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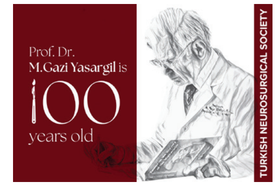

Associations of Blood Pressure and Serum Lactate Levels Upon Admission with One-week Mortality in Patients with Severe Traumatic Brain Injury: A Multi-Center Retrospective Study

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ABSTRACT

AIM: To explore interrelationships between serum lactate (Lac) levels and other hemodynamic parameters, including diastolic blood pressure (DBP) and mean arterial pressure (MAP) and acute-phase mortality in severe traumatic brain injury (sTBI).

MATERIAL and METHODS: Clinical data for sTBI patients (Glasgow Coma Scale (GCS) score ≤8 on admission) were collected from different hospitals from 2013 to 2024. One-week mortality was the endpoint. The associations of all blood pressure (BP) indices and Lac levels with one-week mortality were investigated using mixed effects logistic regression models, and the diagnostic value of mortality analysis based on the Lac levels was evaluated via receiver operating characteristic (ROC) curves and areas under the curve (AUCs). In addition, the relationships between the BP indices and Lac levels were assessed by linear regression analysis.

RESULTS: A total of 1270 sTBI patients were analyzed in this study. Bivariate analysis revealed smooth U-shaped associations of different BP indices upon admission with one-week mortality, and extreme values of the BP indices were found to be associated with increased mortality, with no obvious threshold effect revealed. After adjustments were made for confounding factors, the likelihood of death clearly increased with a SBP<100 mmHg, a DBP<70 mmHg, a MAP<80 mmHg and a Lac>4.5. Furthermore, all three BP indices were significantly negatively correlated with Lac levels. Moreover, MAP has the strongest ability to predict one-week mortality in sTBI patients, and it also has the strongest negative correlation with Lac levels.

CONCLUSION: In the development of guidelines for managing sTBI patients, the definition of hypotension should be reconsidered, and all three BP indices and serum Lac levels should be used as references instead of a single hypotension index of SBP<90 mmHg to improve the survival rate.

KEYWORDS: Traumatic brain injury, Threshold, Hypotension, Mortality, Risk factor

ABBREVIATIONS: sTBI: Severe traumatic brain injury, **AD:** Admission, **Lac:** Lactate, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **MAP:** Mean arterial pressure, **GCS:** Glasgow Coma Scale, **BP:** Blood pressure, **ROC:** Receiver operating characteristic curve, **AUC:** Area under curve, **SBI:** Secondary brain injury, **AIS:** Abbreviated injury scale, **CPP:** Cerebral perfusion pressure, **ICP:** Intracranial pressure, **CSF:** Cerebrospinal fluid, **CI:** Confidence interval, **SD:** Standard deviation

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INTRODUCTION

Approximately 60 million new cases of traumatic brain injury (TBI) are identified around the world each year, with severe TBI (sTBI) accounting for nearly 10% of all cases (8,31). However, estimating the worldwide incidence and mortality of TBI is difficult due to interference of factors such as economic development, public awareness, data collection ability and mortality calculation methods in different countries and areas (17,18). Epidemiological data indicate that TBI results in approximately 1 million deaths every year, and it is expected that neurological damage caused by TBI will remain the leading cause of disability due to neurological diseases until 2030 (22). Owing to the large population base of China, there are more cases of sTBI in China than in other countries, resulting in higher demands for public health management to a certain extent. Studies have shown that the mortality rate of sTBI patients in China is approximately 13 per 100,000 (15). Therefore, improved treatment of severe TBI patients is very important for reducing the burden on society.

