The Association Of Blood Urea Nitrogen To Creatinine Ratio And The Prognosis Of Critically Ill Patients With Cerebral Infarction: A Cohort Study

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Abstract

Background: To evaluate the association between blood urea nitrogen (BUN) to creatinine (Cr) (BUN/Cr) ratio with the in-hospital mortality of critically ill patients with cerebral infarction in intensive care unit (ICU).

Methods: In this cohort study, the data of 3059 participants with cerebral infarction were collected from the Medical Information Mart for Intensive Care (MIMIC)-III and the MIMIC-IV database. After propensity score matching (PSM) on age and gender, 2085 people were involved in and divided into the alive group (n=1390) and the dead group (n=695). All subjects in the ICU were followed up until death or discharge. Multivariate logistic analyses were applied for identifying the confounders and the association between BUN/Cr and mortality of cerebral infraction.

Results: The median follow-up time was 10.5 days. Among 2778 participants, 695 were dead at the end of follow-up. Univariate analysis revealed that BUN/Cr [risk ratio (RR)=1.01, 95% confidence interval (CI): 1.01-1.02] might be associated with the in-hospital mortality of cerebral infraction patients. After adjusting respiratory failure, malignant cancer, anticoagulation, liver disease, white blood cell (WBC), red cell distribution width (RDW) percent, glucose, bicarbonate and temperature, BUN/Cr was associated with an increased risk of in-hospital mortality of cerebral infraction patients (RR=1.01, 95%CI: 1.01-1.02).

Conclusion: This study evaluated the association between BUN/Cr and the in-hospital mortality of cerebral infarction patients in ICU and found BUN/Cr was associated with an increased risk of in-hospital mortality of patients with cerebral infarction in ICU especially in males, and those with respiratory failure, malignant cancer and without liver disease, as well as those receiving anticoagulation. The findings of our study reminded the clinicians to pay attention on the level of BUN/Cr in cerebral infarction patients in ICU.

Background

Cerebral infarction is a kind of brain injury due to the obstruction of blood supply in the brain, which induces ischemic and hypoxic necrosis of innervation (Sun et al. 2018). As one of the most common types of cerebrovascular disease, cerebral infarction accounts for about 70% of all cerebrovascular diseases and approximately 85% of all strokes (Wen & Lv 2021; Zhou et al. 2016). Cerebral infarction has a high incidence, disability, recurrence rate and mortality, which has resulted in a substantial burden to the society (Roth et al. 2015). In China, the incidence of acute cerebral infarction was about 19.04% and the recurrent rate was 62.15% (Feng & Gong 2022). The estimated mortality of cerebral infarction was about 5.5 million every year (Liu et al. 2020). Nearly 1/3 patients with acute cerebral infarction suffered poor outcomes (Zhang & Xiang 2018). To identify essential biomarkers associated with the prognosis of cerebral infarction might be helpful for improving the prognosis of these patients.

The fluid metabolism including dehydration status was reported to be associated with the potential risk for the occurrence of cerebral infarction (Chang et al. 2016). Dehydration can lead to increased blood

viscosity, reduced cardiac output per stroke, impaired collateral blood flow and decreased cerebral perfusion, which may increase the risk of cerebral infraction (Tsai et al. 2018). Blood urea nitrogen (BUN) and creatinine (Cr) are metabolic end products of nitrogen-containing substances in human bodies, which are readily available biomarkers of renal function in clinic (Murata et al. 2018). BUN to creatinine (BUN/Cr) ratio is a laboratory biomarker frequently used for determining the dehydration (Gao et al. 2021). In previous studies, the BUN/Cr was identified as an independent prognostic indicator for poor outcomes in different diseases, including stroke (Deng et al. 2019b), and heart failure (Qian et al. 2019). The potential role of BUN/Cr on the prognosis of patients with cerebral infarction was still unclear.

In the present study, we evaluated the association between BUN/Cr with the in-hospital mortality of critically ill patients with cerebral infarction in intensive care unit (ICU) based on the data from the Medical Information Mart for Intensive Care (MIMIC)-III and the MIMIC-IV. We also stratified the analysis on age, gender, and whether the patient was complicated with respiratory failure, malignant cancer or liver disease, or whether the patient received anticoagulation treatments.

