, elderly people with AF are less likely to receive oral anticoagulation (OAC) therapy, which could substantially reduce the risk of death and severe disability after ischemic stroke in patients with AF (11, 42). This is mainly due to concerns on a higher risk of OAC-associated hemorrhage in the elderly population (43). Therefore, increased age has always been a factor for mortality after stroke. Moreover, differences in mortality after stroke between sexes might be another important issue, and women are reported to have greater mortality after stroke than men (44). Both the higher CHA2DS2-VASc and HAS-BLED scores were associated with and became significant predictors of mortality in patients with AF (45). The CCI score was independently associated with mortality after a cerebrovascular event, for example, ischemic stroke (46).

In this study, before preprocessing data, severe heterogeneity was observed between patients with and without AF; thus, we adapted the PSM method to eliminate the potential influence of confounding factors. Propensity scores have been proposed as a method for equating groups at baseline, especially in studies that do not use randomization. They can be thought of as a balancing score that, like random assignment, attempts to balance the distribution of these measured covariates between two groups (47). Hence, we adapted

the PSM method in age, sex, and scoring systems, including APS III, CHA2DS2–VASc, HAS-BLED, and CCI scores, to obtain a balanced distribution of generalized conditions and to eliminate heterogeneity between the two groups. Thus, we adjusted the detailed covariates between the compared groups using multivariate regression models to maximize the bias-reducing mechanism. After PSM and the development of multivariate regression models, no difference in mortality rate was found, indicating that age, sex, and comorbidities caused the misleading association between AF and a higher mortality rate.

Recently, Gattringer et al. have developed a simple score to estimate the early mortality of patients with ischemic stroke and found that AF, which was clearly associated with mortality in univariate analysis, did not remain an independent predictor of stroke-related mortality after multivariate analysis (48). Therefore, AF was no longer listed as one of the scoring items in predicting early mortality in patients with acute ischemic stroke.

Cerebral infarction weakens the blood–brain barrier, increasing the risk of spontaneous hemorrhage after acute ischemic stroke (49). As patients with the history of ischemic stroke use anticoagulants for secondary prevention, it reduces the risk of recurrent embolism (50). Several meta-analyses also showed that reperfusion therapy might have proportional benefits; however, the risk of fatal intracranial hemorrhage and reperfusion injury remain high during the first few days after treatment (51). In this study, patients with stroke and AF had a risk of intracerebral hemorrhage, even after PSM with adjustment of comorbidities, anticoagulants, and reperfusion therapy. Regarding disabilities after stroke, Alkhouli et al. have shown that patients with ischemic stroke with AF were more likely to undergo gastric tube placement than those without AF (52). Similar findings were observed in this study; moreover, in the matched groups with adjustment model, patients with ischemic stroke with AF also had a higher risk of PEG/PEJ tube placement.

Limitations and Strengths

The main strength of this study is its large-scale, diverse population study design using real-world data. However, the results should be interpreted in the context of the following limitations. First, the study design was retrospective, and the diagnosis of ischemic stroke relied solely on administrative diagnosis codes. We could not confirm the diagnostic accuracy by evaluating the patients directly. Therefore, misclassifications could lead to false associations. Second, although we adjusted as much bias as we could by using PSM and multivariable analysis to balance the baseline differences between the groups and eliminate residual confounding effects, biases related to unmeasured confounders remain a potential issue in this study. Third, given the nature of the MIMIC database, we lacked some potential factors on the National Institute of Health Stroke Scale, the subtypes of ischemic stroke (TOAST classification), onset time of stroke, the timing of AF diagnosis, the categorization of AF type, cardiac function parameters, and the mortality cause. No long-term follow-up events remained; therefore, the 3-month modified Rankin Scale score cannot be measured. Fourth, this was a single-institution study, and selection bias of patients might exit. Because of a narrow window time after symptom onset of ischemic stroke for reperfusion therapy and the evolution of stroke severity, some patients might not be referred from other hospitals. These high-risk patients might not have been included in our cohort. Finally, although novel OAC (NOAC) and warfarin were used for the secondary prevention of stroke in patients with AF, we could not obtain the actual and detailed information or reasons as to why physicians choose to prescribe warfarin or NOACs based on the administrative database, and thus, we could not add these potential factors into the propensity score models or adjust for these factors in our regression models. Furthermore, we enrolled the patients with AF and diagnosed as ischemic stroke in the intensive care unit, and the phase of the stroke diagnosis was not clear. Whether the patient was under an acute stroke phase might have an influence on the dissociation of poor clinical outcome and in-hospital mortality, which would be an another limitation to our study. Because this study focused on the ICU setting, further studies are warranted to examine the external generalizability of our results.

CONCLUSION

This retrospective study showed that patients with acute ischemic stroke with AF have poor clinical characteristics and prognosis compared with those without AF. However, AF might not be an independent risk factor for patients with acute ischemic stroke after adjusting for stroke-related comorbidities.

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/s.

ETHICS STATEMENT

The Multiparameter Intelligent Monitoring in Intensive Care-IV database was approved by the Institutional Review Board (IRB) of the Beth Israel Deaconess Medical Center (IRB Protocol #2001P001699) and was granted a waiver of informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Y-CC and H-JJ conceptualized the research goals, planned the analyses, and guided the literature review. S-HC extracted the

data from the MIMIC-IV database. C-HL, L-YY, and H-JJ participated in processing the data and doing the statistical analysis. C-SW and P-HC wrote the first draft of the paper. All authors have read and approved the final manuscript.

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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.2021.730244/full#supplementary-material

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CASE REPORT
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Case Report: Management of Traumatic Carotid-Cavernous Fistulas in the Acute Setting of Penetrating Brain Injury

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Traumatic carotid-cavernous fistulas (tCCFs) after penetrating brain injury (PBI) have been uncommonly described in the literature with little guidance on optimal treatment. In this case series, we present two patients with PBI secondary to gunshot wounds to the head who acutely developed tCCFs, and we review the lead-up to diagnosis in addition to the treatment of this condition. We highlight the importance of early cerebrovascular imaging as the clinical manifestations may be limited by poor neurological status and possibly concomitant injury. Definitive treatment should be attempted as soon as possible with embolization of the fistula, flow diversion via stenting of the fistula site, and, finally, vessel sacrifice as possible therapeutic options.

Keywords: penetrating brain injury, endovascular intervention, traumatic carotid cavernous fistula, traumatic cerebrovascular injury, neurocritical care

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INTRODUCTION

Traumatic carotid-cavernous fistulas (tCCFs) represent abnormal vascular shunting between the carotid artery, in its cavernous segment, and the cavernous sinus, after direct or indirect trauma (1). tCCFs have a prevalence ranging between 0.2 and 4% in closed brain injury and are typically associated with a basilar skull fracture (2, 3). Common clinical manifestations include proptosis, chemosis, orbital bruits, headache, stroke symptoms, and visual disturbances (1). tCCF clinical syndrome can develop rapidly post injury, though it may take a few days to weeks to become symptomatic (4–6). Sporadic cases have also been reported of tCCFs detected years after the initial injury (6, 7). CCFs are divided into high and low flow lesions. Barrow et al. defined four types (A-D) of CCFs based on the arterial connection to the cavernous sinus. Type A CCFs are direct, high-flow lesions, directly connecting the internal carotid artery (ICA) to the cavernous sinus. Type B-D CCFs are low-flow lesions. Type B CCFs arise from meningeal branches of the external carotid artery (ECA); type C CCFs arise from meningeal branches of the ICA; whereas type D CCFs arise from meningeal branches of both ICA and ECA (1, 8). Among the four subtypes, high flow shunts, or type A fistula per Barrow classification system (8), require more urgent repair as, if left untreated, they have a higher risk to progress causing arterialization of the cavernous sinus and intracerebral veins, and intraparenchymal hemorrhage (9). With the advent of endovascular approaches, endovascular treatment is feasible and preferred over open surgical repair (6, 10–12).

Conversely, low flow tCCFs tend to clinically manifest in a more subacute manner, predominantly presenting with gradually progressive ocular symptoms characterized by conjunctival injection, proptosis, and ophthalmoparesis. Treatment of low-flow tCCFs is endovascular, mostly performed electively, after the acute phase of trauma (1).

In penetrating brain injury (PBI), specifically gunshot wounds to the head, the presence of tCCFs has only been described in a few case series (4, 13–15). The current guidelines for the management of penetrating brain injury, now more than two decades old, recommend treatment with either a surgical or endovascular approach (16). However, there exists no guidance on the timing of the repair, ideal approach, or possible complications related to the respective interventions. Unique to tCCFs associated with gunshot wounds is the potential risk of exsanguination or bleeding into the brain proper; this is related to the fact that oftentimes in such injuries the cavernous sinus dura and the adjacent bone are disrupted by the projectile. Furthermore, the management of tCCF in the GSW population is particularly relevant as gunshot patients represent a unique challenge be it due to the presence of concomitant cranio-cervical vascular injury, other organ involvement, or contraindications for anticoagulation and /or antithrombotic use (17).

In this case series, we describe two patients with gunshot wounds to the head who acutely developed tCCFs. We discuss the specific challenges to timely diagnosis, evaluation, and treatment of this condition, and we review the need for practical recommendations pertaining to the management of this unique population.

CASE PRESENTATION

Case A

Patient A is a 23-year-old female who presented to the emergency department after a gunshot wound to the right side of the head with dural penetration. Her initial Glasgow Coma Scale (GCS) was 7 (E1, V1, M5), prompting urgent intubation. Computerized head tomography (HCT) demonstrated a right temporal lobe penetrating injury with retained bullet fragment, a traumatic subarachnoid hemorrhage in the basal cisterns, diffuse cerebral edema, and a 5 mm right to left midline shift at the foramen of Monroe. Extensive skull fractures were noted along the course of the bullet including the right maxillary sinus, the floor of the middle cranial fossa, and the mastoid portion of the temporal bone. Calvarial fractures extended superiorly through the right greater sphenoid wing to the coronal suture, as well as posteriorly through the right parietal bone to the lambdoid suture. The fracture over the right sphenoid tracked across the skull base to involve the carotid canal. Numerous metallic fragments were retained intracranially including a large 9 mm bullet fragment lodged between the right temporal lobe and parietal lobes. Computerized Tomography angiogram of the neck and head (CTA head and neck) identified an irregularity of the right Internal Carotid Artery (ICA) in the proximity of the carotid canal fracture, concerning vascular injury. Over the subsequent hours, the patient underwent emergent decompressive hemicraniectomy and a right subgaleal drain was placed. Three days later, as hemodynamic stability was demonstrated, conventional cerebral angiography was done revealing a high-flow right tCCF with significant arterialization of cortical veins. The tCCF was embolized via a transvenous approach with a significant reduction of the fistulous flow (**Figures 1A–C**). Seven days after the embolization, the patient developed fixed mydriasis of the right pupil. Repeat conventional cerebral angiography demonstrated preserved patency of tCCF now with prominent flow through the right superficial ophthalmic vein, bilateral cavernous sinus, pterygoid plexus, and inferior petrosal sinus. Following a multidisciplinary discussion, a flow-diverting stent was deployed across the fistula in the cavernous segment with a subsequent significant reduction in arteriovenous shunting (**Figures 1D,E**). The benefit of dual antiplatelet therapy was believed to outweigh the risk of worsening intracranial hemorrhage and bleeding in the setting of recent hemicraniectomy. The patient remained in the hospital for 51 days and suffered multiple neurological complications, including cerebral vasospasm, development of a pseudoaneurysm in the right anterior choroidal artery that was embolized, and hydrocephalus, requiring ventriculo-peritoneal shunting (VPS). The use of dual antiplatelet therapy was maintained throughout her hospitalization; this presented a significant challenge to the management of the pseudoaneurysm, the placement of VPS, and eventually the performance of tracheostomy and percutaneous gastrostomy. She was discharged to a long-term acute care facility. Her GOSE at discharge was two.

Case B

Patient B is a 30-year-old male who presented at the emergency department after a gunshot wound to the left side of the head. Initial GCS was 8 (E2, V1, M5), and the patient was intubated for airway protection. HCT suggests the bullet took a left antero-posterior trajectory with an entry site below the left orbit, dural penetration, and retained bullet fragments in the temporal lobe. In addition, the patient suffered a left hemispheric subdural hematoma, left temporal lobe injury, and diffuse traumatic subarachnoid hemorrhage. The injury also resulted in a temporal bone fracture, lateral to the carotid canal, extensive left facial fractures including the left zygomatic arch, left maxilla, sphenoid left pterygoid process and body, hard palate, left mandibular ramus, and temporomandibular joint as well as left mastoid and left external auditory canal. A CTA of the head and neck revealed mild irregularity of the intracranial left ICA at the carotid canal. A total of 3 days from presentation, CTA of the head and neck was repeated revealing a new 4 mm pseudoaneurysm of the cavernous segment of the left internal carotid artery (**Figure 2A**). Conventional cerebral angiography revealed the presence of a high-flow left tCCF with angiographic evidence of compromised flow intracranially (**Figures 2B,C**). A balloon test occlusion (BTO) was considered. However, blood pressure reduction preceding balloon inflation was associated with loss of somatosensory potentials over the left hemisphere. BTO was subsequently aborted and blood pressure was optimized to ensure appropriate perfusion of the left hemisphere. Following a multidisciplinary discussion, the decision was made to attempt repair of the tCCF with a flow

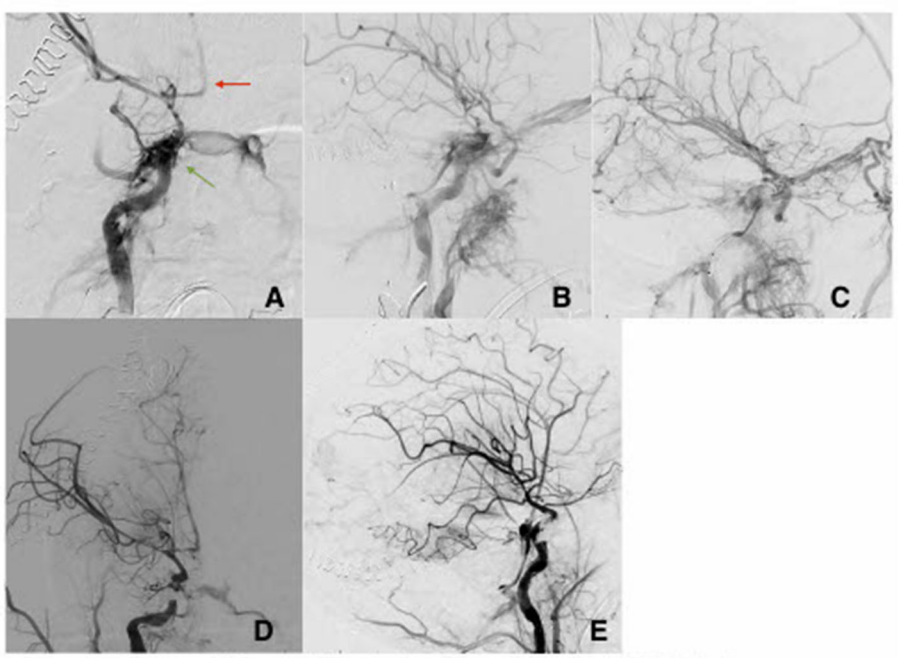

FIGURE 1 | AP view **(A)** and lateral view **(B)** with direct fistula between cavernous segment of the right ICA and the cavernous sinus (green arrow). There is evidence of severe vasospasm in the intracranial vascular tree (red arrow). **(C)** Oblique view post partial coiling of the fistula site. **(D)** AP view and lateral view **(E)** of the right ICA post flow diverting stents and coiling with improvement of the CCF and improved flow intracranially.

diverting stent that may optimize blood flow to the compromised hemisphere and allow for a proper BTO should that be needed. Following deployment of the stent, improved flow to the left hemisphere was immediately noted (**Figures 3A,B**). The patient was started on dual antiplatelet therapy for stent patency. The patient later on developed a CSF leak that necessitated an extensive surgical repair that would not have been possible while on dual antiplatelet therapy. In an attempt to find a therapy that spares dual antiplatelet therapy, the decision was made to repeat the BTO in preparation for a possible left internal carotid artery sacrifice at the site of the tCCF. The patient passed the BTO and the left ICA was successfully embolized from the cavernous segment distally into the distal cervical segment proximally with no evidence of any flow into the carotid-cavernous fistula (**Figures 4A–C**). Dual antiplatelet therapy was discontinued and the patient was maintained on a low dose of aspirin. Facial fractures and CSF leaks were repaired. The patient's length of stay at the hospital was 27 days and he was discharged to an acute rehabilitation facility with no left hemispheric deficits (**Figures 4D,E**). His GOSE at discharge was five.

