Original Article

Prognostic value of initial routine laboratory blood tests in patients with aneurysmal subarachnoid hemorrhage requiring mechanical ventilation: a retrospective cohort study

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Background: Aneurysmal subarachnoid hemorrhage (aSAH) necessitating mechanical ventilation (MV) presents a serious challenge for intensivists. Laboratory blood tests reflect individual physiological and biochemical states, and provide a useful tool for identifying patients with critical condition and stratifying risk levels of death. This study aimed to determine the prognostic role of initial routine laboratory blood tests in these patients.

Methods: This retrospective cohort study included 190 aSAH patients requiring MV in the neurosurgical intensive care unit from December 2019 to March 2022. Follow-up evaluation was performed in May 2022 via routine outpatient appointment or telephone interview. The primary outcomes were death occurring within 7 days after discharge (short-term mortality) or reported at time of follow-up (long-term mortality). Clinico-demographic and radiological characteristics, initial routine laboratory blood tests (e.g., metabolic panels and arterial blood gas analysis), and treatment were analyzed and compared in relation to mortality. Multivariable logistic and Cox regression analyses, with adjustment of other clinical predictors, were performed to determine independent laboratory test predictors for short- and long-term mortality, respectively.

Results: The patients had a median age of 62 years, with a median World Federation of Neurosurgical Societies grade (WFNS) score of 5 and a median modified Fisher grade (mFisher) score of 4. The short- and long-term mortality of this cohort were 60.5% and 65.3%, respectively. Compared with survivors, non-survivors had more severe disease upon admission based on neurological status and imaging features and a shorter disease course, and were more likely to receive conservative treatment. Initial ionized calcium was found to be independently associate with both short-term [adjusted odds ratio (OR): 0.92; 95% confidence interval (CI): 0.86 to 0.99; P=0.020] and long-term mortality [adjusted hazard ratio (HR): 0.95; 95% CI: 0.92 to 0.99; P=0.010], after adjusting for potential confounders. Moreover, the admission glucose level was found to be associated only with short-term mortality (adjusted OR: 1.19; 95% CI: 1.06 to 1.34; P=0.004).

Conclusions: Laboratory screening may provide a useful tool for the management of aSAH patients requiring MV in stratifying risk levels for mortality and for better clinical decision-making. Further study is needed to validate the effects of calcium supplementation and glucose-lowering therapy on the outcomes in this disease.

Keywords: Aneurysmal subarachnoid hemorrhage (aSAH); mechanical ventilation (MV); prognosis; blood glucose; ionized calcium

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is an uncommon but often catastrophic event with increasing prevalence and disproportionally high mortality and morbidity (1,2). Patients with aSAH are usually managed with mechanical ventilation (MV) for respiratory failure, airway protection, altered mental status, seizures, severe brain injury, or the need for analgo-sedation (3-5). According to a large multicenter study, 38.5% of patients with SAH underwent MV, with an in-hospital mortality rate as high as 54.6% (6). Early characterization of these patients with an unfavorable prognosis may facilitate management in the intensive care unit (ICU) and help patient caregivers to better anticipate the course of therapy and assist in decision-making.

The current management of aSAH patients requiring MV in the ICU has become an important research activity in recent years. Long-term MV has been associated with poor functional outcomes in patients with aSAH (7). Subsequently, a predictive score for prolonged MV in patients with aSAH was established by Rass *et al.*, which incorporated the variables reflecting initial disease severity and neuroimaging findings (8). Huang *et al.* further identified a history of diabetes mellitus and Hunt-Hess grade 3–5 as independent predictors for prolonged MV in patients with aSAH after microsurgical clipping (9). In a recent study, Zhao *et al.* demonstrated that alcohol abuse was associated with an increased risk of angiographic vasospasm and delayed cerebral ischemia in aSAH patients requiring MV (10). Despite our knowledge of the characteristics of these patients, the risk factors for mortality of this specific population of critically ill patients have not been investigated.

Laboratory tests performed on blood samples reflect individual physiological and biochemical states and have become an indispensable part in clinical practice. Recent studies using laboratory information have revealed coagulopathy (11), cardiac dysfunction (12), hyper-inflammatory condition (13), and metabolic disturbance (14) occur in patients with aSAH. Despite their significance in aSAH, the role of laboratory data in outcome prediction in aSAH patients requiring MV has not been documented (15). Thus, we performed this retrospective cohort study aimed at revealing the relationship between initial routine laboratory blood tests, as an objective parameter, and clinical outcomes among patients hospitalized with aSAH requiring MV in the ICU. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-854/rc).

Highlight box

Key findings

- Admission glucose and ionized calcium levels are independently associated with the outcomes of aneurysmal subarachnoid hemorrhage (aSAH) patients requiring mechanical ventilation (MV).

What is known and what is new?

- aSAH necessitating MV is associated with disproportionally high mortality, presenting a serious challenge for intensivists. Previous studies focused on risk factors for prolonged MV in these patients.
- This study revealed risk factors, with emphasis of laboratory tests, for outcomes of this specific critically ill patient population.

What is the implication, and what should change now?

- Laboratory tests performed on blood samples upon admission provide useful information for better clinical decision-making. Further study is needed to validate the effects of calcium supplementation and glucose-lowering therapy on the outcomes in this disease.