Results

Comparisons of the baseline characteristics between the alive group and the dead group

This study was a cohort study involving the data of 3059 participants with cerebral infarction. Among all participants, patients aged < 18 years (n = 14) and those admitted to ICU < 24 h (n = 261) were excluded. Finally, the data of 2778 participants were analyzed. After PSM on age and gender, 2085 people were finally included in our study and divided into the alive group (n = 1390) and the dead group (n = 695). The detailed screen process was displayed in Fig. 1.

As observed in Table 1, the proportions of patients with CHF (26.12% vs 30.79%), respiratory failure (31.08% vs 53.67%), renal failure (19.78% vs 26.91%), malignant cancer (11.94% vs 18.27%) and liver disease (4.96% vs 10.65%) were lower in the alive group than the dead group. The proportions of patients with anticoagulation use in the alive group was higher than the dead group (90.36% vs 85.47%). The average heart rate (83.56 times/min vs 88.95 times/min), RDW percent (14.37% vs 15.01%), and potassium level (4.15 mEq/l vs 4.24 mEq/l) and OASIS (31.53 vs 36.17) in the alive group were lower than the dead group. The average temperature (36.59 ℃ vs 36.26 ℃), hematocrit (12.03 g/dL vs 11.55 g/dL), hematocrit percent (36.05% vs 34.93%), and bicarbonate (23.91 mEq/l vs 23.00 mEq/l) were higher in the alive group than in the dead group. The median SOFA score (2 vs 4), SAPSII (35 vs 43), Cr (1.00 mg/dl vs 1.10 mg/dl), BUN (19 mg/dl vs 22 mg/dl) and BUN/Cr (19.00 vs 20.00) were lower in the alive group than in the dead group.

Table 1
Comparisons of the baseline characteristics between the alive group and the dead group

Variables	Total (n = 2085)	Alive (n = 1390)	Dead (n = 695)	Statistics	*P*
CHF, n (%)				χ^2 = 5.062	**0.024**
No	1508 (72.33)	1027 (73.88)	481 (69.21)		
Yes	577 (27.67)	363 (26.12)	214 (30.79)		
AF, n (%)				χ^2 = 0.164	0.686
No	1154 (55.35)	765 (55.04)	389 (55.97)		
Yes	931 (44.65)	625 (44.96)	306 (44.03)		
Diabetes mellitus, n (%)				χ^2 = 0.192	0.662
No	1451 (69.59)	963 (69.28)	488 (70.22)		
Yes	634 (30.41)	427 (30.72)	207 (29.78)		
Respiratory failure, n (%)				χ^2 = 99.754	**< .001**
No	1280 (61.39)	958 (68.92)	322 (46.33)		
Yes	805 (38.61)	432 (31.08)	373 (53.67)		
Renal failure, n (%)				χ^2 = 13.627	**< .001**
No	1623 (77.84)	1115 (80.22)	508 (73.09)		
Yes	462 (22.16)	275 (19.78)	187 (26.91)		
Malignant cancer, n (%)				χ^2 = 15.376	**< .001**
No	1792 (85.95)	1224 (88.06)	568 (81.73)		
Yes	293 (14.05)	166 (11.94)	127 (18.27)		
Thrombolytic, n (%)				χ^2 = 3.202	0.074

CHF: congestive heart failure, AF: atrial fibrillation, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, WBC: white blood cell, PLT: platelets, RDW: red cell distribution width, INR: International Normalized Ratio, SOFA: the Sequential Organ Failure Assessment, SAPSII: the Simplified Acute Physiology Score II, OASIS: the Oxford Acute Severity of Illness Score, BUN: blood urea nitrogen, Cr: creatinine