DISCUSSION

Traumatic carotid-cavernous fistulas after gunshot wounds to the head have been described in limited case series (13, 14, 18). Currently, no substantial data exists on ideal screening modality or timing of screening, ideal approach and timing of repair, or possible complications related to interventions (17). Oftentimes, patients who suffer gunshot wounds to the head may incur concomitant intracranial vascular injury, suffer coagulopathy, and need surgery for cranial or other traumatic injuries (14, 17, 19); yielding an inherent challenge to the potential use of dual antiplatelets often utilized in the setting of flow diverting stents. Furthermore, the acute nature of the tCCF and the vulnerability of the acutely traumatized brain renders therapeutic occlusion of parent vessels at a higher risk of ischemic stroke. Therefore, managing tCCF in these patients is oftentimes more complex as compared to tCCF not associated with gunshot wounds.

Risk factors associated with the development of tCCFs appear to be similar to other cerebrovascular injuries; they include the frontobasal site of entry and evidence of injury in the proximity of the cavernous sinus (20). As a matter of fact, the penetrating nature of gunshot wounds causing tCCF is, arguable, not unique. In the context of seemingly blunt trauma, basilar fractures may be associated with a penetrating mechanism causing vascular disruption (21). Gunshot wounds represent the end of a spectrum of injuries associated with tCCF (17). On one end of the spectrum are blunt injuries with no clear evidence of bony fracture that may directly compromise the integrity of the vessel, causing in most cases a low-flow type of tCCF, and on the other end are gunshot wounds where the bullet trajectory may include a direct disruption to the vessel wall, cavernous dura and the bony structures surrounding it. The latter is mostly associated with high flow, or type A, tCCF. Within this continuum are blunt injuries with extensive skull base fractures where the bone fragmentation may represent a penetrating mechanism (4–6).

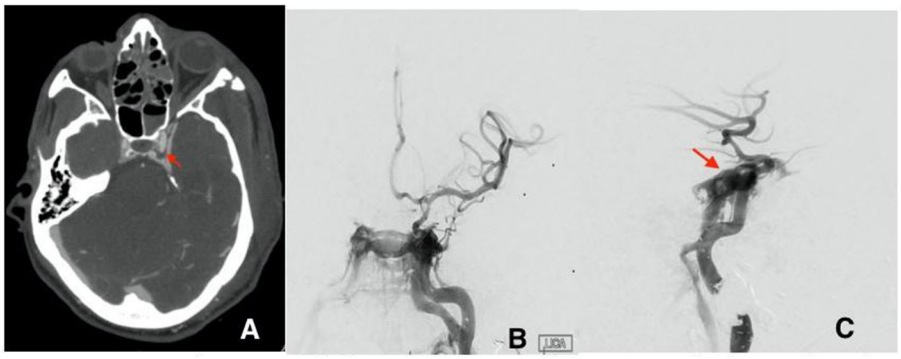

FIGURE 2 | (A) Initial CTA with left cavernous pseudoaneurysm (red arrow). **(B)** first cerebral angiogram AP view and lateral view **(C)** showing the direct fistula between the cavernous segment of the left ICA and the left cavernous sinus at the site of ruptured pseudoaneurysm.

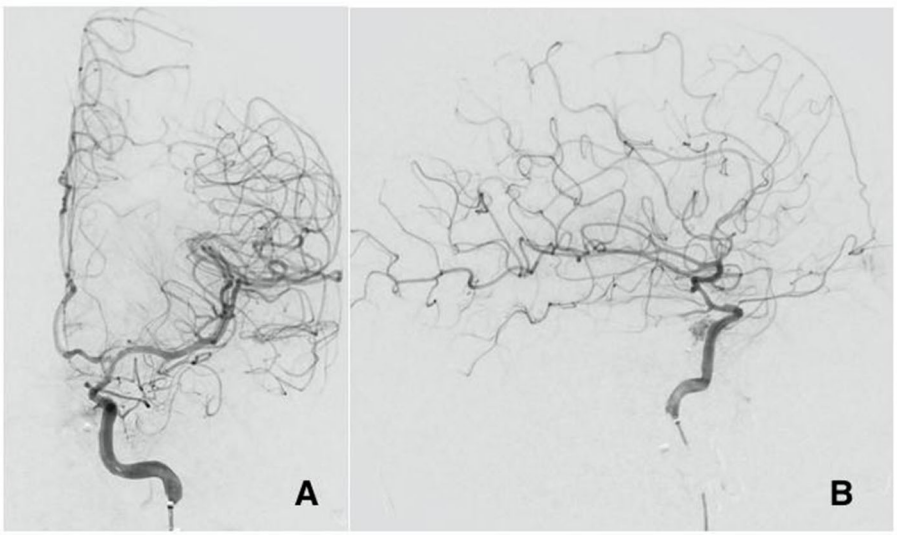

FIGURE 3 | Cerebral angiogram AP view **(A)** and lateral view **(B)** post flow diverter stenting at the site of the ruptured pseudoaneurysm with significant decrease of the flow in the fistula and improved perfusion to the brain.

Screening for vascular injuries, in general, should be considered in any patient with gunshot wounds to the head (14, 17). Our cases demonstrate that the development of tCCF may occur rapidly after the trauma, and screening for cerebrovascular injury, after hemodynamic stabilization is achieved, should be considered in the acute setting. While imaging done at presentation may not be diagnostic, repeat imaging within the first 72 h may reveal previously occult injuries. This is particularly important when the bullet path or associated fractures suggest injury to a particular vascular structure (20). In the cases described above injury to the carotid canal and carotid artery was identified as high flow tCCF. The development of tCCF can occur due to an initial direct injury to the carotid or a result of indirect blast injury. CTA of the head and neck has been shown to perform with good sensitivity in detecting intracranial arterial injury in the carotid artery and first branches of intracranial arteries and, if performed in the hyper-acute phase (immediately on presentation), may detect the presence of a pseudoaneurysm before the development of tCCF (15, 22). However, metallic fragments in the proximity of the cavernous sinus may obscure the presence of arterial injuries. Therefore, when clinical suspicion exists, conventional diagnostic angiography should be considered (22). In the event that hemodynamic stability or clinical suspicion do not justify early conventional angiography, repeating CTA head and neck within 3–7 days from injury may reveal an evolving vascular injury better characterized at that time.

The typical clinical presentation of tCCF, characterized by proptosis, chemosis, orbital bruits, headache, stroke signs, and visual disturbances, is unreliable in this patient population given the critical illness, instrumentation, concomitant globe and facial injury, and compromised level of consciousness (14). Therefore, the investigation of tCCF should not be solely based on clinical presentation.

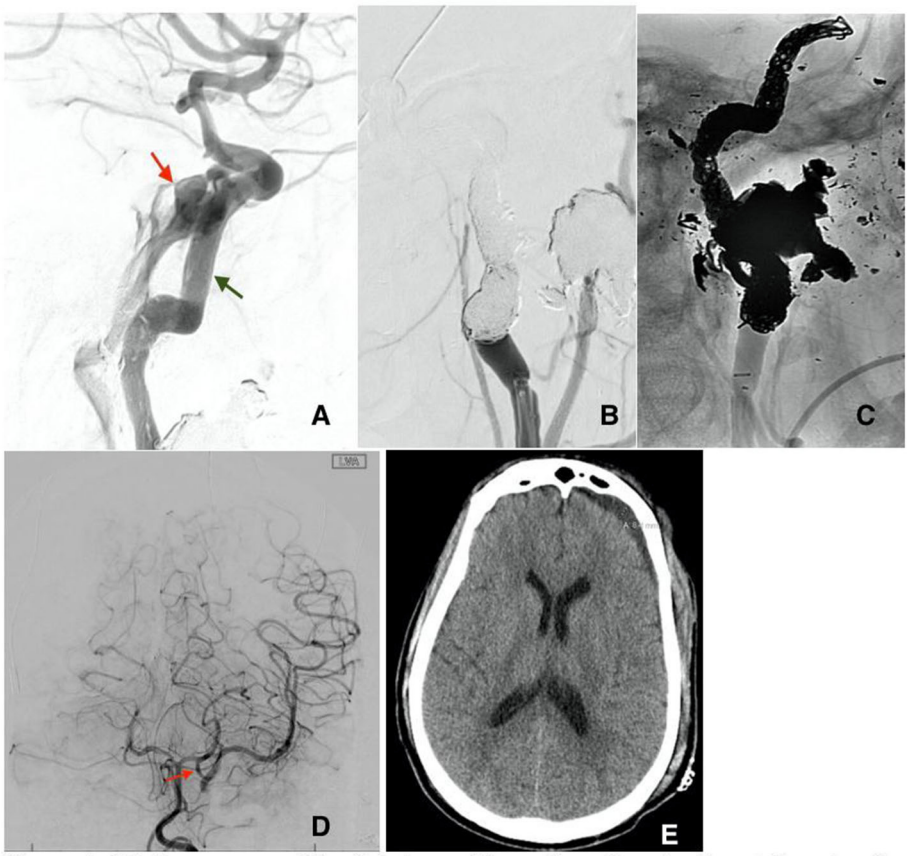

FIGURE 4 | (A) Recurrence of the fistula post flow diversion stenting at the site of the ruptured pseudoaneurysm (red arrow). Notice the misplacement of the previously deployed stents (green arrow) secondary to the high flow of the CCF. Subtracted **(B)** and unsubtracted **(C)** views of the left ICA post sacrifice by means of coiling without any residual flow in the CCF. **(D)** Cerebral angiogram of the left vertebral artery post left ICA sacrifice AP view, showing adequate flow into the left middle cerebral artery through a large left posterior communicating artery (red arrow). **(E)** Head CT before discharge showing residual subdural hematoma with no signs of ischemic changes in the left hemisphere.

Prior to definitive treatment of tCCF, optimizing blood pressure goals is advisable in this patient population. Adequate reduction of blood pressure may be needed to prevent significant shunting from the arterial to the venous systems, causing venous engorgement, parenchymal injury, intraparenchymal hemorrhages, and intracranial hypertension (9). However, overzealous reduction in blood pressure may be associated with a further reduction of blood flow to the ipsilateral hemisphere ultimately compromising cerebral perfusion. Therefore, a specific blood pressure target is difficult to establish, and continuous neurological monitoring, whenever possible, is crucial. That being said, neurological assessments are usually limited in this particular cohort of patients thereby clinically limiting examination-based assessment of hemispheric perfusion. Alternative monitoring methods include invasive (LICOX) or non-invasive such as (Near-infrared spectroscopy) tissue oxygenation monitoring, quantitative electroencephalography (q-EEG), and transcranial doppler (TCD), may provide insight while blood pressure manipulation is underway (23–26).

Repair is advised as soon as possible, hemodynamic status permitting. Ideally, repair of tCCF, or any other cerebrovascular injury, should precede less urgent surgeries, such as facial or ophthalmological intervention. An exception to the above is life-saving procedures, such as emergent decompressive craniectomy in patients with uncontrolled intracranial hypertension or evolving intracranial compartment syndrome, as described in our first case.

A multidisciplinary team approach including neurointensive care, vascular neurosurgery, and neuro-endovascular surgery is advised in these complex patients. Endovascular treatment is nowadays the preferred therapeutic approach for tCCF (10, 11). The repair can occur by means of embolization of the fistula or placement of flow-diverting stents (27, 28). Very importantly, stent placement requires the initiation of antithrombotic therapy to avoid stent thrombosis. Therefore, stenting should be cautiously considered in GSW patients. In fact, the use of antiplatelet therapy may be contraindicated in presence of intracranial hemorrhage, need for additional surgical interventions, placement of intracranial monitoring, or lumbar

drainage. Newer flow-diverting stent technologies necessitating single antiplatelet use are a promising advancement. When repair of the fistula is not possible or unsuitable due to the patient's clinical condition, the sacrifice of the internal carotid artery is a last viable therapeutic resort, ideally after demonstrating adequate collateral cerebral perfusion. In patients with GSW to the head, the presence of vascular injury has been shown to be associated with worse outcomes (14). However, the specific association between tCCF and outcome remains less certain.

CONCLUSION

Traumatic CCF may occur in patients with gunshot wounds to the head, representing an extreme of penetrating mechanisms associated with this type of injury. Current penetrating brain injury guidelines are outdated and provide no consensus on the management of this condition. If possible, immediate and early cerebrovascular imaging is the preferred screening modality in this patient population as relying on clinical manifestations is usually limited by poor neurological status and possibly concomitant injury. Blood pressure control is an important step in the management and should ideally balance between brain perfusion and minimizing flow across the fistula. Definitive repair should be attempted as soon as medically possible. Embolization of the fistula, flow diversion via stenting of the fistula site, and, finally, vessel sacrifice are viable options depending on the size of the fistula, flow grade, collateral flow, phase on injury, and concomitant injury that may dictate permissibility of antithrombotic therapy.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant for the publication of this case report.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.715955/full#supplementary-material

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Machine Learning Techniques in Blood Pressure Management During the Acute Phase of Ischemic Stroke

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Background and Purpose: Elevated blood pressure (BP) in acute ischemic stroke is common. A raised BP is related to mortality and disability, yet excessive BP lowering can be detrimental. The optimal BP management in acute ischemic stroke remains insufficient and relies on expert consensus statements. Permissive hypertension is recommended during the first 24-h after stroke onset, yet there is ongoing uncertainty regarding the most appropriate blood BP management in the acute phase of ischemic stroke. This study aims to develop a decision support tool for improving the management of extremely high BP during the first 24 h after acute ischemic stroke by using machine learning (ML) tools.

Methods: This diagnostic accuracy study used retrospective data from MIMIC-III and eICU databases. Decision trees were constructed by a hierarchical binary recursive partitioning algorithm to predict the BP-lowering of 10–30% off the maximal value when antihypertensive treatment was given in patients with an extremely high BP (above 220/110 or 180/105 mmHg for patients receiving thrombolysis), according to the American Heart Association/American Stroke Association (AHA/ASA), the European Society of Cardiology, and the European Society of Hypertension (ESC/ESH) guidelines. Regression trees were used to predict the time-weighted average BP. Implementation of synthetic minority oversampling technique was used to balance the dataset according to different antihypertensive treatments. The model performance of the decision tree was compared to the performance of neural networks, random forest, and logistic regression models.

Results: In total, 7,265 acute ischemic stroke patients were identified. Diastolic BP (DBP) is the main variable for predicting BP reduction in the first 24 h after a stroke. For patients receiving thrombolysis with DBP<120 mmHg, Labetalol and Amlodipine are effective treatments. Above DBP of 120 mmHg, Amlodipine, Lisinopril, and Nicardipine are the most effective treatments. However, successful treatment depends on avoiding hyponatremia and on kidney functions.

Conclusion: This is the first study to address BP management in the acute phase of ischemic stroke using ML techniques. The results indicate that the treatment choice should be adjusted to different clinical and BP parameters, thus, providing a better decision-making approach.