Methods

Study participants

This retrospective cohort study was conducted at the General Hospital of Northern Theater Command in China. Of the 211 screened patients, 190 consecutive patients with aSAH admitted to the neurosurgical ICU from December 2019 to March 2022 were included in

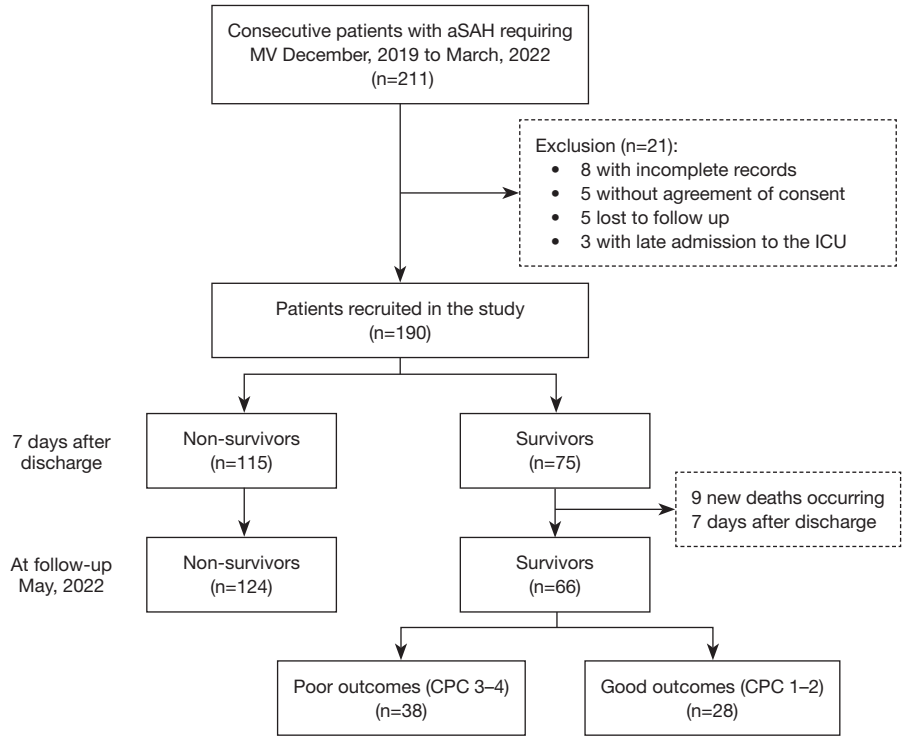

Figure 1 Flow chart of the study design. aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; ICU, intensive care unit; CPC, cerebral performance category.

the current observational cohort (*Figure 1*). The inclusion criteria were as follows: (I) aSAH confirmed on brain computed tomography (CT) and CT angiography or digital subtraction angiography; (II) age ≥18 years. Patients were excluded based on the following criteria: (I) incomplete or unavailable records; (II) refusal to consent; or (III) late admission (>7 days after the ictus of aSAH). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the General Hospital of Northern Theater Command (approval No. Y2021130). The requirement for written informed consent was waived by the ethics committee of the designated hospital.

Data collection

Clinical data including demography (age and sex), medical history, time from onset to admission, clinical or radiographic data for disease grading, laboratory blood tests, and treatment status were collected and independently reviewed by two attending physicians.

Comorbidities included hypertension, diabetes, coronary heart disease (CHD), and cerebral vascular disease (CVD, including symptomatic and asymptomatic cerebral infarction). Neurological status was assessed using the Hunt-Hess grade, Glasgow Coma Scale (GCS), and the World Federation of Neurosurgical Societies grade (WFNS) at the initial presentation after bleeding without sedation. The scores of the sequential organ failure assessment (SOFA) and acute physiology scoring (APS) systems, which are widely used tools for predicting the clinical outcomes of patients admitted to the ICU, were also recorded within the first 24 hours of admission in this study.

Admission CT scans were scored using the modified Fisher grade (mFisher) and subarachnoid hemorrhage early brain edema score (SEBES). Hydrocephalus (quantified by Evan's index) (16), intracerebral hemorrhage, and intraventricular hemorrhage were also recorded on the admission CT scans. Diagnostic angiograms were evaluated with regard to aneurysm characteristics including the number and location.

We focused on the comprehensive laboratory results including the following seven categories: complete blood cell count, coagulative state, myocardial injury markers, liver function tests, kidney function markers, arterial blood gas indicators, and hypersensitive C-reactive protein

(hsCRP). For laboratory blood tests, peripheral arterial and venous blood samples were drawn by venipuncture at our neurosurgery department within 1 hour after hospitalization. After blood draws, the samples were immediately delivered to the clinical lab and analyzed immediately for each participant. Hematological analysis was performed on the UniCel DXH 800 analyzer. Coagulation tests were performed on the STAGO STA-R® Evolution multiparametric analyzer. Routine chemistry testing, including the basic and comprehensive metabolic panels, was performed on the Siemens ADVIA XPT analyzers and Centaur XP analyzers. Arterial blood gasometry was conducted on the Instrumentation Laboratory GEM Premier 4000 analyzer.

The main follow-up evaluation of the patients was performed in May 2022, which included an assessment of the cerebral performance category (CPC) during a routine outpatient appointment or via telephone interview by an independent research assistant trained in neurological evaluation. Poor outcome was defined as a CPC score of 3, 4, or death. The follow-up results showed that most deaths (92.7%, 115/124) occurred within 7 days after discharge. Thus, we defined the primary outcomes as death occurring within 7 days after discharge (short-term mortality) or reported at the time of the follow-up evaluation (long-term mortality).

Patient management

The intensive care of the patients conformed to guidelines proposed by the American Stroke Association (2). After admission, the patients were continuously monitored in the ICU to detect any clinical deterioration. Routine therapy included oxygen inhalation, sedatives and analgesia, and control of hypertension and hyperglycemia. Nimodipine was administered to prevent cerebral vasospasm and delay cerebral ischemia, while an osmotic dehydrating agent was adopted to reduce intracranial pressure. Surgical clipping or endovascular coiling of the ruptured aneurysm was performed as early as feasible after the pre-operative examination. The determination of aneurysm treatment was judged by experienced cerebrovascular surgeons and endovascular specialists based on the characteristics of the patient and the aneurysm. Acute hydrocephalus was treated using a cerebrospinal fluid shunt, and acute cerebral hernia was treated by hematoma removal and decompressive craniotomy. Postoperative management included antiepileptics, antibiotic prophylaxis, early enteral nutrition, and the treatment of other complications.