Variables	Total (n = 2085)	Alive (n = 1390)	Dead (n = 695)	Statistics	*P*
No	1777 (85.23)	1171 (84.24)	606 (87.19)		
Yes	308 (14.77)	219 (15.76)	89 (12.81)		
Anticoagulation, n (%)				χ^2 = 11.088	**< .001**
No	235 (11.27)	134 (9.64)	101 (14.53)		
Yes	1850 (88.73)	1256 (90.36)	594 (85.47)		
Hypertension, n (%)				χ^2 = 3.542	0.060
No	793 (38.03)	509 (36.62)	284 (40.86)		
Yes	1292 (61.97)	881 (63.38)	411 (59.14)		
Liver disease, n (%)				χ^2 = 23.429	**< .001**
No	1942 (93.14)	1321 (95.04)	621 (89.35)		
Yes	143 (6.86)	69 (4.96)	74 (10.65)		
Heart Rate (time/min), Mean ± SD	85.36 ± 20.10	83.56 ± 18.71	88.95 ± 22.21	t=-5.50	**< .001**
SBP (mmhg), M(Q_1,Q_3)	137 (116, 155)	138 (118,155)	134 (113,155)	Z=-2.151	**0.031**
DBP (mmhg), M (Q_1, Q_3)	70 (58, 83)	70 (58, 83)	70 (58, 82)	Z=-0.187	0.851
MAP (mmhg), M (Q_1, Q_3)	89 (76, 102)	89 (77, 103)	88 (75, 102)	Z=-1.072	0.284
Respiratory rate (time/min), M (Q_1, Q_3)	18.00 (15.00, 22.00)	18.00 (15.00, 21.00)	19.00 (15.00, 24.00)	Z = 4.577	**< .001**
Temperature (°C), Mean ± SD	36.48 ± 2.72	36.59 ± 1.80	36.26 ± 3.96	t = 2.15	**0.032**
SOFA, M (Q_1, Q_3)	2.00 (1.00, 5.00)	2.00 (0.00, 4.00)	4.00 (1.00, 6.00)	Z = 7.945	**< .001**

CHF: congestive heart failure, AF: atrial fibrillation, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, WBC: white blood cell, PLT: platelets, RDW: red cell distribution width, INR: International Normalized Ratio, SOFA: the Sequential Organ Failure Assessment, SAPSII: the Simplified Acute Physiology Score II, OASIS: the Oxford Acute Severity of Illness Score, BUN: blood urea nitrogen, Cr: creatinine

Variables	Total (n = 2085)	Alive (n = 1390)	Dead (n = 695)	Statistics	*P*
SAPSII, M (Q_1, Q_3)	38.00 (30.00, 47.00)	35.00 (28.00, 44.00)	43.00 (35.00, 53.00)	Z = 12.891	**< .001**
OASIS, Mean ± SD	33.08 ± 9.92	31.53 ± 9.68	36.17 ± 9.67	t=-10.33	**< .001**
WBC (K/uL), M(Q_1, Q_3)	10.30 (7.80, 13.80)	9.90 (7.70, 13.30)	11.50 (8.00, 15.80)	Z = 5.198	**< .001**
PLT (K/uL), M (Q_1, Q_3)	215.00 (160.00, 279.00)	217.00 (164.00, 276.00)	211.00 (153.00, 285.00)	Z=-1.257	0.209
Hemoglobin (g/dL), Mean ± SD	11.87 ± 2.31	12.03 ± 2.29	11.55 ± 2.32	t = 4.55	**< .001**
RDW percent, Mean ± SD	14.59 ± 1.99	14.37 ± 1.88	15.01 ± 2.11	t=-6.79	**< .001**
Hematocrit percent, Mean ± SD	35.68 ± 6.51	36.05 ± 6.48	34.93 ± 6.53	t = 3.70	**< .001**
Creatinine (mg/dl), M (Q_1,Q_3)	1.00 (0.80, 1.40)	1.00 (0.80, 1.30)	1.10 (0.80, 1.60)	Z = 4.686	**< .001**
INR, M (Q_1,Q_3)	1.20 (1.10, 1.40)	1.20 (1.10, 1.30)	1.20 (1.10, 1.40)	Z = 6.144	**< .001**
BUN (mg/dl), M (Q_1,Q_3)	20.00 (14.00, 29.00)	19.00 (14.00, 27.00)	22.00 (16.00, 34.00)	Z = 6.401	**< .001rep**
Glucose (mg/dl), M (Q_1,Q_3)	130.00 (107.00, 167.00)	126.00 (106.00, 160.00)	136.00 (110.00, 184.00)	Z = 4.853	**< .001**
Bicarbonate (mEq/l), Mean ± SD	23.61 ± 4.26	23.91 ± 3.97	23.00 ± 4.72	t = 4.36	**< .001**
Sodium (mEq/l), Mean ± SD	139.24 ± 4.64	139.37 ± 4.42	138.98 ± 5.03	t = 1.77	0.076
Potassium (mEq/l), Mean ± SD	4.18 ± 0.77	4.15 ± 0.73	4.24 ± 0.83	t=-2.49	**0.013**
Charlson comorbidity index, M (Q_1,Q_3)	5.00 (3.00, 8.00)	5.00 (3.00, 7.00)	6.00 (3.00, 8.00)	Z = 2.891	**0.004**
BUN/Cr, M (Q_1, Q_3)	19.38 (15.00, 24.44)	19.00 (15.00, 23.75)	20.00 (15.00, 25.71)	Z = 2.756	**0.006**