Keywords: stroke, blood pressure, machine learning, hypertension, prediction

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INTRODUCTION

Machine learning (ML) applications in healthcare have significant potential for improving clinical decision-making diagnoses, treatment effectiveness, and healthcare management, including lowering the costs for both healthcare providers and patients (1). ML applications for Knowledge Discovery in Databases (KDD) have been used for more than two decades and are useful for discovering information and extracting knowledge from data and reflect a multi-step process that involves thorough data preparation, pattern searching, and knowledge evaluation (2). The use of ML to extract non-trivial and previously unknown useful information from data may be most beneficial for physicians in areas where the level of evidence or class of recommendation is low and will increase the likelihood of the physicians adopting them (3). The use of ML in clinical research to predict a particular clinical outcome is useful because it has the potential to outperform the best clinical knowledge obtained by current traditional medical research. In this study, we applied the KDD process by using ML techniques to conduct a robust interrogation to identify predictors of blood pressure (BP) management after acute ischemic stroke, thus, having the potential to aid clinicians in improving treatment regimens.

An elevation in BP is common in the acute phase of a stroke and occurs early at the time of arrival to the emergency room. In two-thirds of the patients, elevated BP was transient and resolved within 2 weeks from symptom onset (4). Observational studies have shown that elevated BP during ischemic stroke onset is prognostically associated with an increased risk of early adverse events and mortality. However, acute and aggressive BP lowering within 24 h of stroke onset could also jeopardize the outcome (5). Both elevated and low BP are independent factors that predict poor outcomes among patients with acute ischemic stroke and present a U-shaped relationship between BP and death or disability (6, 7).

High BP in acute stroke can decrease blood perfusion to areas of ischemic brain tissue, which, in turn, can cause neurological damage (8). An extremely high BP can result in intracerebral bleeding and hypertensive emergencies, including renal failure, ischemic heart disease, and pulmonary edema (9). In patients who received thrombolytic treatment, studies concur that there is a strong association between high BP and worse clinical outcomes, including death, disability, and hemorrhagic transformation (7, 10). The AHA/ASA and ESC/ESH guidelines recommend lowering the BP below 180/105 mmHg in patients receiving thrombolysis in the first 24 h after acute stroke, a strong class of recommendation (class I). In patients not receiving thrombolysis, a clinical judgment is defined as whether to treat hypertension when it exceeds 220/120 mmHg, a weak class of recommendation (class II-b) (11, 12). There is no firm evidence regarding BP management in patients with acute ischemic stroke with a BP lower than 220/120 mmHg, who did not receive thrombolysis (12). The specific interval for BP reduction is not well-established, and the current approach of lowering BP by 15% is considered reasonable by a consensus expert opinion (11, 12). The current recommended approach by the AHA/ASA is to treat with labetalol, nicardipine, or clevidipine when systolic blood pressure (SBP) is over 180–230 mmHg or diastolic BP (DBP) is over 105–120 mmHg. If DBP exceeds 140 mmHg or is not controlled by these treatments, sodium nitroprusside is recommended. However, these recommendations are not based on a strong class of recommendations (11, 13).

There are therapeutic strategies for elevated BP that are not included in the current acute stroke guidelines. In most hypertensive emergencies, intravenous (IV) drug administration is considered, although oral therapy with ACEI/ARBs or beta-blockers is effective in the acute setting of hypertensive emergency because of the activation of the renin system. Besides the medications mentioned above for BP lowering in acute ischemic stroke, other treatment options are utilized in various hypertensive emergencies including metoprolol, esmolol, nitroglycerine, clonidine, and enalaprilat. The duration of action of these treatments ranges from several minutes to several hours and enables dose adjustment according to clinical judgment (12). The use of these medications in the treatment of acute ischemic stroke is required.

Few randomized clinical trials have examined the impact of BP reduction immediately after acute stroke with antihypertensive agents (14, 15). The effects of continuous antihypertensive treatment, in previously known patients who were hypertensive after acute stroke in the Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS), showed a statistically significant reduction of 13/8 mmHg in BP at 2 weeks in the continuing group compared to the stop group, and no differences emerged between the groups in rates of serious adverse events, 6-month mortality, or major cardiovascular events (14). However, the aforementioned study had inherent limitations due to the complex clinical situation. It was not placebo-controlled, and there was a multiplicity of pre-existing antihypertensive treatments (14). The China Antihypertensive Trial in Acute Ischemic Stroke (CATIS), a randomized clinical trial, compared patients who received antihypertensive treatment to those who discontinued all antihypertensive medications during hospitalization. The treatment aimed to lower SBP by 10–25% within the first 24 h. The primary outcome of death within 14 days after randomization and major disability at 14 days or hospital discharge did not differ between the groups. However, early antihypertensive therapy was associated with a lower rate of 3-month recurrent stroke among patients with a history of hypertension (15).

Several randomized clinical trials have examined the use of specific antihypertensive agents (16, 17). The Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) randomized controlled trial investigated the effect of BP reduction with labetalol and lisinopril vs. placebo in patients with SBP > 160 mmHg. The SBP reduction within the first 24 h was higher in both treatment groups (16). The Intravenous Nimodipine West European Stroke Trial (INWEST) showed a significant decrease in SBP and DBP with nimodipine treatment vs. placebo in the first 48 h (18). Furthermore, several randomized trials have examined the effects of angiotensin receptor blockers (ARBs) on BP reduction in the acute phase of stroke and observed a modest reduction in BP of up to 10/6 mmHg in the treatment group vs. the placebo group (17, 19, 20).

In many clinical trials evaluating BP-lowering, markedly elevated BP ranges (usually > 220/120 mmHg) were excluded (14–16). However, the guidelines concern the treatment of severe hypertension. In addition, no solid data are available to guide the selection of antihypertensive treatment. Accordingly, the main objective of this research was to develop a decision support tool for improving the management of extremely high BP during the first 24 h after acute ischemic stroke by using ML techniques. To date, no published study has used ML techniques to predict BP management in the acute phase of ischemic stroke.

METHODS

The source codes for the analyses can be found at: https://github.com/OritMazza/BP_managment_AIS.

The MIMIC Code Repository is open source and available online. It was used with minor changes for the variable extraction tasks and can be found at the following link: https://github.com/MIT-LCP/mimic-code.

MIMIC-III and eICU Collaborative Databases

We used two large, public, and freely accessible intensive care unit (ICU) databases of de-identified patients: the eICU Collaborative Research Database (eICU-CRD) and the Medical Information Mart for Intensive Care III (MIMIC-III) database in a diagnostic accuracy study based on retrospective multicenter data. Adult patients admitted to critical care units at the Beth Israel Deaconess Medical Center between 2001 and 2012 with acute ischemic strokes were selected from the MIMIC-III v1.4 Critical Care Database (21). Similar cohorts of adult patients who were admitted to critical care units across 208 hospitals throughout the United States during 2014–2015 were recruited from the eICU Collaborative Research Database v2.0 (22). The two datasets are independent because the hospital source of MIMIC-III is not included in the eICU program (22). The databases were accessed through the Google BigQuery platform, a relational database management system, and the data were extracted from the two reference databases using SQL queries (23).

Cohort Selection

The cohort included adult patients aged 18–88. Older patients were excluded because of the de-identification process of the MIMIC-III and eICU databases, which obscured the identities of patients above 89 years old to comply with the Health Insurance Portability and Accountability Act (HIPAA) regulations (21, 22).

The ICD-9 codes were identified for acute ischemic stroke as follows: 433 (occlusion and stenosis of precerebral arteries), 434 (occlusion of cerebral arteries), and 436 (acute but ill-defined cerebrovascular disease). The ICD-9 codes were selected according to their highly predictive values for actual cases of acute ischemic stroke, as previously described (24). The 433.x0 ICD-9 code was excluded because of the very low PPV in several studies, and 433.x1 was included to select more cases of acute ischemic stroke with little impact on PPV (25). Patients with ischemic stroke who received IV-tPA were identified from the MIMIC-III database according to ICD-9 procedure code 99.1, and those with endovascular treatment (EVT) were identified by ICD-9 code 39.74 (26). Because of the differences between the databases regarding the thrombolytic treatment identification process, patients with acute ischemic stroke who received IV-tPA were identified from the eICU database by using the *treatment* table with the *treatmentString* variable and the keyword "thrombolytics." Table I in the **Supplemental Material** provides a list of the selected ICD-9 codes and the number of diagnoses according to different subgroups of acute ischemic stroke codes.

A time window of 24 h from hospital admission was selected for patients who did not receive EVT/tPA. According to guidelines, tPA is administered at the hospital up to 3–4.5 h from ischemic stroke symptom onset and, therefore, is usually administered at a time window of 24 h from admission to the hospital (11). A time window of 24 h after receiving tPA treatment was selected for patients who received thrombolytic treatment. Therefore, the cohort also included patients who underwent acute ischemic stroke at the hospital and received tPA treatment.

Figure 1A shows the MIMIC-III cohort flowchart. In the MIMIC-III database, exclusion by ICD-9 code sequence as the first or second diagnosis enables accurate selection of patients with acute ischemic stroke during the querying process and prevents the selection of admissions of the same patients with other primary clinical conditions. Left joining with the icustay table (*icustay_id*) for each patient resulted in 1,142 ICU admissions (*icustay_id*) and 1,061 hospital admissions (*hadm_id*). The extraction of the selected time window of 24 h from hospital admission (*admittime*) to the ICU admission time (*intime*) resulted in a unique ICU stay for each patient in the selected cohort.

Figure 1B shows the eICU cohort flowchart. Patients selected according to their ICD-9 codes for acute ischemic stroke were documented as active problems during the ICU stay using the diagnosis table.

Knowledge Discovery in Databases and the ML Approach

The KDD process is divided into three major steps, which we followed in our study and are illustrated in **Figure 2**. The first step is the data pre-processing step, which includes data cleaning, data integration, data selection, and data transformation. Data cleaning involves identifying and handling corrupt, incorrect, inaccurate, and irrelevant data, as well as the missing values. Data integration entails combining data from different sources to generate a unified view and ensuring that the same variables are within the same scale, and each variable has a single meaning. In addition, data are integrated from several file formats, for example, video or audio with text or tables. Data selection entails choosing the relevant data using different methods, such as feature selection or principal component analysis. Data transformation aims to normalize or standardize

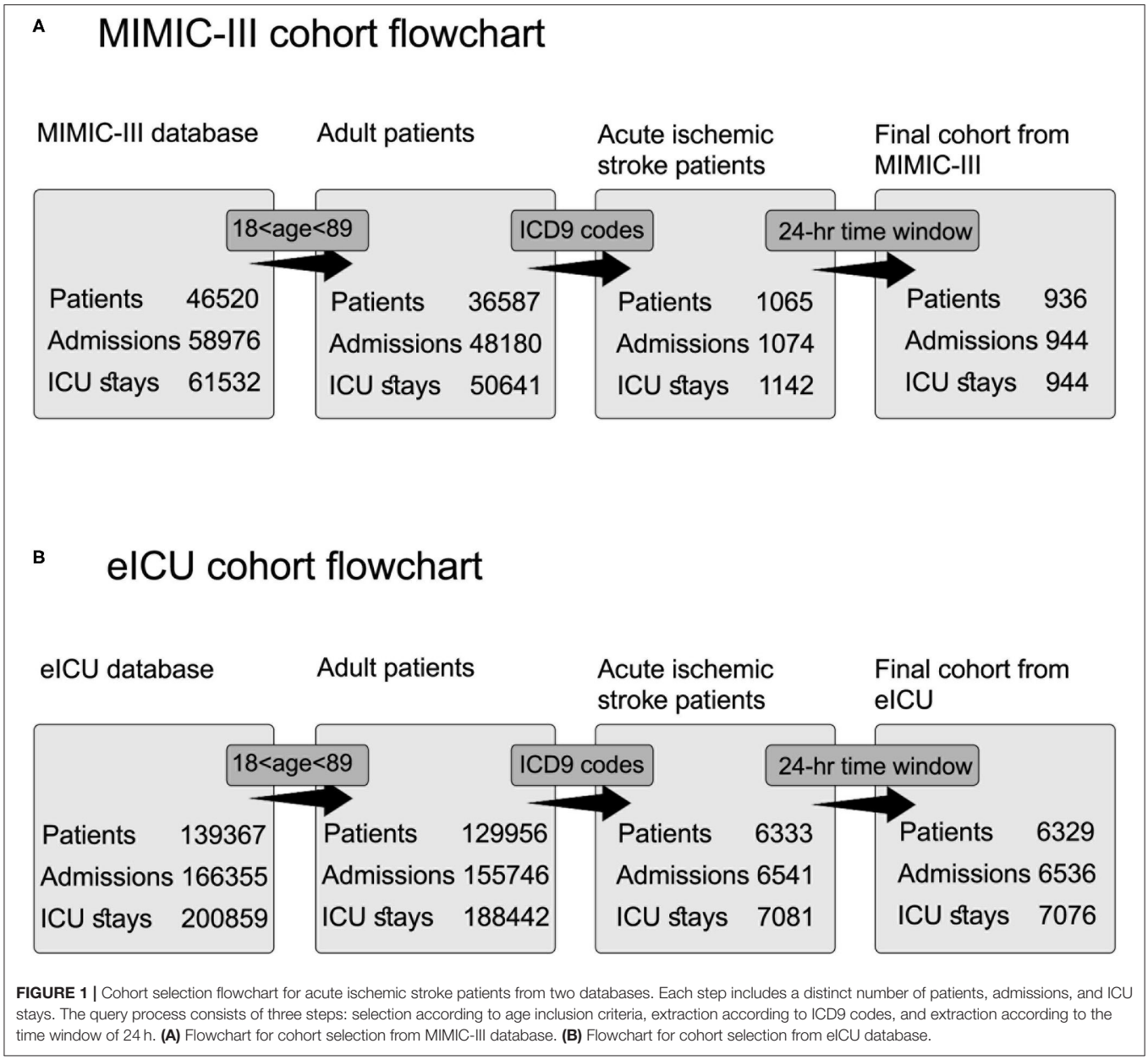

FIGURE 1 | Cohort selection flowchart for acute ischemic stroke patients from two databases. Each step includes a distinct number of patients, admissions, and ICU stays. The query process consists of three steps: selection according to age inclusion criteria, extraction according to ICD9 codes, and extraction according to the time window of 24 h. **(A)** Flowchart for cohort selection from MIMIC-III database. **(B)** Flowchart for cohort selection from eICU database.

the independent variables to avoid bias resulting from using variables with a different range of values.

The second step after preparing the data is the use of ML techniques. According to the research question and the data available, the ML approach is selected (either supervised or unsupervised learning). When the predicted outcome is well-defined and can be labeled, supervised learning is preferred. The selection of specific algorithms is guided by the dependent variable of the prediction task. When the dependent variable is of continuous type, a regression algorithm is typically selected. When the dependent variable is of categorical type, a classification algorithm is typically selected. Some algorithm types, for example, random forest and artificial neural networks, fit both classification, and regression problems. An unsupervised learning approach is considered when the prediction task is unknown. In such cases, pattern identification and recognition techniques can be applied.

The processed data were divided into training and validation datasets. The training dataset is used to produce a trained and fitted model that generalizes well to unknown data. When a large amount of data is available, a sample of the original dataset—the validation dataset—is held back from the training model and is used to evaluate the model performance to obtain an unbiased result of the model's effectiveness. Typically, in this step, different algorithms are compared to identify the best model that fits the prediction task. The final step entails the evaluation of the patterns and their presentation. This step is essential to ensure that useful knowledge is derived from the data.