MV was initiated in the ICU under the following conditions: (I) deteriorated mental status or intracranial hypertension; (II) reduced swallowing or coughing reflexes; (III) signs of respiratory insufficiency or severe acute respiratory distress syndrome; or (IV) the need for analog-sedation. The determination of MV settings and weaning time was performed by the neurointensivists under the guidance of international recommendations (17,18). During MV, analog-sedation was usually achieved to prevent intubation intolerance with continuous intravenous drips of dexmedetomidine, propofol, or midazolam. A percutaneous tracheostomy was performed in those with weaning failure, absence of protective airway reflexes, impairment of respiratory drive, and difficulties in managing secretions (19).

Statistical analysis

No imputation was made for variables with missing data. Quantitative data were expressed as the median [interquartile range (IQR)] and statistically compared using the Mann-Whitney U non-parametric test. The percentage (%) of enumeration data was calculated and compared using the χ^2 test or Fisher's exact test as appropriate. A two-sided $P<0.05$ was considered statistically significant.

To identify risk factors associated with death within 7 days after discharge, variables with a P value of less than 0.1 in the Mann-Whitney U test or χ^2 test were analyzed using univariate logistic regression analysis. Next, variables with P values of less than 0.05 in the univariate analyses and with scientific and clinical merits or proven to relate to disease outcomes in prior studies were considered as potentially independent variables in the multivariate analysis. In the second step, a forward stepwise method was employed to construct multivariate logistic regression models. Variables with a P value <0.05 were retained in the model and considered significant predictors for short-term mortality. Similarly, independent predictors for long-term death were identified using univariate and multivariable Cox regression analyses. All statistical analyses were conducted using SPSS software (22.0, IBM SPSS Statistics, USA).

Results

General characteristics

The data of 190 patients with aSAH requiring MV in the ICU from a total of 211 medical records were analyzed

(*Figure 1*). The included patients had a median age of 62 years (IQR, 53–68), among whom 39.5% were male. Detailed information on demographics, clinical and radiographic features, laboratory items, and treatment is shown in *Tables 1,2*. The patients had a median WFNS score of 5 (IQR, 3.8–5) and a median mFisher score of 4 (IQR, 3–4). Among the 190 patients with an identified aneurysm, 81.1% had aneurysms with an anterior circulation position, 15.3% had multiple aneurysms, and 14.7% (28/190) and 77.9% (148/190) patients exhibited intracerebral hematoma and intraventricular hematoma, respectively. Regarding the treatment of aneurysms, 67 patients had their aneurysms clipped, 94 patients had embolization with coils, and 29 patients were untreated.

The median interval from admission to MV was 2 days (IQR, 0–4). On days 1, 3, and 7 after ICU admission, 29.5% (56/190), 61.1% (116/190), and 88.4% (168/190) of the patients were receiving MV, respectively. As for the time sequence of aneurysm treatment and MV, 22 patients received MV before aneurysm treatment, with a median interval of 1 day (IQR, 1–3), 141 patients received aneurysm treatment before MV with a median interval of 1 day (IQR, 0–3), and the remaining patients did not receive aneurysm treatment. Tracheostomy was performed in 95 patients (50%) 2 days (IQR, 1–4) after admission.

Laboratory factors associated with mortality within 7 days after discharge

In total, 104 patients had died by the day of discharge, and 115 patients were dead within 7 days after discharge. For short-term mortality, the deceased had a higher WFNS score [5 (4 to 5) *vs.* 4 (2 to 5); P=0.024)], and were less likely to receive embolization (60.0% *vs.* 42.6%) and tracheostomy (40.9% *vs.* 64.0%; P=0.002), compared with the survivors. There was also a trend towards older age [63 (55 to 70) *vs.* 58 (52 to 67) years; P=0.072], higher APS score [16 (12 to 20) *vs.* 18 (14 to 21); P=0.065], and a higher incidence of cerebral parenchymal hemorrhage (18.7% *vs.* 9.5%; P=0.083) in the non-survivors (*Table 1*).

In terms of the laboratory indices (*Table 2*), the deceased presented with significantly lower levels of ionized calcium [1.07 (1.03 to 1.10) *vs.* 1.08 (1.05 to 1.11) mmol/L; P=0.011] than the survivors. Notably, there was a trend towards decreased levels of serum glucose in the survivors compared to the deceased [8.3 (7.1 to 10.2) *vs.* 9.4 (7.3 to 12.1) mmol/L; P=0.060]. Interestingly, the survivors had a longer interval between ictus and ICU admission [0.6 (0.4 to 1.0) *vs.* 0.5 (0.3 to 1.0) days; P=0.008] and length of ICU stay [7 (4 to 12) *vs.* 3 (1.5 to 5) days; P=0.000].

Next, we evaluated, by univariate analysis, each variable with a P value of less than 0.1 in the Mann-Whitney U test or χ^2 test. Our analysis revealed that initial WFNS [odds ratio (OR): 1.29; 95% confidence interval (CI): 1.02–1.64; P=0.037], embolization (OR: 0.09; 95% CI: 0.02–0.39; P=0.001), tracheotomy (OR: 0.39; 95% CI: 0.21–0.71; P=0.002), and admission ionized calcium (OR: 0.92; 95% CI: 0.87–0.98; P=0.012) and glucose (OR: 1.11; 95% CI: 0.10–1.21; P=0.030) levels were significantly associated with the death of patients with aSAH requiring MV. The above five variables were further processed using a multivariate logistic regression model, which selected three variables that were predictive of mortality, including tracheotomy (OR: 0.29; 95% CI: 0.15–0.58; P=0.000), ionized calcium (OR: 0.92; 95% CI: 0.86–0.99; P=0.020), and glucose (OR: 1.19; 95% CI: 1.06–1.34; P=0.004) (*Table 3*).