TBI is divided into two stages: primary brain injury and secondary brain injury (SBI) (20). Primary brain injury is any physical injury that is directly caused by violence and is difficult to ameliorate therapeutically. SBI occurs as a result of the activation of multiple molecular and cellular pathways (membrane gradient loss, cellular swelling, disruption of immune and inflammatory mediators), and it has been reported to significantly influence outcomes; more attention should be given to this process (1). Among the types of secondary injuries, hypotension has been extensively studied due to its important role in increasing mortality (23). Hypotension can be used as predictive criteria for the optimization of clinical management,. Lactate (Lac) is a byproduct of anaerobic metabolism that can reflect organ perfusion failure (it has a strong relationship with MAP (13,24,28)), and increased Lac levels can also be used as a biomarker for the prediction of mortality in sTBI patients and provide information beyond that provided by vital signs (21). Although various biomarkers have been proven to be able to predict mortality in sTBI patients (such as S100B, GFAP, and UCH-L1), few of them have been routinely inspected in patients upon hospital admission. Hence, Lac may be a better choice as a biomarker due to its availability.

However, SBP<90 mmHg is the classical definition of hypotension (27); this is a statistical finding that was identified in a healthy population that did not have any great physiological significance. In addition, the latest guidelines do not provide management advice on the higher threshold of SBP or any definite information regarding diastolic blood pressure (DBP) or mean arterial pressure (MAP) (6). Furthermore, many related studies have focused mostly on patients with mild or moderate TBI (GCS>8) (7); furthermore, these studies have not focused on the outcome of mortality within one week of admission, which may be the most dangerous stage of sTBI (almost 50% of TBI deaths occur within two hours of injury) and could be easily influenced by BP upon admission (3,26). In addition, the ability of Lac levels and their relationship with different BP indices to predict mortality in sTBI patients is still limited. There are also epidemiological differences in low- and middle-income countries, and an increasing incidence of TBI has been demonstrated in young people, while the same is true of elderly individuals in high-income countries (22). In addition, race, medical equipment and diagnostic factors could affect the results.

Therefore, the aim of this experiment was to study the associations of different BP indices and Lac levels (within one hour after admission) with one-week mortality among sTBI patients (GCS≤8) and to determine the thresholds that are associated with increased mortality for these variables. This is essential for providing scientific guidance in the early-life treatment of TBI patients.

MATERIAL and METHODS

Study Design and Setting

Baseline data for sTBI patients were collected from different hospitals from 2013-2024 to conduct the cohort study. The prehospital interventions of these patients included only spinal immobilization and supplemental oxygen. This study included patients aged 18 to 80 years who presented with sTBI, which was confirmed by CT scan (head abbreviated injury scale (AIS) score≥3, GCS score≤8) (31). The exclusion criteria were as follows: patients transferred from other institutions or who died upon arrival at the hospital and patients who received cardiac resuscitative interventions before arrival.

This study was approved by the ethics committees of the corresponding hospitals (2021ky-101).

Data Collection

All TBI patients from both hospitals were included in the database by several data collectors, and data related to demographics (age and sex), physiological (SBP, DBP, MAP, serum lactic acid, and mechanism of injury), treatment (emergency operation and transport time) and prognosis (one-week, two-week and 24-hour mortality) were extracted from eligible patients.

Outcome Measures

The primary outcome measures were one-week mortality upon admission and various levels of SBP, DBP, MAP and serum Lac.