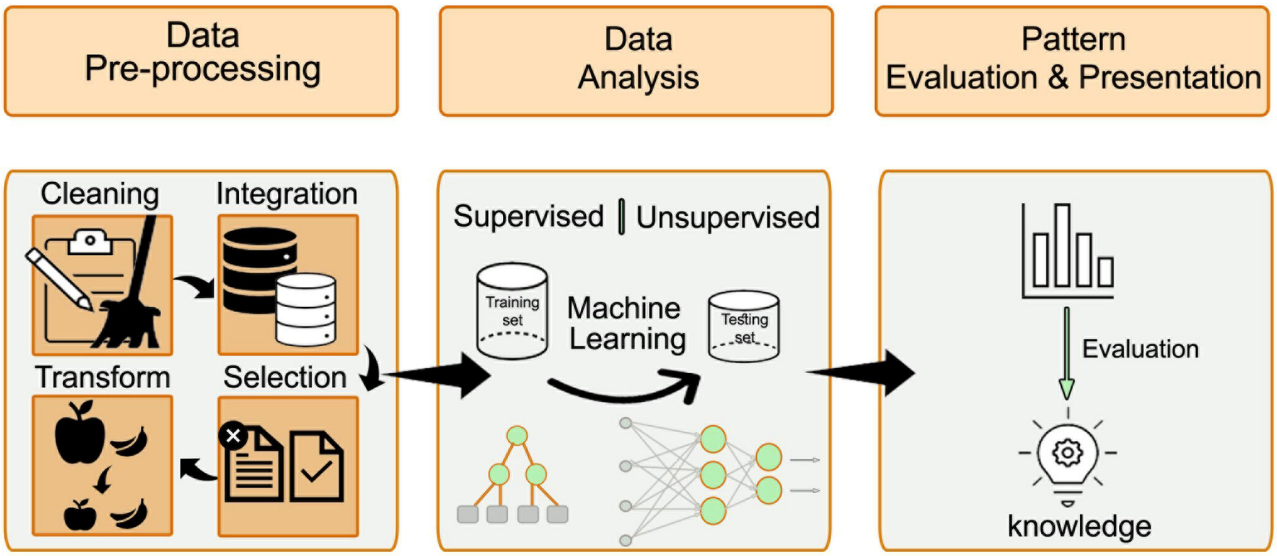

FIGURE 2 | The major steps of the KDD process: data pre-processing, data analysis, and patterns evaluation. The pre-processing step includes data cleaning, data integration, data selection, and data transformation. After preparing the data, the ML approach is selected (either supervised or unsupervised learning). The processed data is divided into training and validation datasets. Different algorithms are compared to find the best model that fits the prediction task.

Primary Outcome

Figure 3 shows the flowchart of how the primary outcome was determined and which criteria were selected for the assessment of BP management. A BP management was determined successful when BP treatment was administered according to the AHA/ASA and ESC/ESH guidelines and resulted in a BP reduction of 10–30% of the maximum value that was measured during the time window of 24 h. Our scheme model, as represented in **Figure 3**, was built in accordance with the guideline recommendations that antihypertensive treatment should be restricted to high BP and, thus, created decision rules according to different BP levels. The threshold for starting antihypertensive treatment after acute ischemic stroke was set at > 180/105 mmHg for patients who received EVT/tPA and > 220/120 mmHg for non-tPA patients (11). There is no evidence regarding the exact interval for BP reduction when it is markedly elevated and exceeds the recommended threshold. However, several studies have suggested that this interval is safe or associated with good clinical outcomes in patients with acute ischemic stroke (15, 27).

Further evaluation of the time-weighted average (TWA) of SBP and DBP was calculated and used as a continuous outcome variable in the prediction of algorithms. The TWA provides a less biased and more accurate estimation of BP than a simple average (28) and can be used to evaluate a BP after admission for acute stroke (10, 29).

Dataset Pre-processing

The MIMIC-III (v1.4) relational database contains 26 different tables relating to unique patients, unique admissions to hospitals, and unique admissions to ICUs (21). The eICU Collaborative Database (v2.0) contains 31 tables concerning each ICU stay (22). We extracted 91 variables from seven different tables in the MIMIC-III database (*diagnoses_icd, patients, admissions, icustays, chartevents, labevents,* and *prescriptions*) and eight different tables in the eICU database (diagnosis, *treatment, vitalaperiodic, apacheapsvar, vitalperiodic, medication, lab,* and *patient*).

We extracted 91 variables as possible attributes for prediction algorithms. The variables were divided into four groups: demographic, hemodynamic and vital signs, laboratory results, and comorbidities. We included 91 out of 103 predictors used by Wang et al.'s pipeline for the MIMIC-III database (30). Because of the large number of missing values, unlike Wang et al. variables that indicated mechanical ventilation were excluded, and instead, we used the covariate of persistence or absence of mechanical ventilation, whether one or more of the following variables were present in the MIMIC-III database: ventilator type, ventilator mode, respiratory pressure, tidal volume, minute volume, inspiratory pressure, plateau pressure, positive end-respiratory pressure (PEEP), airway pressure release ventilation (APRV), high-pressure relief, pressure-controlled ventilation (PCV) levels, time-cycled pressure-controlled ventilation (TCPCV), and pressure support ventilation (PSV) levels. In contrast to the MIMIC-III, the eICU database has the *vent* variable in table *apacheApsVar,* which contains information on whether the patient was ventilated at the time of the worst respiratory rate. Similar to the mechanical ventilation variable, we used the absence or persistence of central venous pressure (CVP), cardiac output (CO), and cardiac index (CI) as covariates in both databases because of their high prevalence of missing values, and the importance of including them as indicators of the need for more intensive monitoring care.

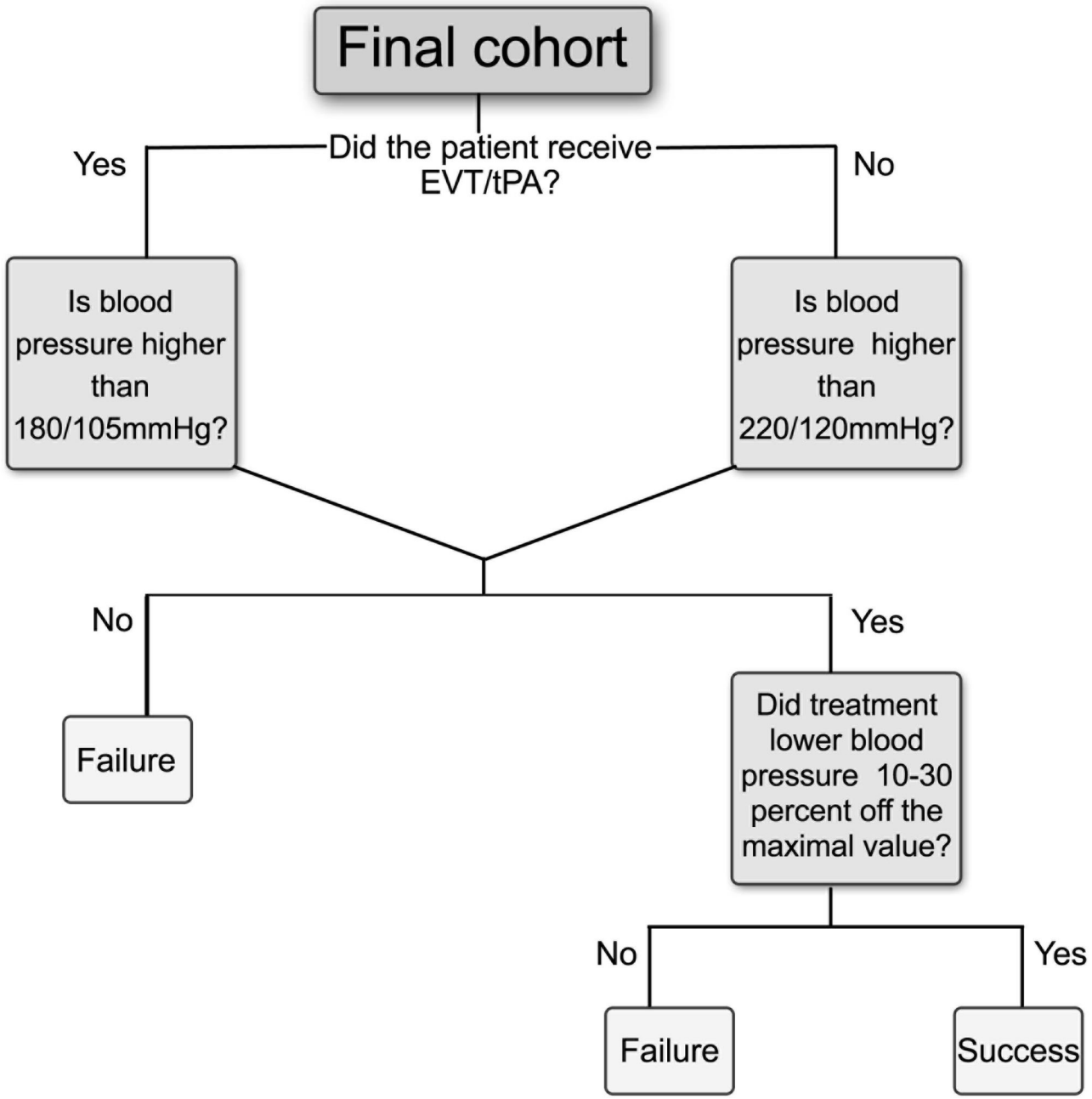

FIGURE 3 | Flowchart for primary outcome criteria to assess BP management in the 24 h after acute ischemic stroke. Positive outcomes are considered as "Success" if initiation of therapy was given according to guidelines thresholds and if the average BP was decreased at least 10% and up to 30% off the maximum value during the selected time window, otherwise determined as "Failure." Different thresholds for starting antihypertensive treatment were determined according to whether patients received EVT or tPA, or not. EVT, Endovascular treatment; tPA, tissue plasminogen activator.

Comorbidities in the MIMIC-III and eICU databases were selected according to Quan et al. and enhanced the ICD9-CM coding algorithm, which is also provided in the MIMIC-III repository (30, 31). We used the U.S. National Library of Medicine RxMix application programming interface (API) (https://mor.nlm.nih.gov/RxMix/) to identify the members of each antihypertensive drug class. Then, we extracted prescriptions for antihypertensive medications in the first 24 h in the ICU or from the time of onset of the tPA treatment. The output for each drug class was stored as a binary result, namely, whether the medication from the specific drug class was administered (1) or not (0). We included 106 antihypertensive medications, which were divided into eight different drug classes. **Table 1** shows the drugs that were used

TABLE 1 | Drugs and classes of antihypertensive medications.

Class	Drugs	Routh of administration	Positive observations (n = 8,025)	%
CCBs	Amlodipine (38.1%)	Enteral	683	5.2
	Diltiazem (21.1%)	Enteral		
	Nicardipine (35%)	IV±PRN		
	Nifedipine (0.4%)	IV		
	Nimodipine (0.9%)	Enteral		
	Verapamil (0.2%)	Enteral		
	Combinations (4.3%)	Enteral		
Beta-blockers	Atenolol (0.8%)	Enteral	2,374	29.2
	Carvedilol (4.8%)	Enteral		
	Esmolol (0.04%)	IV		
	Labetalol (45.62%)	IV±PRN		
	Metoprolol (33.6%)	Enteral/IV±PRN		
	Nadolol (0.04%)	Enteral		
	Combinations (15.1%)			
ACE-inhibitors	Captopril (1.7%)	Enteral	408	5
	Enalapril (1.2%)	Enteral/IV		
	Lisinopril (96.8%)	Enteral		
	Quinapril (0.3%)	Enteral		
ARBs	Losartan (90%)	Enteral	40	0.5
	Valsartan (10%)	Enteral		
Diuretics	Bumetanide (0.9%)	Enteral/IV	655	8
	Furosemide (84.8%)	Enteral/IV		
	Hydrochlorothiazide (8.2%)	Enteral		
	Spironolactone (4.2%)	Enteral		
	Combinations (4.1%)			
Direct vasodilators	Hydralazine (100%)	Enteral/IV±PRN	1,163	14.4
Sympatholytic agent	Clonidine (100%)	Enteral/TD	79	1
Other	Nitroprusside (100%)	IV±PRN	34	0.4

CCBs, Calcium channels blockers; ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers. Enteral includes the following routes of administrations: PO (Per os), NG (nasogastric), and PZ (Per Zonda), PEG (Percutaneous endoscopic gastrostomy). IV: Intravenous. PRN (Pro-re-nata) refers to the administration of prescribed medication as needed or as the situation arises according to physician instructions. TD, Transdermal.

in the selected time window and the prevalence of use in the selected cohort.

The data cleaning process included excluding variables, which were marked as errors by physicians using the error variable of the *chartevents* table. To ensure that a single maximum value is not subjected to outliers or erroneous measurements, we added a variable that counts the number of times that the BP values elevated beyond the thresholds and excluded the BP values that were only elevated once in the selected time window. Different *itemids* for laboratory results or vital signs were grouped according to their clinical taxonomy to reduce missingness and duplicate measures, similar to other studies (30). All variable units with more than one *itemid* were examined. Height, weight, and temperature with different measuring units were standardized to meters, kilograms, and degrees Celsius, respectively. We used the minimum, maximum, and average of the numerical values of the time series variables. A similar approach was used by Purushotham et al. and Wang et al. to aggregate time series variables using average values or summations at their selected time windows (30, 32). The same variables were selected from the eICU database with the same measuring units as those in the MIMIC-III database. Additionally, the eICU time series variables were treated the same as in the MIMIC-III database.

Variables with more than 20% of missing values were excluded from the dataset to avoid bias in the standard deviation. We could not include two important risk factors as predictors, namely, lipidogram and smoking status, because of insufficient data. Missing values were replaced with average values.

Numerical variables were normalized in the range of 0–1 ($0 \leq z(i) \leq 1$) for better performance according to the following formula:

$$Z(i) = \frac{x\,(i) - min(x)}{(x)\ - min(x)}$$

where Z(i) is the normalized variable, and x(i) is the original variable at index i=1, 2, …, 91.

We examined the interactions between the independent variables and excluded the highly correlated predictors to avoid multicollinearity problems. Then, to successfully apply our data mining techniques to our dataset, we had to decrease the number of input variables to simplify the results and provide a better understanding and visualization (33). We selected a subset of our original variables using the feature selection method, which does not transform the variables and selects them from the existing dataset (34). The results were produced using the freely available software R, version 3.6.3 (35). Bidirectional stepwise elimination was used with the *step ()* function from the MASS package in R (36). The training dataset included two-thirds of the sample, and one-third was used to test the dataset. A description of the variables can be found in Table 2 in the **Supplementary Appendix**.

Models

Decision tree models are useful for decision-making and are prevalent in healthcare research and, thus, were selected as our primary approach for evaluating the data (37). We compared the performance of this model with logistic regression, random forest, and neural network algorithms. The performance of the different models on the classification task was measured by the *confusionMatrix ()* function using the R package *caret* (38). We used the mean accuracy, kappa, and F-score values of the validated dataset to assess the overall performance of the classification models. To predict the regression task, the root means square error (RMSE) and the mean absolute error (MAE) were used to evaluate the performance of the regression tree model.