Laboratory factors associated with long-term mortality at follow-up

Nine patients died 7 days after discharge. Thus, at the time of follow-up, there were 66 survivors and 124 non-survivors. Among the 66 survivors, 28 patients achieved favorable outcomes, with CPC scores of 1 or 2 (*Figure 1*). Compared with the survivors, non-survivors had lower GCS scores [7 (4 to 10) *vs.* 8 (6 to 14); P=0.026], but higher WFNS scores [5 (4 to 5) *vs.* 4 (2 to 5); P=0.003] and Hunt-Hess score [4 (3 to 4) *vs.* 4 (3 to 4); P=0.036]. As for treatment, the non-survivors had a lower incidence of embolization (42.7% *vs.* 62.1%) and tracheotomy (44.4% *vs.* 60.6%; P=0.033) (Table S1). In terms of the initial laboratory blood tests, the deceased presented with significantly lower levels of blood lymphocytes [1.0 (0.7 to 1.5) *vs.* 0.9 (0.6 to 1.3); P=0.039] and ionized calcium [1.07 (1.03 to 1.10) *vs.* 1.08 (1.05 to 1.12); P=0.007]. In addition, there was a trend towards higher levels of serum glucose [9.3 (7.3 to 11.9) *vs.* 8.2 (7.0 to 10.2) U/L; P=0.063] and aspartate transaminase [26.1 (20.3 to 36.1) *vs.* 22.3 (17.1 to 31.9) U/L; P=0.079] in the survivors compared to the non-survivors (Table S2).

We then employed univariate Cox analysis to identify the parameters strongly associated with death at the time of follow-up, which included the initial GCS score, Hunt-Hess score, WFNS score, embolization, tracheotomy, and admission ionized calcium and glucose levels (Table S2). Next, these variables were further processed using a multivariate Cox regression model, which selected four

Table 1 Clinical characteristics of 190 patients with aSAH requiring MV included in the study, in relation to death occurring within 7 days after discharge

Variable	Total (n=190)	Survivors (n=75)	Non-survivors (n=115)	P
Age (years)	62 [53–68]	58 [52–67]	63 [55–70]	0.072
Male gender	75 (39.5)	32 (42.7)	43 (37.4)	0.467
Delay between onset and ICU admission (days)	0.5 [0.3–1.0]	0.6 [0.4–1.0]	0.5 [0.3–1.0]	0.008
Medical history				
Hypertension	103 (54.2)	46 (61.3)	57 (49.6)	0.110
Diabetes	22 (11.6)	8 (10.7)	14 (12.2)	0.751
CHD	14 (7.4)	3 (4.0)	11 (9.6)	0.151
CVD	12 (6.3)	5 (6.7)	7 (6.1)	1.000
Clinical features				
GCS score	7 [5–12]	8 [5–14]	7 [4–10]	0.154
WFNS score	5 [3.8–5]	4 [2–5]	5 [4–5]	0.024
Hunt-Hess grade	4 [3–4]	4 [3–4]	4 [3–4]	0.199
mFisher score	4 [3–4]	4 [2–4]	4 [3–4]	0.215
SOFA score	4 [3–6]	4 [3–6]	4 [3–6]	0.733
APS score	17 [12.8–20]	18 [14–21]	16 [12–20]	0.065
Radiographic findings				
Anterior circulation position	154 (81.1)	61 (81.3)	93 (80.9)	0.936
Multiple aneurysms (n>1)	29 (15.3)	12 (16.0)	17 (14.8)	0.820
Intracerebral hematoma	28 (14.7)	7 (9.5)	21 (18.7)	0.083
Intraventricular hematoma	148 (77.9)	59 (79.7)	89 (79.5)	0.965
SEBES score	2 [2–4]	2 [2–4]	2 [2–4]	0.661
Evans' index	0.28 [0.26–0.31]	0.28 [0.26–0.31]	0.28 [0.26–0.31]	0.873
Treatment				
Aneurysm treatment				0.000
No obliteration performed	29 (15.3)	2 (2.7)	27 (23.5)	
Clipping	67 (35.3)	28 (37.3)	39 (33.9)	
Coiling	94 (49.5)	45 (60.0)	49 (42.6)	
Decompressive craniotomy	53 (27.9)	21 (28.0)	32 (27.6)	0.979
External ventricular drain	110 (57.9)	39 (52.0)	71 (61.7)	0.184
Tracheotomy	95 (50.0)	48 (64.0)	47 (40.9)	0.002
Length of ICU stay (days)	4 [2–8]	7 [4–12]	3 [1.5–5]	0.000

Values are expressed as the median [interquartile range 25–75%] or n (%). aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; CHD, coronary heart disease; CVD, cerebral vascular disease; GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies; mFisher, modified Fisher score; SOFA, Sequential Organ Failure Assessment; SEBES, subarachnoid hemorrhage early brain edema score; APS, acute physiology scoring; ICU, intensive care unit.

Table 2 Laboratory characteristics of 190 patients with aSAH requiring MV included in the study, in relation to death occurring within 7 days after discharge