CHF: congestive heart failure, AF: atrial fibrillation, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, WBC: white blood cell, PLT: platelets, RDW: red cell distribution width, INR: International Normalized Ratio, SOFA: the Sequential Organ Failure Assessment, SAPSII: the Simplified Acute Physiology Score II, OASIS: the Oxford Acute Severity of Illness Score, BUN: blood urea nitrogen, Cr: creatinine

The Association Between Bun/cr And Mortality Of Participants With Cerebral Infarction

The variables with statistical difference between the alive group and the dead group were included in the multivariable regression analysis Model 1. The results depicted that BUN/Cr (RR = 1.01, 95%CI: 1.01–1.02), respiratory failure (RR = 2.34, 95%CI: 1.90–2.87), malignant cancer (RR = 1.68, 95%CI: 1.27–2.22), anticoagulation (RR = 0.44, 95%CI: 0.33–0.60), liver disease (RR = 1.63, 95%CI: 1.11–2.37), WBC (RR = 1.01, 95%CI: 1.00-1.03), RDW percent (RR = 1.08, 95%CI: 1.03–1.14), glucose (RR = 1.01, 95%CI: 1.01–1.01), bicarbonate (RR = 0.97, 95%CI: 0.95–0.99) and temperature (RR = 0.95, 95%CI: 0.92–0.99) might be associated with the in-hospital mortality of cerebral infraction patients. After adjusting respiratory failure, malignant cancer, anticoagulation, liver disease, WBC, RDW percent, glucose, bicarbonate and temperature, BUN/Cr was associated with an increased risk of in-hospital mortality of cerebral infraction patients (RR = 1.01, 95%CI: 1.01–1.02) (Table 2).

Table 2
The association between BUN/Cr and mortality of participants with cerebral infarction

Variables	Model 1		Model 2	
	RR (95%CI)	P	RR (95%CI)	*P*
BUN/CR	1.01 (1.01–1.02)	**0.045**	1.01 (1.01–1.02)	0.025
CHF	0.98 (0.78–1.24)	0.884		
Respiratory failure	2.34 (1.90–2.87)	**< 0.001**	2.50 (2.04–3.05)	< 0.001
Renal failure	1.10 (0.86–1.41)	0.438		
Malignant cancer	1.68 (1.27–2.22)	**< 0.001**	1.72 (1.31–2.26)	< 0.001
Anticoagulation	0.44 (0.33–0.60)	**< 0.001**	0.46 (0.34–0.61)	< 0.001
Liver disease	1.63 (1.11–2.37)	**0.012**	1.72 (1.19–2.49)	0.004
Heart Rate	1.00 (1.00-1.01)	0.086		
SBP	1.00 (1.00-1.01)	0.259		
Respiratory rate	1.02 (1.00-1.03)	0.088		
Temperature	0.95 (0.92–0.99)	**0.007**	0.95 (0.93–0.97)	< 0.001
WBC	1.01 (1.00-1.03)	**0.023**	1.01 (1.01–1.03)	0.023
Hemoglobin	0.91 (0.76–1.08)	0.270		
RDW percent	1.08 (1.03–1.14)	**0.004**	1.11 (1.06–1.16)	< 0.001
Hematocrit percent	1.03 (0.97–1.10)	0.281		
INR	0.98 (0.89–1.09)	0.740		
Albumin	0.94 (0.79–1.11)	0.451		
Glucose	1.01 (1.01–1.01)	**0.008**	1.01 (1.01–1.01)	0.002
Bicarbonate	0.97 (0.95–0.99)	**0.033**	0.96 (0.94–0.99)	0.001
Sodium	0.99 (0.98-1.00)	0.248		
Potassium	1.05 (0.93–1.19)	0.402		
Charlson comorbidity index	1.01 (0.98–1.05)	0.552		
Mode l included variables with statistical difference between the alive group and the dead group				
Model 2: Multivariable logistic regression analysis adjusting respiratory failure, malignant cancer, anticoagulation, liver disease, temperature, WBC, RDW percent, glucose and Bicarbonate				
CHF: congestive heart failure, SBP: systolic blood pressure, WBC: white blood cell, RDW: red cell distribution width, INR: International Normalized Ratio, BUN: blood urea nitrogen, Cr: creatinine				