Statistical Analysis

Continuous parametric data are presented as the mean ± standard deviations, continuous nonparametric data are presented as medians (with interquartile ranges), and categorical data are presented as proportions. To establish whether there were differences between groups on a univariate level, the independent Student’s t test was conducted for continuous parametric data, the Mann-Whitney U test was used for continuous nonparametric data, and the chi-square test was performed for categorical variables. For bivariate analyses, the associations between mortality and exposure are shown in a graph with different BP indices as continuous variables. A modeling technique known as restricted cubic spline, which can accurately characterize nonlinear associations, was used to examine the relationships. Therefore, it was possible to establish whether there was a threshold value for different BP indices by examining the inflection points in the plots. Multivariate logistic regression was performed as a means of further exploring the relationships between mortality (dependent variable) and different admission BP indices (exposure variables). All three BP indices were categorized -in increments of 10 mmHg and compared with the unexposed reference range, where inflection points and odds of death were calculated for different levels of BP. All the odds ratios (ORs) were subsequently adjusted to avoid bias. Moreover, because a sparse effect may cause an inflated odds ratio (34), we used the method of data smoothing to reduce this effect. In addition, multivariable logistic regression was performed to control for confounding variables. Initially, relationships between the binary outcomes and each plausible predictor variable were assessed on a univariate level, and variables with a *p* value of less than 0.2 were included in a multivariable logistic regression model. The variables with $p<0.05$ in the analysis were considered significant. The cutoff of serum Lac level was calculated via a receiver operating characteristic (ROC) curve and Youden's test. Moreover, we conducted ROC analysis of Lac levels and mortality at different stages.; A delay test and sensitivity analysis for ROC comparison were also performed with R software. Linear regression analysis was then performed to evaluate the underlying relationships between Lac levels and the three BP indices. All the statistical analyses were conducted via SPSS (version 29.0) and R software (v4.1.0).

RESULTS

Data from 2974 trauma patients were obtained in this investigation, and 1270 adult patients suffering from sTBI were included in the analysis (Figure 1). Seventy percent of the patients were male, the mean age was 58 ± 17 years, the mean SBP, DBP and MAP values upon admission were 133 ± 37 mmHg, 77 ± 22 mmHg and 96 ± 26 mmHg, respectively, and the mean serum lactic acid level was 4.78 ± 3.45 mmol/L. The rate of mortality was 62.2%, and the rate of operative intervention was 51.0%. Significant differences in several demographic parameters and vital signs were observed between the groups. The sTBI patients who died had lower BP indices upon admission and higher Lac levels upon admission compared to those who survived. Traffic accidents were the primary mechanism of injury in both groups. The detailed parameters of the study can be found in Table I.

Furthermore, following a bivariate analysis, the predicted mortality was presented from an unadjusted logistic regression of one-week mortality against different admission BP indices and modeled via restricted cubic splines. The three smooth U-shaped relationships were then observed without any threshold effect (Figure 2). The probability of minimum mortality was significantly increased, with an SBP of 123.2, a DBP of 91.8 and a MAP of 104.8. Increased poor outcomes were found to be associated with both higher and lower BP values.