Variable	Normal range	Total (n=190)	Survivors (n=75)	Non-survivors (n=115)	P
Blood routine test					
WBC, $\times10^9$/L	3.5 to 9.5	14.3 (10.4 to 18.0)	13.8 (10.0 to 18.6)	14.6 (10.7 to 17.8)	0.433
NEU, $\times10^9$/L	1.8 to 6.3	12.6 (9.1 to 16.2)	12.0 (8.1 to 16.6)	13.1 (9.3 to 16.2)	0.301
LYM, $\times10^7$/L	1.1 to 3.2	0.9 (0.7 to 1.3)	0.9 (0.7 to 1.5)	0.9 (0.6 to 1.3)	0.148
RBC, $\times10^{12}$/L	4.3 to 5.8	4.4 (4.0 to 4.8)	4.4 (4.0 to 4.9)	4.3 (3.9 to 4.7)	0.104
PLT, $\times10^9$/L	125 to 350	221 (180 to 257)	218 (179 to 255)	221 (180 to 259)	0.866
Liver and kidney function indices					
TBIL, mol/L	0 to 23.0	11.2 (8.5 to 15.1)	11.8 (8.5 to 15.3)	10.8 (8.5 to 15.1)	0.411
DBIL, mol/L	0 to 4.0	3.1 (2.4 to 4.5)	3.1 (2.3 to 4.4)	3 (2.5 to 4.7)	0.667
ALT, U/L	7.0 to 40.0	19.3 (14.9 to 30.3)	19.6 (15.7 to 31.4)	19.0 (13.9 to 30.1)	0.370
AST, U/L	13.0 to 35.0	24.5 (19.6 to 35.5)	22.7 (18.1 to 33.8)	25.8 (19.9 to 35.8)	0.434
A/G	1.5 to 2.5	1.4 (1.3 to 1.6)	1.4 (1.3 to 1.6)	1.4 (1.3 to 1.6)	0.729
Cr, mol/L	57.0 to 111.0	58.6 (48.9 to 76.1)	59.4 (51.1 to 79.5)	57.5 (47.2 to 71.2)	0.410
CysC, mg/L	0 to 1.03	0.72 (0.59 to 0.87)	0.71 (0.59 to 0.88)	0.72 (0.57 to 0.86)	0.763
Myocardial injury markers					
CKMB, U/L	0 to 24.0	17.5 (13 to 25.3)	17.9 (12.5 to 25.3)	17.4 (13 to 25.3)	0.755
hsTnT, ng/L	0 to 40.0	22.5 (9.0 to 132.5)	23.0 (9.0 to 215.0)	22.0 (9.0 to 119.0)	0.669
BNP, pg/mL	<300	325 (106 to 1,353)	323 (130 to 1,437)	336 (96 to 1,301)	0.944
Myo, ng/mL	17.4 to 105.7	74.9 (35.2 to 175.5)	82.4 (38.1 to 261.0)	73.9 (31.8 to 171.1)	0.330
LDH, U/L	120.0 to 250.0	235.0 (199.0 to 283.5)	236.5 (200.5 to 268.0)	232.0 (196.0 to 290.5)	0.872
Coagulation function test					
PT, s	11.0 to 13.7	13.3 (12.9 to 14.0)	13.3 (13.0 to 13.9)	13.4 (12.7 to 14.0)	0.856
APTT, s	31.5 to 43.5	31.6 (29.1 to 34.1)	32.6 (29.6 to 35.7)	31.3 (28.9 to 33.9)	0.210
D-Dimer, mg/L	0.01 to 0.55	3.21 (1.58 to 6.34)	4.02 (1.51 to 8.22)	2.96 (1.60 to 5.72)	0.344
ATIII, %	80 to 120	102 (91 to 111)	103 (91 to 109)	102 (90 to 112)	0.956
Electrolytes and glucose					
pCO_2, mmHg	35.0 to 48.0	36.0 (30.0 to 40.0)	36.5 (30.0 to 40.0)	35.0 (29.0 to 40.0)	0.869
Ca^{2+}, mmol/L	1.15 to 1.35	1.07 (1.04 to 1.10)	1.08 (1.05 to 1.11)	1.07 (1.03 to 1.10)	0.011
Lac, mmol/L	0.5 to 2.2	2 (1.2 to 3.5)	2.4 (1.1 to 3.9)	2 (1.2 to 3.2)	0.504
BE (B), mmol/L	–2.0 to 3.0	0.1 (–2.3 to 1.9)	0.3 (–2.2 to 2.0)	–0.1 (–2.4 to 1.6)	0.693
Glu, mmol/L	3.9 to 6.1	8.8 (7.2 to 11.0)	8.3 (7.1 to 10.2)	9.4 (7.3 to 12.1)	0.060
K^+, mmol/L	3.5 to 5.3	3.7 (3.4 to 3.9)	3.6 (3.3 to 3.9)	3.7 (3.4 to 4.0)	0.087
Na^+, mmol/L	137.0 to 147.0	139.5 (137.4 to 141.83)	139.8 (137.4 to 141.7)	139.2 (137.5 to 141.9)	0.776
hsCRP, mg/L	0.0 to 3.0	13.4 (4.5 to 49.6)	13.1 (5.1 to 44.1)	13.8 (3.4 to 55.9)	0.976

Values are expressed as the median (interquartile range 25–75%). aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; RBC, red blood cell; PLT, blood platelet; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; A/G, albumin/globulin ratio; Cr, creatinine; CysC, cystatin C; CKMB, creative kinase MB; hsTnT, hypersensitive troponin T; BNP, brain natriuretic peptide; Myo, myoglobin; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; ATIII, antithrombin III; Lac, lactate; BE (B), buffer excess; Glu, glucose; hsCRP, hypersensitive C-reactive protein.

Table 3 Logistic regression analyses of the risk factors for death within 7 days after discharge in patients with aSAH requiring MV

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Ionized calcium, per 0.01 mmol/L increase	0.92 (0.87, 0.98)	0.012	0.92 (0.86, 0.99)	0.020
Glucose, per 1 mmol/L increase	1.11 (1.10, 1.21)	0.030	1.19 (1.06, 1.34)	0.004
WFNS score	1.29 (1.02, 1.64)	0.037	–	–
Embolization (ref = clipping)	0.09 (0.02, 0.39)	0.001	–	–
Tracheotomy	0.39 (0.21, 0.71)	0.002	0.29 (0.15, 0.58)	0.000

The multivariable model contains WFNS score, embolization, tracheotomy, ionized calcium, and glucose. aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies.

variables that were predictive of mortality, including initial WFNS score [hazard ratio (HR): 1.26; 95% CI: 1.05–1.51; P=0.015], ionized calcium (HR: 0.95; 95% CI: 0.91–0.98; P=0.010), embolization (HR: 0.33; 95% CI: 0.21–0.53; P=0.000), and tracheotomy (HR: 0.47; 95% CI: 0.32–0.69; P=0.000) (Table S3).

Discussion

Therapeutic decisions for patients with less severe aSAH are largely standardized. However, any additional prognostication tool would be valuable for the management of more severe aSAH. In this retrospective study of mechanically-ventilated patients with aSAH in the ICU, the in-hospital mortality rate was 54.7% (104/190). This was comparable to that reported in a previous multi-state population-based study (6). We tested the prognostic value of initial laboratory blood tests as a risk factor for mortality in patients with aSAH requiring MV after adjustment for other confounding variables such as disease severity, therapy, and radiologic findings. Interestingly, we found initial glucose and ionized calcium levels independently predicted survival in these patients, which were in accordance with prior literature emphasizing the prognostic role of these indicators in patients with other neurological diseases, such as spontaneous intracerebral hemorrhage (20,21) and traumatic brain injury (22,23), and a broader spectrum of critical ill patients including cardiac and septic causes (24-27). These findings may provide useful information for better clinical decision-making by both clinicians and families.