The Association Between Bun/cr And Mortality Of Patients With Cerebral Infarction In Different Subgroups

According to the data in Table 3, no significant effect of BUN/Cr on the in-hospital mortality was observed in patients aged ≥ 65 years or < 65 years (all $P > 0.05$). In terms of the gender, BUN/Cr was associated 1.02-folds risk of in-hospital mortality in male patients with cerebral infarction in ICU (RR = 1.02, 95%CI: 1.01–1.04), but had no statistical effect on female patients ($P > 0.05$). BUN/Cr was correlated with the increased risk of in-hospital mortality in cerebral infarction patients with respiratory failure (RR = 1.02, 95%CI: 1.01–1.03) or malignant cancer (RR = 1.03, 95%CI: 1.01–1.05). In cerebral infarction patients received anticoagulation, the risk of in-hospital morality was increased by 0.01 as one-unit increase of BUN/Cr (RR = 1.01, 95%CI: 1.01–1.02). As in patients without liver disease, BUN/Cr was a risk factor for the in-hospital mortality of cerebral infarction patients in ICU (RR = 1.01, 95%CI: 1.01–1.02).

Table 3
The association between BUN/Cr and mortality of patients with cerebral infarction in different subgroups

Subgroup	Model	
	RR (95%CI)	*P*
Age		
≥65	1.01 (1.00-1.02)	0.099
<65	1.01 (0.99–1.03)	0.273
Gender		
M	1.02 (1.01–1.04)	**0.023**
F	1.01 (0.99–1.02)	0.445
Respiratory failure		
Yes	1.02 (1.01–1.03)	**0.041**
No	1.01 (0.99–1.03)	0.286
Malignant cancer		
Yes	1.03 (1.01–1.05)	**0.032**
No	1.01 (1.00-1.02)	0.126
Anticoagulation		
Yes	1.01 (1.01–1.02)	**0.028**
No	1.02 (0.98–1.05)	0.341
Liver disease		
Yes	1.02 (0.99–1.05)	0.242
No	1.01 (1.01–1.02)	**0.040**
Multivariable logistic regression analysis adjusting respiratory failure, malignant cancer, anticoagulation, liver disease, temperature, WBC, RDW percent, glucose and Bicarbonate		
BUN: blood urea nitrogen, Cr: creatinine		

Discussion

In the current study, the effect of BUN/Cr on the in-hospital mortality of cerebral infarction patients in ICU was assessed. The results delineated that BUN/Cr was associated with an increased risk of in-hospital mortality of patients with cerebral infarction in ICU. In addition, the increased risk of in-hospital mortality of cerebral infarction patients was also observed in males, and those with respiratory failure, malignant

cancer and without liver disease, as well as those receiving anticoagulation. The findings of our study might highlight the role of BUN/Cr in the prognosis of patients with cerebral infarction, and reminded the clinicians to concern on the BUN/Cr level of patients and make timely interventions on those with high level of BUN/Cr.

Herein, we found that BUN/Cr was associated with an increased risk of in-hospital mortality of patients with cerebral infarction in ICU. BUN/Cr is a composite index of BUN and Cr, the added value in addition to BUN or Cr has been explored before. In a study of Akimoto et al, BUN/Cr was disproportionately increased in patients with cerebral infarction, which might be the contributor for the occurrence of cerebral infarction (Akimoto et al. 2011). Previously, Kim et al. depicted that BUN/Cr was an independent risk factor for venous thromboembolism in patients with acute ischemic stroke (Kim et al. 2017). In addition, the increased BUN/Cr ratio was associated with poor outcome in patients with ischemic stroke (Schrock et al. 2012). BUN/Cr $\geq$ 15 was reported to be an independent risk factor for predicting the long-term outcome of thrombolysed patients with acute ischemic stroke (Li et al. 2017). The mechanisms underlying the association between BUN/Cr and the in-hospital mortality of cerebral infarction in ICU may be due to that BUN/Cr is an important indicator for dehydration, which is indicated by an increased BUN/Cr ratio and serves a clinical maker for deterioration in acute stroke (Deng et al. 2019a). Dehydration can reduce the brain perfusion, and impair the neuroplasticity (Font et al. 2010; Hillis et al. 2003). Previous studies also indicated that dehydration might increase the event of venous thromboembolism after acute infarction (Liu et al. 2014). In addition, BUN/Cr levels were also associated with abnormal inflammation (Giribabu et al. 2017), oxidative stress (Vaziri et al. 2003), and endothelial dysfunction (Legrand & Rossignol 2020) in patients, which might be other potential mechanisms.