Balanced Dataset According to Different Antihypertensive Treatments

For comparison purposes, we used the technique of treating the imbalanced classification problems to lower biased predictions that resulted from an imbalanced dataset that includes a

different number of medications that were used. For example, in the original datasets, 239 patients received nicardipine, while 1,082 patients received labetalol in the first 24 h, as presented in **Table 1**. The differences between the absolute number of medications that were used might result from specific suggestions in guidelines for the acute lowering of BP in the treatment time window or from the inherent heterogeneity of a multicenter study, which may stem from differences in practice, including differences in maximum doses and titration protocols between different centers. This may partly explain the differences in the probability of a successful BP lowering between different medications. We were unable to include the doses that were used because the doses were recorded differently at different centers and their aggregation would have resulted in inaccurate doses. To reduce this bias, we created a new, balanced synthetic dataset based on the different medications that were used. In each iteration, new synthetic data were created for a specific treatment. To balance the data, the medications that were used as independent variables in the original dataset were used as dependent variables to create the balanced synthetic data. After creating balanced synthetic observations for each treatment, all the new synthetic observations were aggregated to a final balanced dataset. In the final balanced dataset, we included the same absolute number of eight medications (the most prevalent in use in this dataset and have at least 30 records in the dataset), specifically labetalol, metoprolol, carvedilol, hydralazine, lisinopril, furosemide, amlodipine, and nicardipine. The final balanced dataset included 300 observations for each treatment, resulting in a total of 2,400 observations for eight different treatments that were detected. In the balanced dataset, we only included the patients who were treated with a single antihypertensive treatment and excluded all the observations of patients who were treated with more than one drug. Apart from the balanced observations of patients who were treated with one antihypertensive treatment, we included patients who were not treated with antihypertensive drugs in the first 24-h window. The balanced dataset was prepossessed in a manner similar to that of the original dataset. The original dataset was divided into training and testing datasets at a 2:1 ratio. The test set was left aside and saved to examine the performance of the balanced dataset on the original test set that reflects real-world data. We used the Random Over Sampling Example (ROSE) package to generate a new synthetic, balanced dataset for each treatment based on sampling methods and the smoothed bootstrap approach. The new synthetic data are generated from the conditional kernel density. We used the *ovun.sample ()* function, which enables simultaneous oversampling and undersampling (39, 40).

RESULTS

The final cohort included 7,265 patients with acute ischemic stroke, 7,470 admissions to hospitals, and 8,020 ICU stays. Among all ICU stays, 1,579 (20%) were treated with tPA or EVT. Of the ICU-stay cases, 694 (10%) met the criteria for "Success" of the primary outcome. **Table 2** shows the characteristics of the study population.

TABLE 2 | Characteristics of the study population.

Patient characteristic	Prevalence, (%) or Mean ± SD
Sex	
Women	46.8
Age, y	66.5 ± 13.6
18–29 (%)	1.5
30–49 (%)	9.8
50–69 (%)	42.3
70–89 (%)	46.6
Ethnicity	
Caucasian (%)	74.4
African	12
American (%)	
Hispanic (%)	4.5
Asian (%)	2
Other (%)	7.1
Selected comorbidities (%)	
Hypertension (%)	27.4
Cardiac arrhythmias (%)	17.2
Diabetes uncomplicated (%)	7.4
Diabetes complicated (%)	0.5
Renal failure (%)	7.8
Congestive heart failure (%)	6.7
Chronic pulmonary disease (%)	7.2
Hypothyroidism (%)	3
Alcohol abuse (%)	1.7
Received endovascular or thrombolytic treatment (%)	19.7
Antihypertensive drug class	
Beta-blockers (%)	29.2
Direct vasodilators (%)	14.4
CCBs (%)	8.4
Diuretics (%)	8
ACE-I (%)	5
Sympatholtics agent (%)	1
ARBs (%)	0.5
Nitroprusside (%)	0.4
Number of antihypertensives drug classes	
0 (%)	60.9
1 (%)	19.4
2 (%)	13.7
3 (%)	4.6
4 (%)	1.3
5 (%)	0.2
Time-weighted average SBP (mmHg)	133.6 ± 20.1
Time-weighted average DBP (mmHg)	70.3 ± 18.2

SD, Standard deviation; CCBs, Calcium channels blockers; ACE-I, Angiotensin-converting enzyme inhibitor; ARBs, Angiotensin receptor blockers.

Decision Tree Model

The tree is constructed by a hierarchical binary recursive partitioning algorithm, which enables the visual representation of statistically significant results as a tree. Unlike popular techniques for building trees, CART and C4.5, the conditional interference

tree (Ctree) method examines whether the covariates and the response variable are statistically significant ($p < 0.05$) and have a better handle on the overfitting problem and selection bias toward covariates with many possible splits (41). The Ctree was implemented using the *ctree ()* function with the R package *party*, which is useful for predicting both the categorical outcome (classification trees) and continuous outcomes (regression trees). The minimum criterion for each split was selected as $p < 0.05$, and the input variable with the smallest p-value was used for the next division (41).

Figures 4A, **5A** show the two main branches of the conditional interference tree. A variation of this tree is represented in **Figures 4B**, **5B** as subtrees. In **Figures 4B**, **5B**, the drug classes were replaced with the specific medications that were used in the first 24 h, as shown in **Table 1**. Additional information regarding the specific medications that reduce BP to the selected interval provides clinicians with more information regarding which medication is most effective for BP reduction from every drug class. For each branch, three subtrees were constructed and are represented by asterisks (*, **, and ***). The different drug classes were replaced by the drug that induced the greatest reduction, as shown in **Figures 4B**, **5B**.

In **Figures 4A**, **5A**, at the top of the tree, the strongest associated variable ($p < 0.001$) is the maximum DBP. The splitting criteria for the first node are based on whether the maximum DBP that was observed in the 24-h time window was above 120 mmHg (left branch) or equal to or below 120 mmHg (right branch). **Figure 4A** shows the right branch of the tree. The second split is based on whether the patient received tPA or EVT, as follows: TagtPA = 1 for "received" and TagtPA = 0 for "not received" (node 2). On the right side for patients who received EVT or tPA, when the DBP was between 105 and 120 mmHg (node 15), and the SBP was below 188 mmHg (node 19), the probability of BP reduction with beta-blockers was 0.9 (terminal node 20, $p = 0.048$). When the DBP was below 105 mmHg (node 15), patients who received beta-blockers (BetaB = 1) had a probability of 0.7 to manage the treatment successfully when the SBP was above 180 mmHg (terminal node 18, $p < 0.001$). Two effective treatments from the beta-blocker class were identified. Metoprolol with a 0.9 probability of reducing BP to the selected interval when the SBP was above 181 mmHg (**, node 6), and the DBP was between 106 and 120 mmHg. Labetalol had a probability of 1 when the DBP was between 97 and 120 mmHg.

Patients who received EVT/tPA and were treated with vasodilators (DirectVasoD = 1, node 7) had a probability of 0.8 for predicting the primary outcome (terminal node 8, $p < 0.001$). However, the treatment of Hydralazine (***, node 7) was found to be less effective in predicting BP reduction to the selected interval (0.4 probability). Patients who received EVT/tPA had a very low probability of BP reduction when ACE-I (node 9), CCBs (node 11), or diuretics (node 14) were administered ($p < 0.001$). On the left side, patients who did not receive EVT/tPA with SBP above 220 mmHg (node 3) and those who received beta-blockers (node 4) had a probability of 0.8 for the prediction of the primary outcome ($p < 0.001$). The most significant treatment from the beta-blocker drug class was labetalol (*, node 4), with the same probability of BP reduction.

Figure 5A represents the left branch of the tree, where the MaxDBP is above 120 mmHg. On the left side, in patients who received beta-blockers (BetaB = 1, node 22), success in predicting the primary outcome was related to sodium levels (node 34, $p = 0.01$). For patients with SBP below or equal to 202 mmHg (node 33) and sodium levels higher than 129 mEq/L, using beta-blockers lowered the BP with a probability of 0.9 (terminal node 36). In comparison, for sodium values lower than 129 mEq/L, the probability of lowering the BP was 0.5 (terminal node 35), that is, random probability, and, thus, does not contribute to hypertension management.

The subtree for the beta-blocker class is shown in **Figure 5B** (*, node 22). When labetalol is administered, the probability of reducing BP is 0.9 (terminal node 38) if the SBP is below or equal to 200 mmHg. However, when BP is above 200 mmHg, the probability is 0.6 (terminal node 39). When metoprolol (node 40) is administered, the probability is 0.7 (terminal node 41).

On the right, patients who did not receive beta-blockers (BetaB=0, node 22) but received ACE inhibitors (node 29), direct vasodilators (node 23), and CCBs (node 31) had a probability of 1, 0.8, and 0.8, respectively ($p < 0.001$). Patients who received diuretics (node 24) had a high probability, 1, when the SBP was equal to or below 197 mmHg (node 26); however, when the SBP was above 197 mmHg, the probability of BP reduction was incredibly low and equal to 0.3 ($p = 0.002$).

As evident in **Figure 5B**, the most significant treatment from the ACE-I class is lisinopril (node 24, subtree ***), with the same probability of 1 to reduce BP to the interval. Amlodipine (node 30, subtree ***) was the most significant drug treatment from the CCB class and resulted in the reduction of BP with a higher probability (0.9). Furosemide (node 26, subtree ***) lowers BP with a probability of 0.8 (terminal node 22, subtree***) when the SBP (node 27) is below or equal to 204 mmHg. However, when the SBP is above 204 mmHg, the probability to lower BP to the selected interval is very low and equal to 0.1 (terminal node 29). Hydralazine (node 23, subtree**) lowers BP with a probability of 0.9 (terminal node 36) if the SBP is above 225 mmHg and lisinopril is not administered.

The decision trees presented in **Figures 4**, **5** yielded accuracy, F-score, and kappa values of 0.977, 0.884, and 0.871, respectively, for the original dataset and slightly lower values of 0.971, 0.857, and 0.841, respectively, for the reduced dataset, as shown in **Table 3**. The performance of the variant tree that yielded the subtrees in **Figure 4** was similar to that of the original tree with accuracy, F-score, and kappa values of 0.971, 0.845, and 0.861, respectively.

We further evaluated the TWA of SBP and DBP with regression trees to assess the effect of the different antihypertensive drugs on BP reduction during the first 24 h of treatment. This additional assessment provided information regarding the level of BP achieved with the use of the different treatments. The diastolic (**Figure 6B**) and systolic BP values (**Figure 6C**) were evaluated independently as TWA over 24 hours. Only labetalol and hydralazine demonstrated a predictive association on regression analysis ($p < 0.001$).

Treatment with Labetalol predicted a TWA BP of 138.5/72.6 mmHg. When Hydralazine was used, the predicted TWA BP

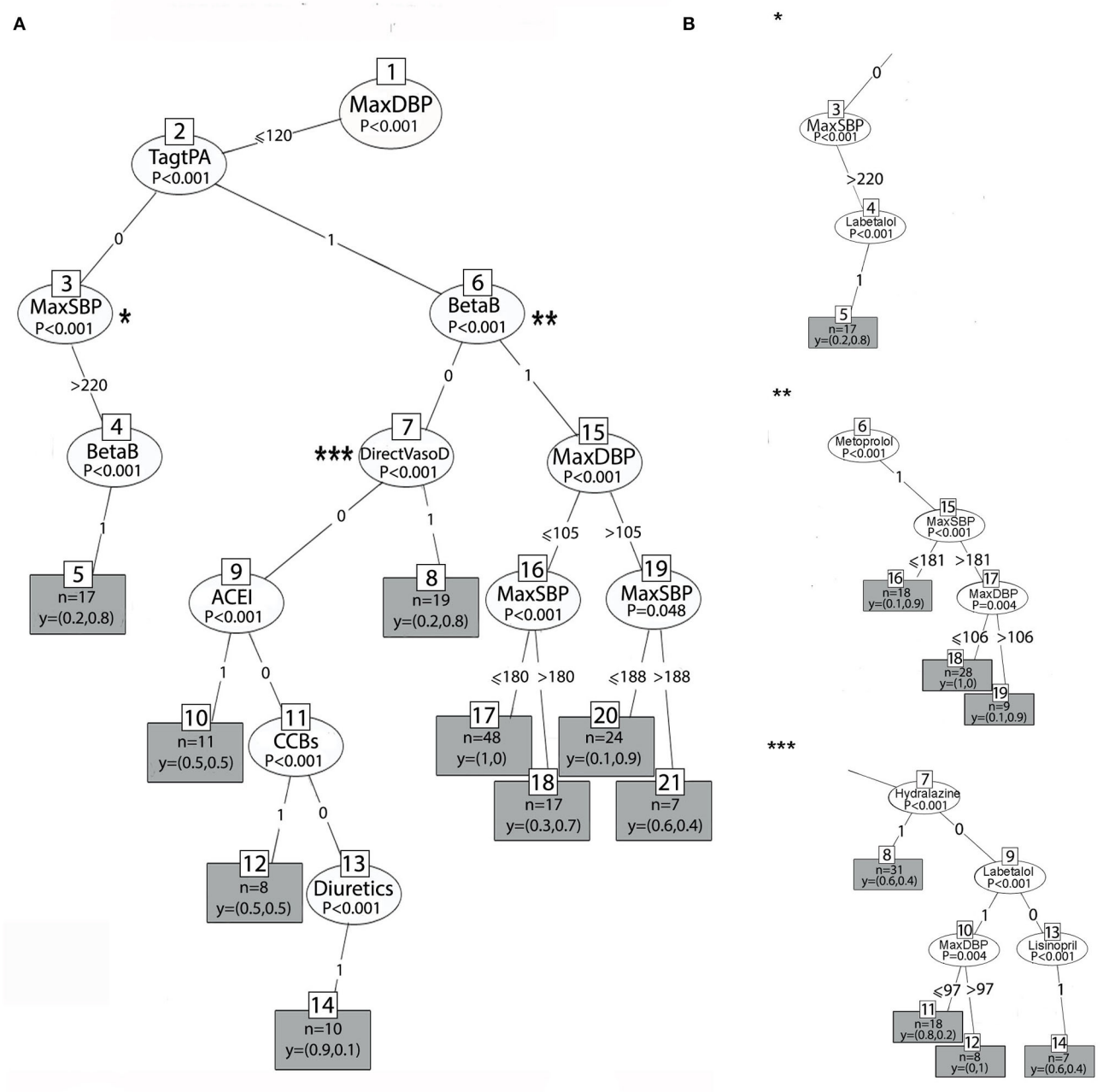

FIGURE 4 | (A) The right branch of the classification tree. Each split is represented by a node. The first split is the root node, and the others are the intermediate nodes. For each node, the Bonferroni-adjusted *P*-values are given. Each rectangle is a terminal node which is showing the probability distribution of occurrence over the two classes of the primary outcome and includes the number of observations associated with the specific node result that files the decision claims. **(B)** Subtrees represent the most prominent medication that lowers BP to the selected interval from each drug class by astricts.

was 140.9/80 mmHg. The predicted TWA SBP for patients who received tPA was 134.7 mmHg.

Both regression trees showed a prediction of BP according to different sodium levels. When the sodium levels were higher than 132 mEq/L, the predicted TWA SBP was 131.6 mmHg, and for lower sodium levels, the predicted TWA SBP was 126 mmHg. When the sodium levels were higher than 133 mEq/L, the predicted TWA DBP was 70 mmHg, while for lower sodium levels, the predicted TWA DBP was 67.5 mmHg.

The RMSE of the TWA SBP regression tree model was 19.72 mmHg, and the MAE was 15.9 mmHg. Regarding the TWA DBP regression tree model, the RMSE was 24.6 mmHg, and the MAE was 10.22 mmHg.