The role of serum calcium has been well characterized in hemorrhagic stroke. Among patients with intracerebral hemorrhage, lower levels of admission serum calcium were associated with higher hematoma volume, more severe neurologic deficits upon admission (28,29), and unfavorable clinical outcomes (30). Hypocalcemia on admission also conferred higher risks of hemorrhagic transformation after intravenous thrombolysis in patients with ischemic stroke (31). Concerning the role of serum calcium in aSAH, Can *et al.* in 2018 first demonstrated that hypocalcemia at diagnosis was significantly associated with ruptured aneurysms (32). Recently, Epstein *et al.* showed that hypocalcemia was associated with worse neurological outcomes at discharge as well as the development of early hydrocephalus in endovascularly-treated patients with spontaneous SAH (33). We further demonstrated that the admission ionized calcium level was independently related to both short- and long-term survival in patients with aSAH requiring MV in the ICU (*Table 2*).

The pathophysiology of hypocalcemia in patients with stroke has not been clarified. The proposed mechanisms include excessive activation of the sympathetic system, impaired parathyroid gland function or end-organ resistance to parathyroid hormone, and disrupted vitamin D synthesis and function. All of these pathophysiological changes are related to the production of pro-inflammatory cytokines (34,35). Several mechanisms have been suggested to explain the association between hypocalcemia and the clinical course of spontaneous SAH patients. First, calcium-dependent pathways have a cardinal role in platelet aggregation; activation of factors IX, X, and VIIIa; cleavage of prothrombin to thrombin; and crosslinking of fibrin (36). Therefore, hypocalcemia may lead to more severe aSAH by impairing platelet function and affecting the coagulation cascade. Second, serum calcium might induce arterial relaxation and secondary reduction of blood pressure through perivascular receptor activation. Thus, hypocalcemia may lead to bleeding aggravation via changes in vascular tone. Supporting this hypothesis,

Epstein *et al.* observed a trend toward higher blood pressure among spontaneous SAH patients with lower calcium levels (33). Third, as a significant extracellular signaling molecule, extracellular calcium may also benefit patients with hemorrhagic stroke by activating intracellular anti-apoptotic pathways and affecting the integrity of the blood-brain barrier (37). All of these hypotheses require further investigations in basic studies and clinical trials.

As part of the systemic metabolic response to stress, hyperglycemia is frequent seen during critical illness, even in the absence of pre-existing diabetes (38). It is significantly associated with increased mortality in critically ill individuals owing to the detrimental effects, including compromised immune function, increased inflammation and coagulation, and injury of the endothelium (39). Current clinical evidence supports ongoing consideration of hyperglycemia as a therapeutic target to improve outcomes in hospitalized patients (40). Also frequently encountered in various types of brain injury, hyperglycemia has been observed in 83–100% of patients with spontaneous SAH on admission. Initial hyperglycemia is recognized as an indicator of the severity of the ictus, as reflected by clinical grading and CT findings, in patients with spontaneous SAH (41,42). High glucose levels on admission were also more pronounced in aSAH patients with symptoms and significantly related to the development of delayed cerebral ischemia (43,44). The first report proposing initial hyperglycemia as an aid for assessing the prognosis of aSAH was published by Lanzino *et al.* in 1993 (42). In clinical investigations over the years, accumulating evidence suggests that admission glucose levels can serve as an objective prognostic indicator after spontaneous SAH, independent of the severity of bleeding (41,43-46). Consistent with the previous literature, our work further revealed high admission glucose levels to be an independent prognosticator of long-term mortality in aSAH patients under severe conditions that necessitate MV (*Table 2*).

The correlation between glucose levels and disease severity implies the interpretation of hyperglycemia as a reflection of metabolic disturbance caused by aSAH. Elevated blood glucose after cerebrovascular injury is regarded as stress hyperglycemia, describing metabolic derangement due to sympathetic hyperactivity in severe vascular brain diseases (47,48). This phenomenon is especially evident in the case of aneurysm rupture with a hypothalamic lesion, leading to the surge of circulating catecholamines that subsequently elevate glucagon levels and decrease insulin secretion (49,50). Hyperglycemia is a contributing factor in the pathway from poor conditions to poor outcomes. Although hyperglycemia may provide abundant substrates for anaerobic glycolysis in the brain under conditions of brain injury (45), it may also impair the brain via multiple mechanisms including brain edema, inflammatory reaction, free radical injury, and excitotoxic or apoptotic cell death (51-54). Considering the detrimental effects of hyperglycemia on the clinical outcomes of aSAH, the issue of glycemic control in the domain of critical care of aSAH requires further research in the future.

In addition to laboratory indicators, other clinical variables were also valuable in these patients: tracheostomy was indicative of both short- and long-term mortality, whereas WFNS score and embolization were only independent predictors of long-term mortality. According to the statistical analyses presented herein, we could infer that non-survivors exhibited more severe disease upon admission (indicated by an initially higher WFNS score and a shorter interval between ictus and ICU admission), quickly deteriorated to a critical condition (indicated by the shorter length of ICU stay), and were less likely to receive aneurysm treatment and tracheotomy. Therefore, the superior therapeutic advantage of embolization over clipping (55,56) may not be the main reason for its prognostic significance in survival. In fact, the severe condition may change therapeutic modality, imposing a safer embolization or even conservative treatment on more patients. Similarly, non-survivors with rapid disease deterioration may have fewer opportunities for tracheotomy. Another point worth mentioning is that multiple logistic regression analysis showed only initial laboratory blood tests were independently associated with short-term mortality, which seemed to contradict prior studies emphasizing the role of imaging findings and clinical symptoms in predicting disease outcomes of aSAH (57). This discrepancy might be owing to different objects of study. This critical ill population we emphasized in this study usually exhibited severe symptoms and diffuse blood in CT scans (*Table 1*). Therefore, imaging and clinical factors may fail to discriminate those with unfavorable outcomes. Instead, laboratory tests, as an objective indicator, reflect individual response to the stress induced by brain injury, and thus may better correlate with disease outcomes of this population.