In this study, the increased risk of in-hospital mortality of cerebral infarction patients was observed in subgroups including males and those with respiratory failure, malignant cancer and without liver disease, as well as those receiving anticoagulation. Patients with respiratory failure and malignant cancer might be associated with a higher infection and inflammation status (Boopathi & Thangavel 2021; Wu et al. 2022). Anticoagulation is applied for the treatment of venous thrombosis and prophylaxis of post-operative venous thrombosis (Patel et al. 2018). In patients receiving the anticoagulation, abnormal BUN/Cr ratio might be a more reliable indicator associated with the mortality in cerebral infarction patients. For male patients and those with respiratory failure, malignant cancer and without liver disease, as well as those receiving anticoagulation, BUN/Cr level should be paid special attention. For those with high BUN/Cr levels, timely interventions should be provided.

Our study evaluated the role of BUN/Cr on the in-hospital mortality of cerebral infarction patients in ICU. BUN/Cr was identified as an indicator for in-hospital mortality of these patients. BUN and Cr are easily obtained biomarkers and can be widely applied in clinic. We also performed subgroup analyses, and found the associations of BUN/Cr with specific cerebral infarction patients. The limitation in the present study was that the data were extracted from MIMIC-III and MIMIC-IV database, some important variables including the detailed data on the treatments during the ICU stay was not included, which might affect the

outcomes of patients. In the future, more randomized controlled trials were required to verify the findings of the current study.

Conclusion

This study evaluated the association between BUN/Cr and the in-hospital mortality of cerebral infarction patients in ICU and found BUN/Cr was associated with an increased risk of in-hospital mortality of patients with cerebral infarction in ICU especially in males, and those with respiratory failure, malignant cancer and without liver disease, as well as those receiving anticoagulation. The findings of our study reminded the clinicians to pay attention on the level of BUN/Cr in cerebral infarction patients in ICU.

Materials And Methods

Study design and population

In this cohort study, the data of 3059 participants with cerebral infarction were collected from MIMIC database, including 1568 in the MIMIC-III and 1491 in the MIMIC-IV. The MIMIC-III is a large, single-center open database comprising the electronic health records including demographic characteristics, monitoring vital signs, laboratory and microbiological examination, imaging examination, observation and recording of intake and output, drug treatment, length of stay, survival data, and discharge or death records of more than 60,000 individuals admitted to an ICU at the Beth Israel Deaconess Medical Center between 2001 and 2012 (Johnson et al. 2016). The MIMIC-IV database is an updated version of the MIMIC-III and improvements have been made including simplifying the structure, adding new data elements, and improving the usability of previous data elements. The MIMIC-IV involves the comprehensive and high-quality electronic health records of patients admitted to the ICU or emergency department of the Beth Israel Deaconess Medical Center from 2008 to 2019 (Tao et al. 2021). The database got the approval from the institutional review boards of the Massachusetts Institute of Technology (Cambridge, Massachusetts) and the Beth Israel Deaconess Medical Center (Boston, Massachusetts). Cerebral infarction with ICU admission was diagnosed based on International Classification of Diseases, Ninth Revision (ICD-9) code and the Tenth Revision (ICD-10) code. ICD-9: 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411 and 43491; ICD-10: I63. In our study, patients aged < 18 years were excluded. Those admitted to ICU < 24 h were also excluded. Finally, the data of 2778 participants were analyzed. All people were divided into the alive group (n = 2083) and the dead group (n = 695). After propensity score matching (PSM) on age and gender, 2085 people were involved in and divided into the alive group (n = 1390) and the dead group (n = 695).