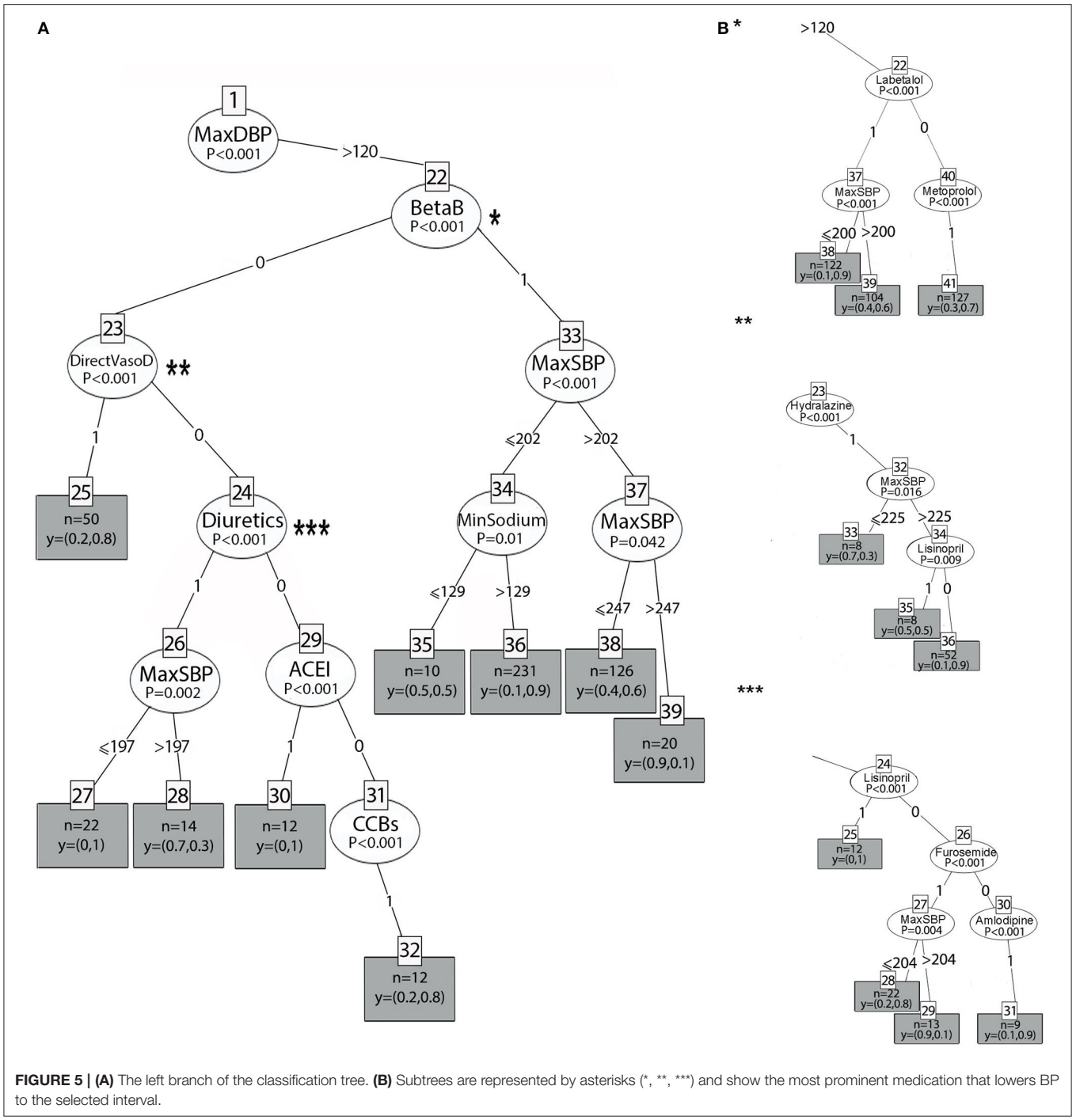

FIGURE 5 | (A) The left branch of the classification tree. **(B)** Subtrees are represented by asterisks (*, **, ***) and show the most prominent medication that lowers BP to the selected interval.

TABLE 3 | Comparison of the performances of the different models.

Model	Original dataset			Dataset after feature selection		
	Accuracy	Kappa	F-score	Accuracy	Kappa	F-score
Ctree	0.977	0.871	0.884	0.971	0.841	0.857
RandomForest	0.984	0.91	0.901	0.972	0.843	0.864
Logistic regression	0.93	0.52	0.557	0.928	0.531	0.569
Neural networks	0.963	0.769	0.789	0.968	0.822	0.840

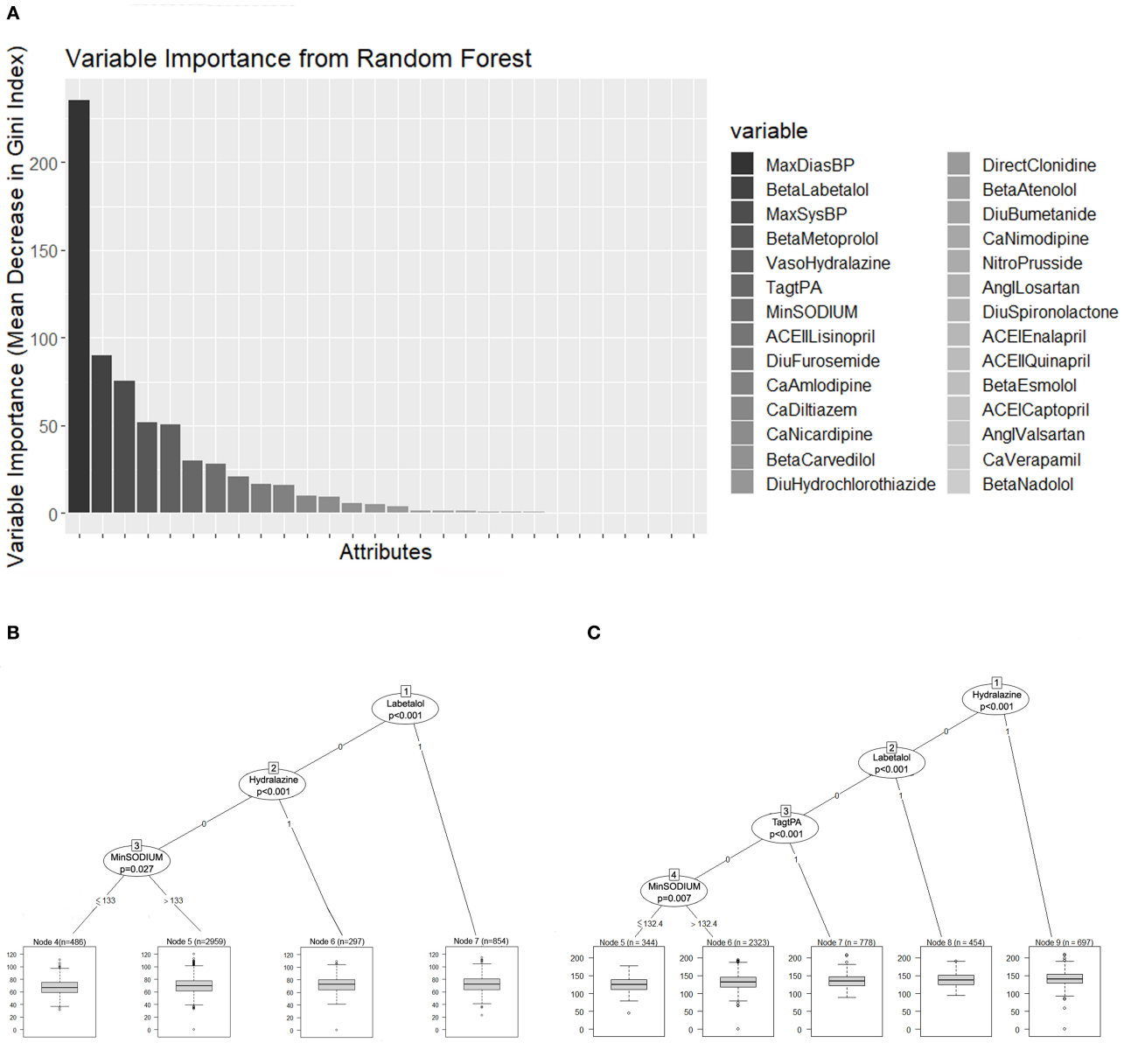

FIGURE 6 | (A) Random forest variable importance by mean decrease in Gini index. **(B,C)** Represent the regression trees that predict the TWA of DBP and SBP, respectively. Each terminal node has a boxplot that shows the median, IQR, and outliers. TWA, time-weighted average; DBP, Diastolic blood pressure; SBP, systolic blood pressure; IQR, interquartile range.

Classification Model for the Balanced Dataset

The results of the decision tree analysis based on the balanced dataset are shown in **Figure 7**. Similar to the imbalanced dataset, DBP was the main variable that predicted the primary outcome. In addition, when the maximum DBP is below 120 mmHg, BP management depends on the thrombolytic status. Of the eight medications that were selected to be included in the balanced dataset, only two medications in this group of patients who received tPA/EVT showed statistically significant results for lowering BP to the selected interval: Labetalol and Amlodipine. Both had a probability of 1 to lower BP, 10–30% of the maximum value in the first 24 h after stroke onset. This means that when a physician will treat patients who receive tPA/EVT according to guidelines (BP> 180/120 mmHg), he/she will lower the average BP until the end of the first 24 h by 10–30% of the maximum value if they will be treated with labetalol or amlodipine. When the DBP is above 120 mmHg, the probability of lowering BP depends on the SBP and on the specific treatment that was administered. In addition, BP reduction also depends on the sodium level

and kidney function (creatinine levels). Accordingly, when the BP is above 163/120 mmHg, the probability of lowering BP with amlodipine was 1, whereas when the SBP was below 163 mmHg, the probability of decreasing BP to the interval was only 0.5, that is, a random probability ($p = 0.024$, terminal nodes 14 and 13, respectively). When Labetalol is administered, the probability is 0.7 ($p < 0.001$, terminal node 37). This means that in high levels of BPs, there is a 70% probability that BP will be lowered by Labetalol to the selected interval, but in the other 30%, whether BP is decreased is unknown. When Hydralazine is administered, the probability is 0.6 ($p < 0.001$, terminal node 17). When lisinopril is administered, the probability of lowering BP to the interval depends on the sodium levels: above 138 mEq/L, the probability is 0.9, while for lower sodium levels, the probability is much lower and equals 0.5. The probability of lowering BPs with nicardipine depends on the BP levels, kidney function, and sodium levels, and accordingly, is equal to 0.9 when the SBP is below 195 mmHg, the creatinine levels are below 1.47 mg/dL, and the sodium levels are 133 mEq/L. However, when the sodium levels are lower, the probability of lowering the BP to the interval is 0. The probability of lowering BP when the DBP is below 120 mmHg with metoprolol is low and equals 0.6 ($p < 0.001$, node 26). The probability of lowering BP with furosemide depends on the SBP levels. When the SBP was above 200 mmHg, the probability was 0.83. However, for SBP < 200 mmHg, the probability was 0 ($p < 0.001$, terminal nodes 25 and 26, respectively). The performance of the balanced tree yielded high accuracy, F-score, and kappa values of 0.94, 0.8, and 0.75, respectively.

Random Forest Model

Random forest algorithms aggregate many decision trees and add randomness to the model, thus, improving the performance of the decision trees and reducing overfitting (42). The classification random forest algorithm was implemented using the R package *randomForest* (43). It was tuned with a random search of the number of variable samples at each split using *the caret* package in R (38).

Each decision tree was randomly selected from a given dataset using different bootstrap samples. The random forest algorithm obtains a prediction from each tree, performs a vote for each predicted result, and then selects the best solution with the majority of votes. The most important variables used in the algorithm are those with a lower probability of incorrect classification.

Figure 6A represents the random forest variable importance based on the mean decrease in the Gini index. MaxDBP, Labetalol, MaxSBP, Metoprolol, Hydralazine, Tag tPA, and minimum sodium levels are the most important variables in the prediction task, similar to the results represented by the decision trees.

Neural Networks

The feed-forward multi-layer perceptron (MLP) neural network algorithm was implemented using the R package *nnet* (36). As shown in **Figure 8**, 24 input variables were received in the first layer on the left and processed within a hidden intermediate layer, using a weighted summation and an activation function. Within the hidden layer, a learning algorithm optimizes the weight between two connected neuron-like units. The bias nodes shift the activation function and generate better prediction results. The output layer on the right produces the result for a given input from the hidden layer.

Comparing the different classification models, the highest performance was found for the random forest model with accuracy, kappa, and F-score values of 0.984, 0.91, and 0.901, respectively, for the original dataset, and 0.972, 0.843, and 0.864, respectively, for the reduced dataset. The results of the performance of the different models are listed in **Table 3**.

The moderate model performance of the logistic regression model is shown by lower accuracy, kappa, and F-score values of 0.93, 0.52, and 0.557, respectively, for the original dataset, and 0.928, 0.531, and 0.569, for the reduced dataset. After the random forest and decision tree, the neural network algorithm showed high accuracy, F-score, and kappa values.

DISCUSSION

This study assesses whether a patient who receives antihypertensive treatment, according to recommended thresholds, is an effective treatment that lowers BP in the range of 10–30% below the maximum BP value in the first 24 h after the acute ischemic stroke onset. In comparison to randomized clinical trials that were tested in conventional methods, one or two medications in each clinical trial and compare the results to a placebo group, our study simultaneously examined over 100 antihypertensive medications using ML techniques.

This study has three major findings:

1. Blood pressure (BP) management in the first 24 h after a stroke should be managed according to different BP levels and other clinical variables, mainly kidney functioning and sodium levels. Diastolic blood pressure (DBP) is the main variable predicting the probability of BP reduction in the first 24 h after acute ischemic stroke.
2. For patients receiving tPA/EVT, labetalol and amlodipine are effective treatments when antihypertensive treatment is administered in cases where SBP $>$ 180 mmHg and DBP $<$ 120 mmHg.
3. Monitoring and treating low sodium levels ($<$133 mEq/L) is important for successful BP reduction in the first 24 h after the acute ischemic stroke in patients with very high BP (DBP$>$ 120 mmHg). The independent regression analysis predicting the TWA BP supports the relationship between sodium levels and BP.