The limitations of this study include the sample size, retrospective design, and single-center nature. Thus, we can only make conclusions about associations instead of causalities, and external and prospective validations of these results are urgently needed. Moreover, since all participants

included were those requiring MV in the ICU, the findings may not be generalizable to all patients with aSAH, especially those with less severe injury. Additionally, this study only addressed the association between initial laboratory blood tests and the clinical outcomes of these patients. Recent evidence has illustrated that glucose variability, as opposed to absolute glucose values, is an important indicator for patients with intracranial pathology (58). Therefore, further studies using the metric of glucose or calcium variability are required to verify the results obtained in this study. Next, only conventional laboratory parameters were adopted in this study, while those unconventional indicators which have been revealed to identify aSAH patients at risk of poor outcome in prior studies, such as heart-fatty acid binding protein and nucleoside diphosphate kinase A (59), were not investigated. Many studies have explored the genetic susceptibility of aSAH, and the association between lysyl oxidase family gene polymorphisms and aSAH has been clarified in a recent case-control study (60). These state-of-art laboratory blood tests might hold promise for outcome prediction of aSAH patients requiring MV. Last, ventilation was not initiated homogeneously; some patients required MV at admission, and others required it later in the hospital course. Further studies are needed to investigate the clinical characteristics of patients requiring early- and late-ventilation or pre- and post-operative ventilation. Despite these limitations, this study is meaningful since it touches on an important asset of MV use in a select patient population and provides fundamental evidence for further investigations to improve the prognosis of aSAH patients.

Conclusions

Our retrospective study suggests that patients with aSAH requiring MV have high mortality, and non-survivors have more severe disease upon admission, a shorter disease course, and are more likely to undergo conservative treatment compared with survivors. Laboratory findings, including initial glucose and ionized calcium levels, are associated with survival in this specific population of critically ill patients. Our findings provide new information on the understanding and management of this disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-854/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-854/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-854/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the General Hospital of Northern Theater Command (approval No. Y2021130). The requirement for written informed consent was waived by the ethics committee of the designated hospital.

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Supplementary

Table S1 Clinical characteristics of 190 patients with aSAH requiring MV included in this study, in relation to death at the time of follow-up

Variable	Survivors (n=66)	Non to survivors (n=124)	P
Age (years)	59 (52 to 67)	63 (54 to 69)	0.181
Male gender	27 (40.9)	48 (38.7)	0.768
Delay between onset and ICU admission (days)	0.7 (0.4 to 1.0)	0.4 (0.3 to 1.0)	0.002
Medical history			
Hypertension	41 (62.1)	62 (50.0)	0.110
Diabetes	8 (12.1)	14 (11.3)	0.865
CHD	3 (4.5)	11 (8.9)	0.427
CVD	5 (7.6)	7 (5.6)	0.835
Clinical features			
GCS score	8 (6 to 14)	7 (4 to 10)	0.026
Hunt-Hess grade	4 (3 to 4)	4 (3 to 4)	0.036
mFisher score	4 (2 to 4)	4 (3 to 4)	0.225
WFNS score	4 (2 to 5)	5 (4 to 5)	0.003
SOFA score	4 (3 to 6)	4 (3 to 6)	0.722
APS score	18 (13 to 21)	16 (12 to 20)	0.303
Radiographic findings			
Anterior circulation position	54 (81.8)	100 (80.6)	0.844
Multiple aneurysms (n>1)	12 (16.0)	17 (14.8)	0.414
Intracerebral hematoma	6 (9.2)	22 (18.2)	0.104
Intraventricular hematoma	51 (78.5)	97 (80.2)	0.783
SEBES score	2 (2 to 4)	2 (2 to 4)	0.843
Evans' index	0.28 (0.26 to 0.30)	0.28 (0.26 to 0.31)	0.499
Treatment			
Aneurysm treatment			0.000
No obliteration performed	1 (1.5)	28 (22.6)	
Clipping	24 (36.4)	43 (34.7)	
Coiling	41 (62.1)	53 (42.7)	
Decompressive craniotomy	19 (28.8)	34 (27.4)	0.841
External ventricular drain	32 (48.5)	78 (62.9)	0.055
Tracheotomy	40 (60.6)	55 (44.4)	0.033
Length of ICU stay (days)	7 (4 to 12)	3 (2 to 6)	0.000

Values are expressed as the median (interquartile range 25–75%) or n (%). aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; CHD, coronary heart disease; CVD, cerebral vascular disease; GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies; mFisher, modified Fisher score; SOFA, Sequential Organ Failure Assessment; SEBES, subarachnoid hemorrhage early brain edema score; APS, acute physiology scoring; ICU, intensive care unit.