Variables

The main variable investigated was BUN/Cr. Covariables analyzed in the study including comorbidities [congestive heart failure (CHF) (yes or no), atrial fibrillation (AF) (yes or no), diabetes mellitus (yes or no),

respiratory failure (yes or no), renal failure (yes or no), malignant cancer (yes or no), hypertension (yes or no), and liver disease (yes or no)], medication use [thrombolytic (yes or no), and anticoagulation (yes or no)], laboratory data [heart rate (time/min), systolic blood pressure (SBP) (mmhg), diastolic blood pressure (DBP) (mmhg), mean arterial pressure (MAP) (mmhg), respiratory rate (time/min), temperature (°C), white blood cell (WBC) (K/uL), platelets (PLT) (K/uL), hemoglobin (g/dL), red cell distribution width (RDW) percent, hematocrit percent, Cr (mg/dl), International Normalized Ratio (INR), BUN (mg/dl), glucose (mg/dl), bicarbonate (mEq/l), sodium (mEq/l), and potassium (mEq/l)], and the Sequential Organ Failure Assessment (SOFA) Score, the Simplified Acute Physiology Score II (SAPSII), the Oxford Acute Severity of Illness Score (OASIS), and charlson comorbidity index.

Outcome Variable

The outcome variable in the present study was the in-hospital death of participants with cerebral infarction in ICU. All subjects in the ICU were followed up until death or discharge. The median follow-up time was 10.5 days. Among 2778 participants, 695 were dead at the end of follow-up.

Sensitivity Analysis

The missing values of all variables were shown in Supplementary Table 1. The results of sensitivity analysis revealed that no statistical difference was observed in the data before and after multi-interpolation. As exhibited Supplementary Table 2, the age was statistically different between the alive group and the dead group (66.42 years vs 71.51 years). To make the baseline data equilibrium between the alive group and the dead group, PSM was applied. After PSM, the age and gender showed no statistical difference between the two groups.

Statistical analysis

The continuous variables were in the forms of mean ± standard deviation (SD) if the data were normally distributed or M (Q_1, Q_3) if the data were not normally distributed. Student's t test was used to compare the difference between groups. The categorical variables were displayed as n (%), and chi-square and Wilcoxon rank sum test were applied to judge the differences between groups. The data with missing value < 10% were multi-interpolated, and with missing value ≥ 10% were excluded. PSM was performed in the data. Sensitivity analysis was performed between the data before multi-interpolation and after multi-interpolation as well as before PSM and after PSM. Multivariate logistic analyses were applied for identifying the confounders of the association between BUN/Cr and mortality of cerebral infraction. Model 1 included all variables with statistical difference between the alive group and the dead group. Model 2 included BUN/Cr, respiratory failure, malignant cancer, anticoagulation, liver disease, temperature, WBC, RDW percent, glucose and bicarbonate. Subgroup analysis was performed to assess the association between BUN/Cr and the mortality of cerebral infraction in different groups of people concerning age, gender, and whether the patient was complicated with respiratory failure, malignant

cancer or liver disease, or whether the whether the patient received anticoagulation treatments. The risk ratio (RR) was employed to evaluate the association between BUN/Cr and the mortality of cerebral infraction in ICU. The confidence level was set as $\alpha = 0.05$. All statistical analysis was conducted via SAS 9.4, and R 4.0.3.

Abbreviations

MIMIC: the Medical Information Mart for Intensive Care

ICU: intensive care unit

RR: risk ratio

CI: confidence interval

CHF: congestive heart failure

AF: atrial fibrillation

SBP: systolic blood pressure

DBP: diastolic blood pressure

MAP: mean arterial pressure

WBC: white blood cell

PLT: platelets

RDW: red cell distribution width

INR: International Normalized Ratio

SOFA: the Sequential Organ Failure Assessment

SAPSII: the Simplified Acute Physiology Score II

OASIS: the Oxford Acute Severity of Illness Score

BUN: blood urea nitrogen

Cr: creatinine

ICD-9: International Classification of Diseases, Ninth Revision (ICD-9)

Declarations

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Author contributions

Ting Chen conceived and designed the experiments, analyzed the data, performed the experiments,prepared figures and tables authored or reviewed drafts of the paper, and approved the final draft.

Ai-Ping Li performed the experiments,prepared figures and/or tables, and approved the final draft.

Qi Gong and Lin Zhou performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.

Yi-Xuan Zhao conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.