In accordance with the AHA/ASA recommendations, we found that the group of patients receiving tPA would benefit from beta-blockers when DBP ranges from 105 to 120 mmHg with a high probability of reducing BP to the selected interval with Labetalol ($p = 0.004$). These results are supported by the analysis of both balanced and imbalanced datasets. Labetalol also lowers BP with a probability ranging between 0.6 and 0.7 when the BP is above 200/120 mmHg, that is, in 30–40% of cases, and the

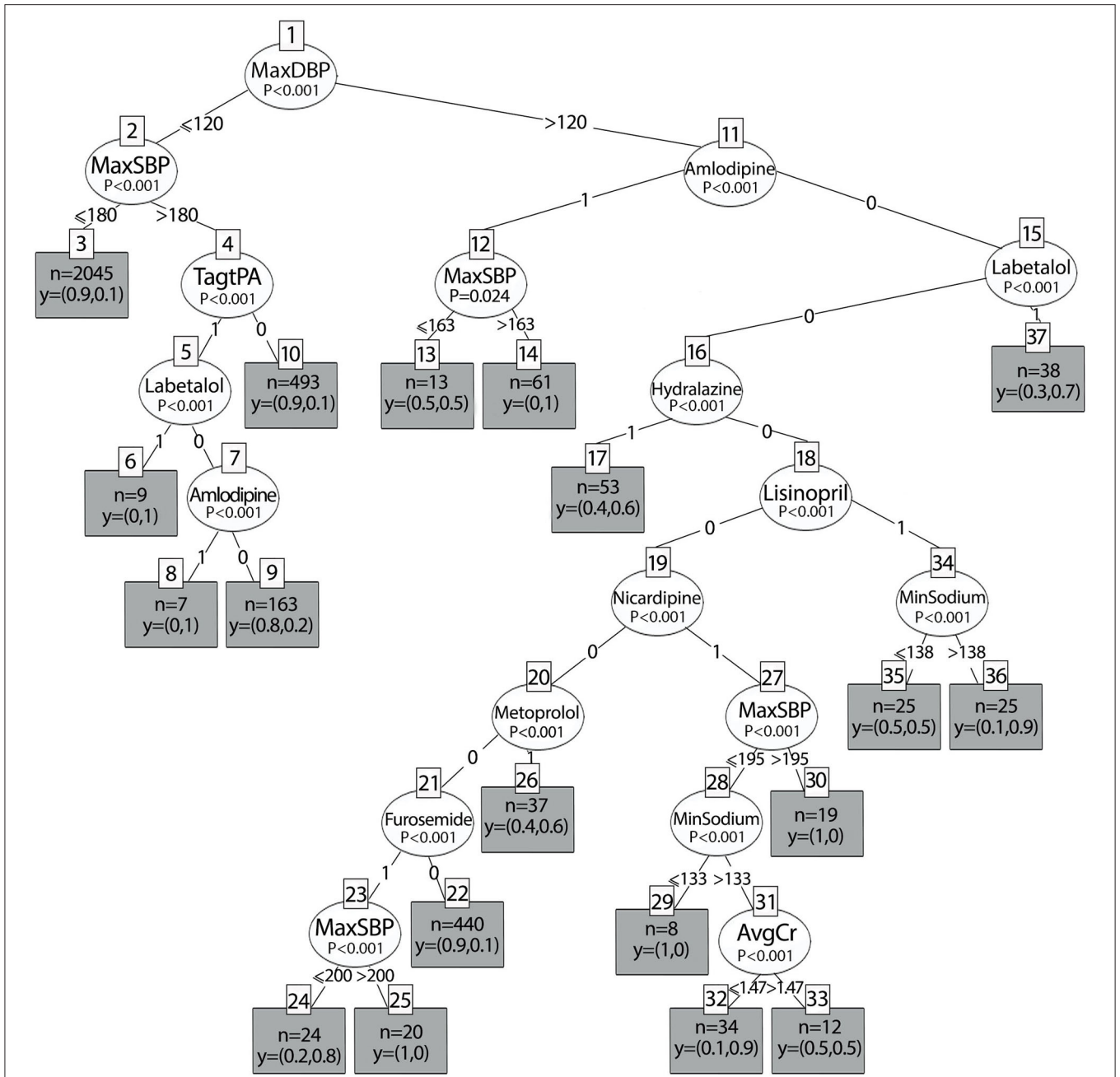

FIGURE 7 | Decision tree results of the balanced dataset according to different antihypertensive treatments.

goal of BP reduction to the interval is not reached. This may reflect the difficulty of lowering BP with labetalol in patients with excessively high BP. Treatment with labetalol predicted a TWA BP of 138.5/72.6 mmHg ($p < 0.001$) in the hyper-acute phase after a stroke. Unlike current recommendations, patients receiving EVT/tPA with DBP < 120 mmHg had a low probability of BP reduction over the prescribed range with CCB therapy ($p < 0.001$) as a class group. However, the balanced dataset analysis showed very good results with the use of amlodipine. The use of amlodipine for patients receiving tPA/EVT should be further studied as a potential antihypertensive treatment in this group of patients. This is a novel finding that emerged from this study and has practical importance.

Another important finding is the significance of electrolyte balance, especially sodium levels, in BP management. In patients with DBP above 120 mmHg, successful BP management is related to sodium levels. According to the balanced results, both lisinopril and nicardipine treatments depend on avoiding hyponatremia. Sodium levels lower than 129–133 mEq/L do not contribute to hypertension management in acute stroke

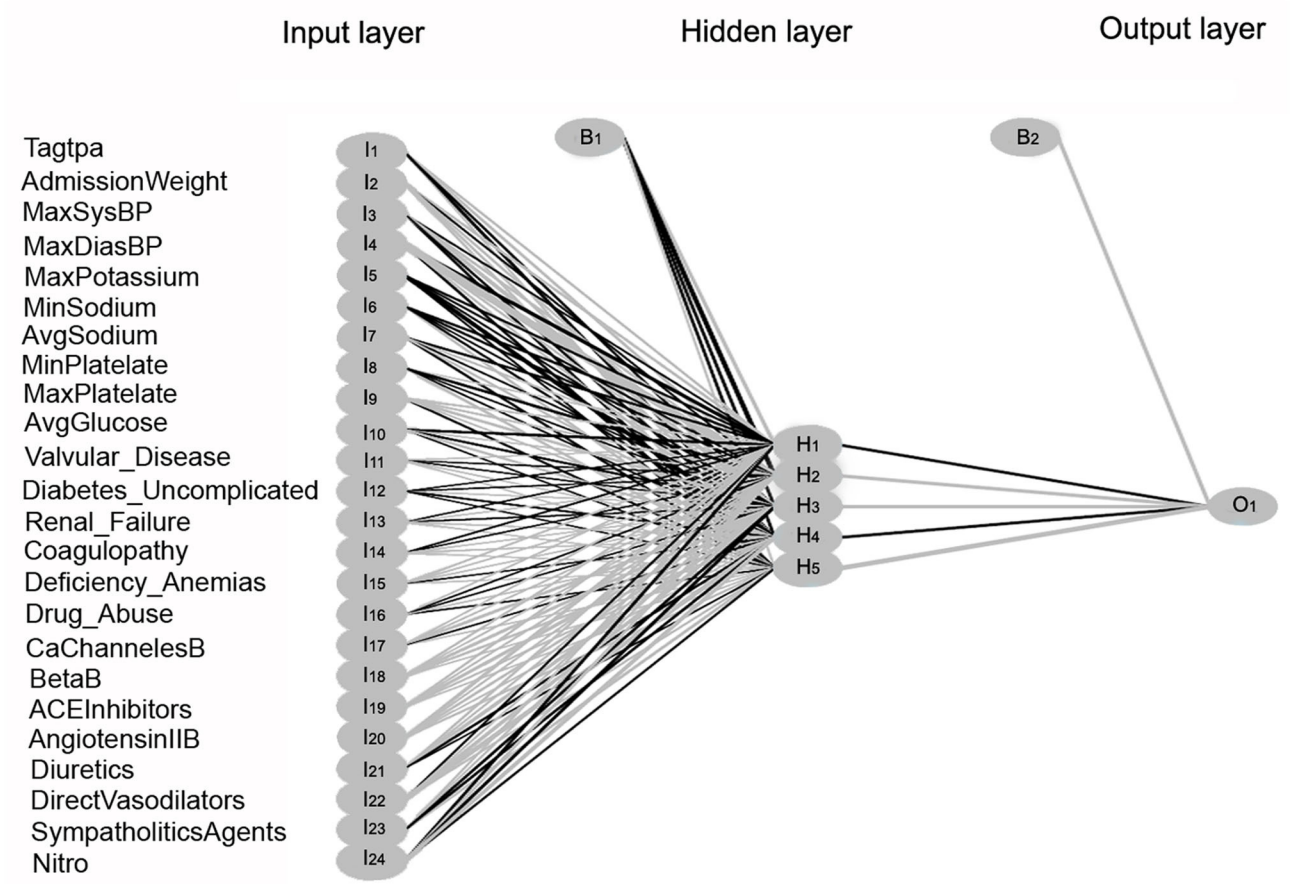

FIGURE 8 | Multi-Layer Perceptron neural network model illustration. Three layers within the neural network are shown: the input layer, hidden layer, and output layer. Twenty-four input variables labeled as I1-I24 are transmitted to the hidden layer. Within the hidden layer, neuron-like units are labeled as H1-H5. The bias nodes are labeled as B1 and B2. The response variable in the output layer is labeled as O1.

because the probability of BP reduction is 0–0.5. Nicardipine is also effective only when kidney functioning is normal or only slightly elevated (creatinine <1.47 mg/dl) and when the SBP is below 195 mmHg. Above an SBP of 195 mmHg, the probability of lowering BP to the interval with nicardipine was very low. However, we cannot exclude a temporary response to a lower BP with nicardipine. According to the analysis of the imbalanced dataset, nicardipine was not included in the results of the decision tree algorithms. This might have resulted from the relatively lower number of observations with nicardipine treatment. The balanced dataset corrected the bias of minority representation of nicardipine, which can be attributed to different protocols that were used in different ICU units and found to be statistically significant for the prediction task. Similar results for the regression trees indicated a significant relationship between BP and sodium levels. The regression trees predicted higher DBP and SBP for higher sodium levels above 132 mEq/L and a modest reduction in BP of 5.6/2.5 mmHg ($p < 0.05$) for lower levels of sodium.

Hyponatremia is common in patients with acute stroke and is attributed to stroke-related causes, such as elevated secretion of antidiuretic hormone (ADH) and salt-wasting syndrome, as well as to non-stroke-related causes, such as comorbidities, the use of certain medications, and iatrogenic causes (44). The different mechanisms by which hyponatremia occurs in acute stroke patients might account for the difficulty in predicting the success of the BP-lowering strategy in patients with hyponatremia. The relationship between sodium levels and BP during the acute phase of ischemic stroke is not well-established; however, in certain circumstances, hyponatremia is related to fluid imbalance and might impair BP regulation (45).

In accordance with the AHA/ASA recommendations to use CCBs (nircadipine, clevidipine) and the INWEST trial that showed a significant decrease in SBP and DBP with nimodipine (18), we found that nircadipine and amlodipine are efficient in lowering BP to the target interval under certain conditions. Regarding amlodipine, when BP is above 163/120 mmHg, the probability of lowering BP ranges between 0.9 and 1. In patients receiving tPA/EVT with DBP < 120 mmHg, only amlodipine was found to be effective. As discussed above, treatment with nicardipine is effective when SBP< 195 mmHg, and success depends on sodium and creatinine levels.

Similar to the CHHIPS trial that showed a significant decrease with lisinopril (16), our results show that patients with DBP > 120 mmHg who received lisinopril had a high probability (0.9–1) to lower the BP to the target interval, with a statistical significance of $p < 0.001$. These results are supported by the analysis of both balanced and imbalanced datasets. According to the imbalanced dataset, Lisinopril showed a low probability of reducing BP when the DBP was lower than 120 mmHg. Treatment with lisinopril was not included in the results of the balanced dataset for DBP< 120 mmHg (right branch of the tree, **Figure 6**), because it did not meet the minimum criteria of split $p < 0.05$, or because other variables (selected by the decision tree algorithm) had a lower p-value and contributed more to the prediction task.

When DBP was above 120 mmHg, both hydralazine and metoprolol showed a low probability of lowering BP (0.6). The imbalanced dataset showed that treatment with Hydralazine was effective when SBP was above 225 mmHg. However, for lower BPs, hydralazine lowered BP with a very low probability. This is not reflected in the balanced dataset analysis. This might result from the fact that the imbalanced dataset also included patients who received more than one antihypertensive treatment. Therefore, we can see that subtree** in **Figure 5** includes more than one medication, and part of the results depend on administering hydralazine with lisinopril as an adjuvant treatment. Metoprolol lowers BP with a probability of 0.6–0.7 when the DBP is above 120 mmHg. When the DBP is between 106 and 120 mmHg, the probability of lowering BP to the interval is high and equals 0.9, according to the imbalanced analysis. As with lisinopril, metoprolol was not included in the analysis of the imbalanced dataset when the DBP was below 120 mmHg.

The algorithm shows that BP reduction with furosemide is effective when the SBP is below 200 mmHg with a high probability, 0.8, which will reduce BP. However, in patients with SBP > 200 mmHg, the probability of lowering BP is very low. This might be related to the fact that furosemide inhibits the Na-K-Cl cotransporter, resulting in the increased secretion of sodium in the urine. This explanation is suggested because the results indicate that effective treatment depends on avoiding low sodium levels for certain medications (nicardipine and lisinopril).

We emphasize that the analysis with ML techniques to predict outcomes indicates the relationships between predictors and outcomes rather than causality.

In our research, ARBs were not included in the decision tree results because the variable did not reach the minimum criterion of $p < 0.05$. These results are consistent with the trials that showed a significant decrease of <10/6 mmHg when compared to placebo (19, 20). This decrease is likely not to exceed a threshold of a 10% reduction in BP.

We found that both decision tree (Ctree) and random forest algorithms have very high accuracy, kappa, and F-score values. We chose a subset of features by using a bidirectional stepwise algorithm that selected the most relevant features from the original dataset and, thus, decreased the model complexity without significantly reducing the prediction accuracy. The high kappa and F-score values indicate the high validity of the models. The moderate model performance of the logistic regression model vs. the decision tree algorithm is evident by the lower kappa and F-score values. Similar results of better accuracy performance when tree algorithms were compared to logistic regression were found when tested on large datasets (46). The neural network algorithm also showed high accuracy, F-score, and kappa values, but these values were slightly lower than those of the decision tree and random forest algorithms. However, the neural-network algorithm showed better performance after the feature selection process. Nonetheless, it is difficult to visually represent and explain neural networks.

Limitations

This study has several limitations. Our study reflects the current general recommendations and current practices for hypertension management after acute stroke. However, the two databases that were used included data that were collected during 2001–2012 (MIMIC-III) and 2014–2015 (eICU) and may reflect the management of stroke patients before the up-to-date recommendations that replaced the 2013 guidelines for the early BP management of patients with acute ischemic stroke. In addition, the exact range of BP lowering in extremely high BP is not well-established yet. Patients with severe hypertension (> 220/120 mmHg) were usually excluded from studies that examined the clinical outcomes related to BP lowering after acute ischemic stroke. Thus, whether a lowering of 10–30% from the maximum BP for highly elevated BP is too drastic should be further studied. Another important issue that clinicians should take into consideration is that the decision-making in hypertension management after acute stroke should not guide treatment alone, and clinical judgment is cardinal, especially for patients with acute concomitant comorbidities (such as acute myocardial infarction, acute heart failure, aortic dissection, or preeclampsia/eclampsia) in whom treatment should be individualized. In addition, it is important to pay attention to the contraindications of certain antihypertensive drug classes. The use of beta-blockers in acute decompensation of heart failure or the use of beta-blockers in patients with asthma exacerbation are some of the examples. Further research is needed to examine the outcomes of BP lowering in the acute phase after ischemic stroke, especially in patients with severe hypertension (>220/120), who are underrepresented in clinical trials. Outcomes according to different BP-lowering intervals should be further examined.

CONCLUSION

This is the first study to address BP management in the acute phase following ischemic stroke using ML techniques. The study shows that the choice of antihypertensive treatment in the context of acute ischemic stroke should be adjusted to different BP levels and clinical features of the patient, thus providing a better decision-making approach. Further work will clarify whether there are different subgroups of patients for whom specific BP management options are better, and might include additional outcomes such as morbidity levels, mortality, readmission to hospitals, and recurrent stroke. ML techniques are used to discover hidden patterns from data and to apply robust interrogation to datasets; however, there is a risk of overfitting. However, the potential improvement in BP management in acute

ischemic stroke suggested in this study should not be ignored. Rather, follow-up studies should further examine the strategies to reduce inherent ML risks and attempt to replicate the results of clinical studies.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: Johnson, A., Pollard, T., & Mark, R. (2019). MIMIC-III Clinical Database Demo (version 1.4). PhysioNet. https://doi.org/10.13026/C2HM2Q. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, and Badawi O. Scientific Data (2018). http://dx.doi.org/10.1038/sdata.2018.178. Available from: https://www.nature.com/articles/sdata2018178.

ETHICS STATEMENT

MIMIC-III and eICU databases have received ethical approval from the Institutional Review Boards (IRBs) at BIDMC and MIT and because the database does not contain protected health information, a waiver for the requirement for informed consent was included in the IRB approval. Researchers using those databases are required to formally request access. There are two key steps that must be completed before access is granted: the researcher must complete a recognized course in protecting human research participants that includes Health Insurance Portability and Accountability Act (HIPAA) requirements. The researcher must sign a data use agreement, which outlines appropriate data usage and security standards, and forbids efforts to identify individual patients. Access was granted to OM on July 28, 2019. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception, design of the work, contributed to revising it critically for important intellectual content, and gave their final approval of the version to be published. OM was also responsible for the extraction, analysis of the data, and manuscript drafting.