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Table S2 Laboratory characteristics of 190 patients with aSAH requiring MV included in the study, in relation to death at the time of follow-up

Variable	Normal range	Total (n=190)	Survivors (n=66)	Non to survivors (n=124)	P
Blood routine test					
WBC	(3.5 to 9.5)×10^9/L	14.3 (10.4 to 18.0)	13.8 (10.0 to 18.6)	14.5 (10.5 to 17.8)	0.617
NEU	(1.8 to 6.3)×10^9/L	12.6 (9.1 to 16.2)	12.1 (8.0 to 16.7)	13.0 (9.3 to 16.2)	0.422
LYM	(1.1 to 3.2)×10^7/L	0.9 (0.7 to 1.3)	1.0 (0.7 to 1.5)	0.9 (0.6 to 1.3)	0.039
RBC	(4.3 to 5.8)×10^{12}/L	4.4 (4.0 to 4.8)	4.5 (4.1 to 4.8)	4.3 (3.9 to 4.7)	0.101
PLT	(125 to 350)×10^9/L	221 (180 to 257)	225 (180 to 261)	221 (179 to 255)	0.553
Liver and kidney function indices					
TBIL	0 to 23.0 mol/L	11.2 (8.5 to 15.1)	11.8 (8.5 to 11.4)	10.8 (8.5 to 15.1)	0.530
DBIL	0 to 4.0 mol/L	3.1 (2.3 to 4.5)	3.2 (2.3 to 4.4)	3 (2.4 to 4.7)	0.777
ALT	7.0 to 40.0 U/L	19.3 (14.9 to 30.3)	19.3 (15.7 to 29.4)	19.3 (14.4 to 30.5)	0.757
AST	13.0 to 35.0 U/L	24.5 (19.6 to 35.5)	22.3 (17.1 to 31.9)	26.1 (20.3 to 36.1)	0.079
A/G	1.5 to 2.5	1.4 (1.3 to 1.6)	1.4 (1.3 to 1.6)	1.4 (1.3 to 1.6)	0.959
Cr	57.0 to 111.0 mol/L	58.6 (48.9 to 76.1)	59.4 (51.9 to 78.4)	57.6 (47.8 to 71.6)	0.497
CysC	0 to 1.03 mg/L	0.72 (0.59 to 0.87)	0.72 (0.6 to 0.91)	0.72 (0.57 to 0.85)	0.466
Myocardial injury markers					
CKMB	0 to 24.0 U/L	17.5 (13.0 to 25.3)	17.8 (12.3 to 27.0)	17.5 (13 to 24.9)	0.717
hsTnT	0 to 40.0 ng/L	22.5 (9.0 to 132.5)	22 (8.3 to 180.8)	25.5 (9.0 to 132.5)	0.903
BNP	<300 pg/mL	325 (106 to 1353)	329 (130 to 1437)	325 (96 to 1301)	0.987
Myo	17.4 to 105.7 ng/mL	74.9 (35.2 to 175.5)	67.9 (37.2 to 161.6)	75.7 (32.5 to 180.2)	0.908
LDH	120.0 to 250.0 U/L	235.0 (199.0 to 283.5)	248.0 (200.0 to 268.0)	231.5 (196.5 to 288.3)	0.762
Coagulation function test					
PT	11.0 to 13.7 s	13.3 (12.9 to 14)	13.25 (13.0 to 13.8)	13.5 (12.8 to 14.1)	0.544
APTT	31.5 to 43.5 s	31.6 (29.1 to 34.1)	32.5 (29.5 to 35.6)	31.4 (29.0 to 34.0)	0.338
D to Dimer	0.01 to 0.55 mg/L	3.21 (1.58 to 6.34)	3.51 (1.50 to 7.57)	3.03 (1.61 to 5.93)	0.653
ATIII	80 to 120%	102 (91 to 111)	103 (93 to 109)	102 (90 to 112)	0.637
Electrolytes and glucose					
pCO_2	35.0 to 48.0 mmHg	36.0 (30.0 to 40.0)	36.0 (30.0 to 40.0)	35.5 (29.3 to 40.0)	0.660
Ca^{2+}	1.15 to 1.35 mmol/L	1.07 (1.04 to 1.10)	1.08 (1.05 to 1.12)	1.07 (1.03 to 1.10)	0.007
Lac	0.5 to 2.2 mmol/L	2 (1.2 to 3.5)	2 (1.1 to 4.0)	2.1 (1.2 to 3.2)	0.678
BE (B)	–2.0 to 3.0 mmol/L	0.1 (–2.3 to 1.9)	0.3 (–2.2 to 2.1)	–0.1 (–2.5 to 1.6)	0.709
Glu	3.9 to 6.1 mmol/L	8.8 (7.2 to 11.0)	8.2 (7.0 to 10.2)	9.3 (7.3 to 11.9)	0.063
K^+	3.5 to 5.3 mmol/L	3.7 (3.4 to 3.9)	3.6 (3.3 to 3.9)	3.7 (3.4 to 4.0)	0.112
Na^+	137.0 to 147.0 mmol/L	139.5 (137.4 to 141.8)	139.9 (137.7 to 141.8)	139.1 (137.1 to 141.9)	0.479
hsCRP	0.0 to 3.0 mg/L	13.4 (4.5 to 49.6)	13.5 (5.1 to 48.0)	13.2 (4.1 to 51.9)	0.785

Values are expressed as the median (interquartile range 25–75%). aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; RBC, red blood cell; PLT, blood platelet; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; A/G, albumin/globulin ratio; Cr, creatinine; CysC, cystatin C; CKMB, creative kinase MB; hsTnT, hypersensitive troponin T; BNP, brain natriuretic peptide; Myo, myoglobin; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; ATIII, antithrombin III; Lac, lactate; BE (B), buffer excess; Glu, glucose; hsCRP, hypersensitive C-reactive protein.

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Table S3 Cox regression analyses of the risk factors for death at the time of follow-up in patients with aSAH requiring MV

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Ionized calcium, per 0.01 mmol/L increase	0.95 (0.91, 0.98)	0.005	0.95 (0.92, 0.99)	0.010
Glucose, per 1 mmol/L increase	1.06 (1.01, 1.10)	0.011	–	–
GCS score	0.94 (0.90, 0.98)	0.009	–	–
Hunt-Hess grade	1.28 (1.04,1.57)	0.021	–	–
WFNS score	1.24 (1.05, 1.46)	0.011	1.26 (1.05, 1.51)	0.015
Embolization (ref = clipping)	0.26 (0.17, 0.40)	0.000	0.33 (0.21, 0.53)	0.000
Tracheotomy	0.51 (0.35, 0.72)	0.000	0.47 (0.32, 0.69)	0.000

The multivariable model contains WFNS score, embolization, tracheotomy, ionized calcium, and glucose. aSAH, aneurysmal subarachnoid hemorrhage; MV, mechanical ventilation; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies.

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