Zhi-Wen Zhou and Wen-Sheng Zhou conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

Ethics

The MIMIC-III and MIMIC-IV database are two freely used critical care medical databases. Access to the databases for research were approved by the Institutional Review Boards of the Massachusetts Institute

of Technology and the Beth Israel Deaconess Medical Center (researchers certification number 9266789).

Declaration of Competing Interest

The authors declare that they have no competing interests.

Availability of data and materials

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

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Figures

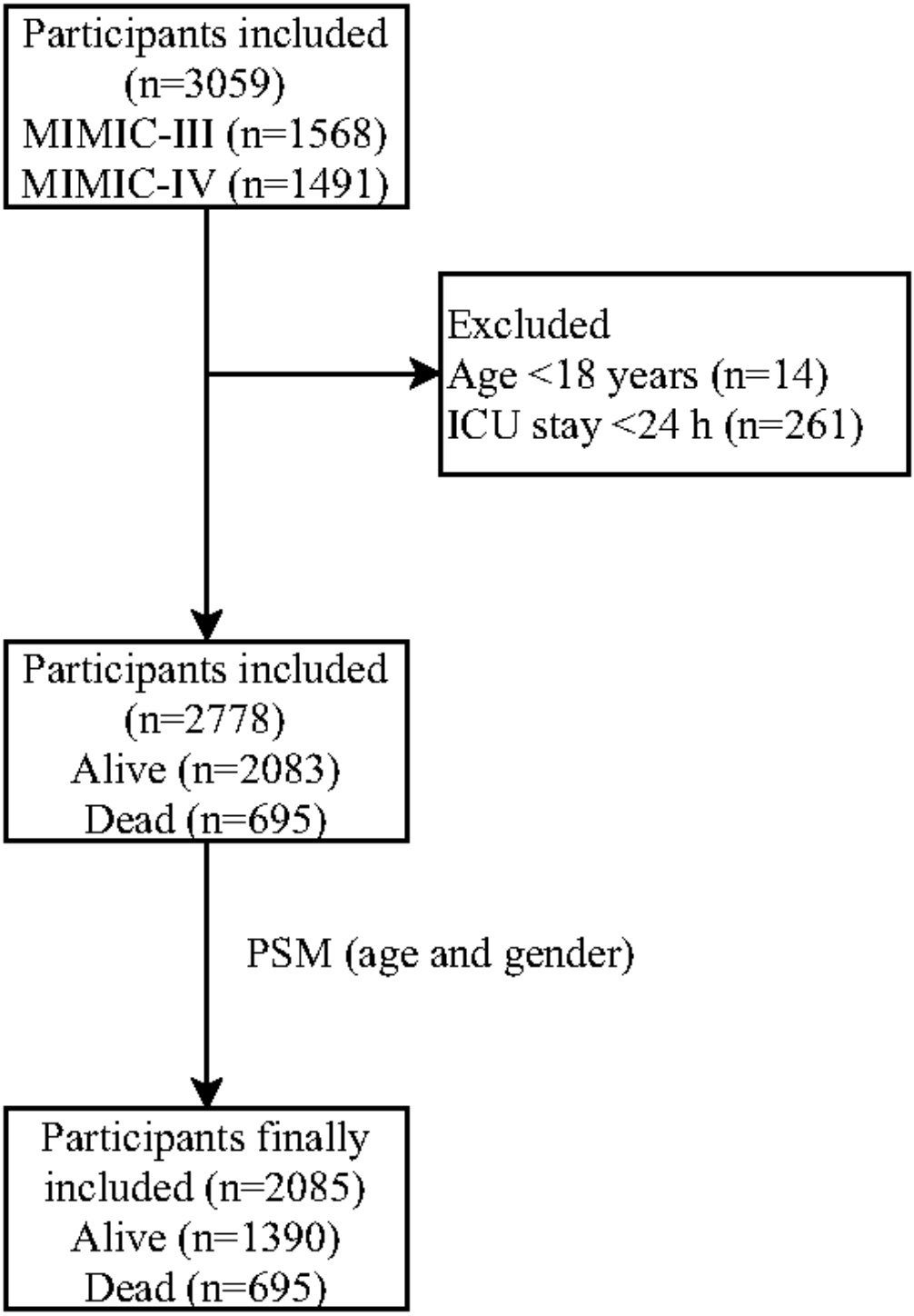

Figure 1

The screen process of participants in this study.

Supplementary Files

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