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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.2021.743728/full#supplementary-material

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BRIEF RESEARCH REPORT
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The Impact of Mean Arterial Pressure and Volume Contraction in With Acute Ischemic Stroke

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Background and Purpose: Hydration at the time of stroke may impact functional outcomes. We sought to investigate the relationship between blood pressure, hydration status, and stroke severity in patients with acute ischemic stroke (AIS).

Methods: We evaluated hydration status, determined by blood urea nitrogen (BUN)/creatinine ratio, in consecutive patients with AIS from a single comprehensive stroke center. Baseline mean arterial pressure (MAP) was analyzed using a linear spline with a knot at 90 mmHg. Baseline stroke severity was defined based on admission NIH Stroke Scale scores (NIHSSS) and MRI diffusion-weighted imaging.

Results: Among 108 eligible subjects, 55 (51%) presented in a volume contracted state. In adjusted models, in the total sample, for every 10 mmHg higher MAP up to 90 mmHg, NIHSSS was 2.8 points lower ($p = 0.053$), without further statistically significant association between MAP above 90 and NIHSSS. This relationship was entirely driven by the individuals in a volume contracted state: MAP was not associated with NIHSSS in individuals who were euvolemic. For individuals in a volume contracted state, each 10 mmHg higher MAP, up to 90 mmHg, was associated with 6.9 points lower NIHSSS (95% CI −11.1, −2.6). MAP values above 90 mmHg were not related to NIHSSS in either dehydrated or euvolemic patients.

Conclusions: Lower MAP contributes to more severe stroke in patients who are volume contracted, but not those who are euvolemic, suggesting that hydration status and blood pressure may jointly contribute to the outcome. Hydration status should be considered when setting blood pressure goals for patients with AIS.

Keywords: hydration, blood pressure, stroke severity, acute ischemic stroke, hospital care, early recovery

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INTRODUCTION

Despite advances in stroke care and identification of acute therapies for ischemic stroke, stroke remains a leading cause of adult disability. (1). Blood pressure management is a critical component of patient management in the early stroke recovery period. A growing body of evidence suggests that patients who are dehydrated, volume contracted, or both at the time of stroke have worse functional outcomes independent of age, size of the stroke, or presence of complex comorbidities (2, 3). The mechanism behind this relationship is yet unknown, though many hypothesize that the worse outcome is due to blood pressure variations that alter cerebral perfusion during a period of disrupted autoregulation. We propose that hydration status may play an independent role.

Surprisingly, rehydration after stroke has received little attention in the United States outside of a small study of induced hypertension and a series of hemodilution studies (4–7). Expert consensus drives the current acute stroke recommendation for rehydration for patients who are in a volume contracted state (8). These are challenging to implement as there is no single objective measure for dehydration and the duration of therapy is not specified especially in the setting of comorbid conditions (9). There are several approaches to quantifying hydration status with varying levels of data to support such practices: non-invasive cardiac output monitoring with passive leg raise and fluid challenge, bioelectric impedance vector analysis, and serum markers of hydration status (10–14). In this study, we use blood urea nitrogen (BUN) to creatinine ratio as a surrogate objective marker of hydration status with the threshold for volume contracted state as BUN/creatinine $>$ 15 since it is readily available for use globally (15–17). We sought to explore the relationship between hydration status, blood pressure, and stroke severity in order to test the relative contributions of these physiologic factors in patients with acute ischemic stroke (AIS). Specifically, the present study sought to determine whether or not hydration status modifies the relationship between blood pressure and stroke severity. We additionally wished to identify similar relationships between hydration and blood pressure and longer-term functional outcome, measured at 3 months using modified Rankin Scores (mRS).

METHODS

Data Source

Consecutive patients with ischemic stroke were prospectively screened for eligibility between 2014 and 2015. Subjects were included if they had MRI-confirmed ischemic stroke within 12-h from stroke onset and did not have signs of active infection, gastrointestinal bleeding, or chronic kidney disease. Indirect measures of volume status including BUN/creatinine ratio were collected with a threshold of BUN/creatinine ratio $>$ 15 sets as the indicator of a volume contracted state. Stroke severity was determined by the NIH Stroke Scale (NIHSSS) at the time of hospital presentation. Mean arterial pressure (MAP) was calculated using standard equations based on the first blood pressure obtained on arrival to the hospital. Infarct volume was calculated using baseline MRI diffusion-weighted imaging (DWI) sequences and diffusion to perfusion (PWI) mismatch calculated if perfusion study was obtained as the standard of care upon admission to the hospital using OleaSphere software (OleaSphere 3; Olea Medical, La Ciotat, France) by a single primary rater blinded to both diagnosis and hydration status. The study was approved by the university's Institutional Review Board.

Statistical Analysis

Statistical analysis was performed using Stata Statistical software version 13 (StataCorp LP, College Station, TX, USA). The primary outcome was stroke severity defined by NIHSSS. Comparisons of key clinical characteristics based on hydration status and MAP were made using Fisher's exact tests for categorical variables and the *t*-tests for continuous variables. Given the appearance during descriptive analysis using a LOWESS curve of a non-linear pattern between MAP and NIHSSS, a linear spline was used, with a single knot at 90 mmHg.

Statistically significant variables derived from univariable analysis as well as other variables that may be plausibly associated with stroke severity were considered as covariates; however, final model selection was based on the Akaike Information Criterion. Multivariable linear regression models evaluating MAP using this spline, and considering NIHSSS as the dependent variable, were adjusted for age, sex, atrial fibrillation, diabetes, and infarct volume. Exploratory analysis of the functional outcome was based on an a priori dichotomized mRS: 0–1 $=$ favorable functional outcome and $>$ 1 $=$ poor outcome, in similarly-adjusted logistic regression models.

To investigate the relationship between hydration status and blood pressure at the time of stroke, we used the above-described linear regression models, adjusted for the same potential confounders, evaluating the effect of MAP on baseline NIHSSS, but stratified models by hydration status, along with formal testing for interaction between MAP and hydration status. Univariate analysis and multivariable logistic regression models were used to evaluate dichotomized 3-month outcomes (mRS 0–1 or mRS $>$ 1) by hydration status and MAP.

RESULTS

A total of 312 subjects were screened for this study. Among those 185 subjects were excluded for reasons of presentation to the hospital $>$ 12 h from stroke onset, unable to complete MRI or presence of baseline renal disease. Of the 126 subjects remaining, 108 had sufficient labs and baseline blood pressure data for analysis of which 55 (51%) were in a volume contracted state at the time of hospital presentation. Mean initial MAPs in the volume contracted and euvolemic groups were 112.3 mmHg and 112.5 mmHg respectively ($p = 0.97$). With this sample size, we have 80% power to detect a difference between groups with alpha 0.05 (**Table 1**).

In adjusted models including the total sample, for every 10 mmHg higher MAP up to 90 mmHg, NIHSSS was 2.8 points lower ($p = 0.053$), without further statistically significant association between MAP above 90 mmHg and NIHSSS (**Table 2**). When analyses were stratified, however, it was apparent that this relationship was entirely driven by the individuals in a volume contracted state: MAP was not associated with NIHSSS in individuals who were euvolemic. For individuals in a volume contracted state, each 10 mmHg higher MAP, up to 90 mmHg, was associated with 6.9 points lo8wer NIHSSS (95% CI −11.1, −2.6; $p = 0.002$) (**Figure 1**). The formal test for interaction between MAP and dehydration status for MAP values below 90 mmHg was statistically significant ($p = 0.01$). For subjects with initial MAP above 90 mmHg, there was no association between increased MAP and severity in the volume contracted or euvolemic groups. There was

TABLE 1 | Demographics for the analytic sample.

		Total sample stratified by BUN/creatinine status (*N* = 108)			Total sample stratified by initial MAP (*N* = 108)		
	All (*N* = 108)	**Normal BUN/creatinine (*N* = 53)**	**Elevated BUN/creatinine (*N* = 55)**	***P* value**	**MAP < 90 mmHg (*N* = 18)**	**MAP > 90 mmHg (*N* = 90)**	***P* value**
Age (years) (Mean ± SD)	60 ± 14	58	62	0.12	57	60	0.34
Sex (Female) *N* (%)	48 (44%)	19 (36%)	29 (53%)	0.09	8 (44%)	40 (44%)	1.00
Atrial fibrillation *N* (%)	15 (14%)	10 (19%)	5 (9%)	0.17	3 (17%)	12 (13%)	0.71
Hypertension *N* (%)	83(77%)	44 (83%)	39 (71%)	0.17	11 (61%)	72 (80%)	0.12
Diabetes *N* (%)	35 (32%)	15 (28%)	20 (36%)	0.42	5 (28%)	30 (33%)	0.79
Ejection Fraction below 50%* *N* (%)	19 (18%)	11 (22%)	8 (15%)	0.44	4 (24%)	15 (17%)	0.51
Acute revascularization therapy† *N* (%)	25 (23%)	14 (26%)	11 (20%)	0.43	3 (17%)	22 (24%)	0.56
Serum Sodium (mean ± SD)	140 ± 3	140.5	139.6	0.15	139	140	0.12
Baseline Hemoglobin	13.4 (2.2)	13.7	13.1	0.11	13.4	13.4	0.07
Length of stay (days) (mean ± SD)	6.1 ± 6.2	5.6	6.5	0.47	6.0	6.1	0.95
Initial NIHSS (mean ± SD)	6.0 ± 5.4	6.4	5.7	0.48	7.7	5.7	0.27
Lesion volume (cc)	9.8 ±19.6	10.8	8.9	0.61	14.9	8.8	0.43
DWI:PWI mismatch present**	62 (73%)	29 (71%)	33 (75%)	0.81	7 (64%)	55 (74%)	0.48

**Ejection Fraction available on N = 103. † (Intravenous tPA and/or endovascular therapy). Lesion volume available on N = 108; **DWI:PWI mismatch defined as > 1.2; N = 85.*

TABLE 2 | Effect of mean arterial pressure (per 10 mm Hg) on stroke severity and outcome: multivariable regression analysis.

	Stroke severity: baseline NIHSS score (*N* = 108)			Functional outcome: 3 month modified rankin scale (mRS > 1 vs. mRS 0–1)**		
	N	**Adjusted beta§ (95% CI) for MAP up to 90 mm Hg#**	**Adjusted beta§ (95% CI) for MAP above 90 mm Hg**	***N***	**Adjusted OR§ (95% CI) for MAP up to 90 mmHg**	**Adjusted OR§ (95% CI) for MAP above 90 mmHg**
All patients	108	−2.8 (−5.6, 0.04)	−0.1 (−0.3, 0.5)	86	0.25 (0.02, 3.42)	1.11 (0.86, 1.44)
Volume contracted patients	55	−6.9 (−11.1, −2.6)	0.3 (−0.4, 1.1)	45	0.38 (0.004, 40.76)	1.45 (0.86, 2.43)
Euvolemic patients	53	1.3 (−3.0, 5.5)	−0.1 (−0.7, 0.4)	41	0.25 (0.007, 8.93)	0.98 (0.69, 1.39)

*§ Adjusted for age, gender, atrial fibrillation, diabetes, and lesion volume. # p-interaction for MAP within this range and dehydration status = 0.01. **3 month mRS dichotomized a priori as bad outcome (mRS > 1) vs. good outcome (mRS 0–1).*

no difference in odds of poor 3-month outcome mRS based on differences in initial MAP (unadjusted OR 1.05; 95% CI 0.85, 1.29).

In terms of MRI findings, the size of the stroke lesion was measurable in all 108 subjects. The average ischemic lesion size based on diffusion-weighted imaging was 9.8 ± 19.6 cc. In this cohort, 84/108 (78%) subjects had perfusion imaging sufficient for interpretation if diffusion to perfusion mismatch. There was no difference in diffusion to perfusion mismatch based on hydration status nor mean arterial pressure.

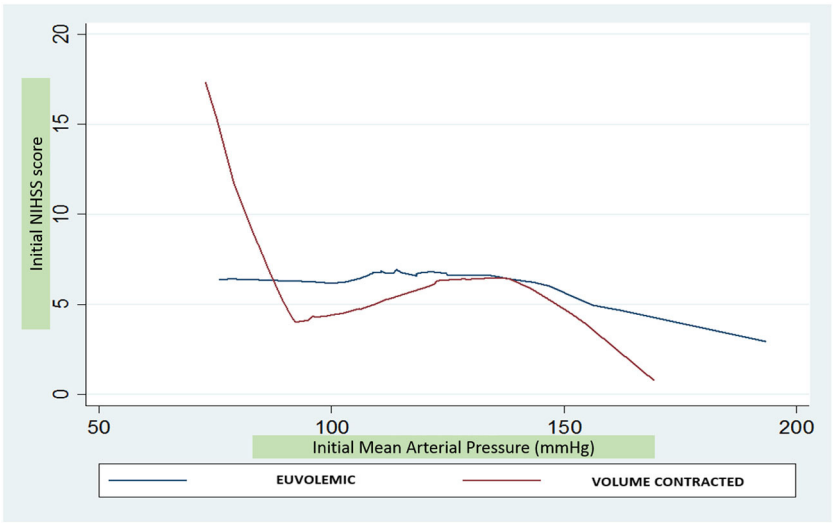

FIGURE 1 | Comparison of NIH stroke scale score and mean arterial pressure by hydration status.

DISCUSSION

Although limited by a relatively small sample size, these data suggest that lower MAP may be an important variable in subjects who are volume contracted at the time of stroke. It suggests that volume contracted patients with ischemic stroke may be at higher risk for more severe stroke, particularly if they also have low blood pressure. Notably, there was no significant difference between blood pressures in the volume contracted and euvolemic patients.

A large percentage of patients with AIS are volume contracted at the time of stroke (2–4, 15, 16). Intravascular volume is one component in blood pressure and avoidance of low blood pressure has been standard in acute stroke care (8). These data suggest that avoidance of low blood pressure may be especially important in patients who are dehydrated. Therefore, hydration status may be an important consideration when setting early blood pressure goals.

This study also expands on the knowledge generated from earlier studies of induced hypertension as a potentially helpful adjunct therapy after ischemic stroke (18–20). These studies used a combination of pharmacological agents and volume expanders to elevate blood pressure at the time of stroke and demonstrated improved clinical outcomes. Our results suggest an opportunity for potential benefit using a simpler treatment using solely intravenous saline. This is especially important given that the largest burden of stroke worldwide is in low-resourced settings, and intravenous saline could represent a scalable intervention to improve stroke outcomes even in these settings.

There are multiple potential reasons for hydration and stroke severity to be linked, independent of MAP. First, blood viscosity may be impacted by hydration, such that lower viscosity improves perfusion. Next, patients who are chronically volume contracted may have more accumulation of brain disease prior to the stroke event thus impacting severity. Finally, comorbidities such as diabetes and heart failure might be associated with volume contraction and influence outcome. This study further clarifies the relationship between hydration status, blood pressure, and stroke severity. That is, the combination of low blood pressure and volume contraction is more strongly associated with higher stroke severity than either alone.

This study has several limitations, including those common to the small sample size. Further, only 80% of these subjects had 3 month mRS completed limiting our ability to assess functional outcomes in the entire cohort. Next, data collected within the standard care environment are subject to variation in technique, specifically when related to the measurement of initial blood pressure. Nevertheless, these data yield the important finding that blood pressure and hydration status are potentially independent factors contributing to stroke severity, independent of infarct volume, and suggest that dehydrated stroke patients with lower MAP are at high risk. This high-risk subgroup may benefit from rehydration strategies.

CONCLUSIONS

Lower MAP contributes to more severe stroke in patients who are volume contracted but not in those who are euvolemic. The topic of patient hydration status may deserve more attention in the early treatment period after stroke. These results suggest a potentially modifiable risk factor to improve functional outcomes with low cost, broadly available interventions like rehydration.

DATA AVAILABILITY STATEMENT

Raw data will be made available for any reasonable request of the authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Johns Hopkins School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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