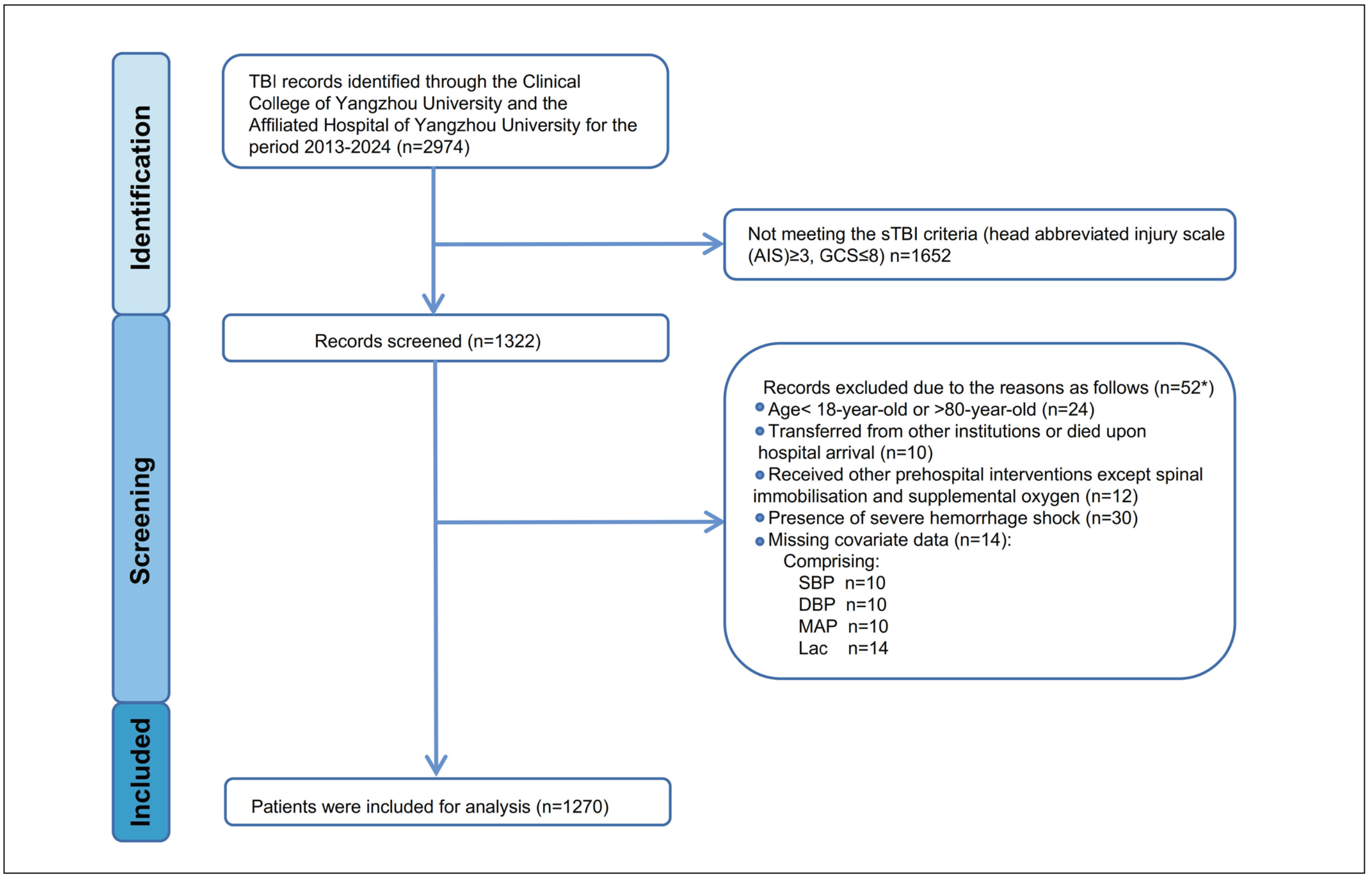

Figure 1: Flowchart showing the derivation of the study participants. *Patients may have been excluded for more than one factor.

Table I: Characteristics of sTBI Patients Upon Admission in the Analysis of the Complete Case

Characteristics	Overall	Dead	Survived	p-values
Number of patients	1270	790	480	
Age, mean ± SD (years)	58 ± 17	60 ± 18	55 ± 16	**<0.001**
Male, %	70	70	71	0.88
Transport time, mean ± SD (hours)	4.0 ± 5.1	4.5 ± 5.7	3.3 ± 4.0	**0.004**
Vital signs				
SBP, mean ± SD (mmHg)	133 ± 37	130 ± 42	136 ± 28	**<0.001**
DBP, mean ± SD (mmHg)	77 ± 22	75 ± 24	81 ± 18	**<0.001**
MAP, mean ±SD (mmHg)	96 ± 26	92 ± 30	98 ± 20	**<0.001**
Lac, median [IQR] (mmol/L)	3.7 (2.0-6.6)	4.8 (2.2-8.5)	2.8 (1.8-4.7)	**<0.001**
GCS, median [IQR]	3 (3-7)	3 (3-6)	4 (3-7)	0.12
Injury parameters				
Head AIS, median [IQR]	5 (4-5)	5 (4-5)	4 (4-5)	0.16
Face AIS, median [IQR]	1 (1-2)	1 (1-2)	1 (1-2)	0.24
Neck AIS, median [IQR]	1 (1-3)	1 (1-3)	1 (1-2)	0.57
Chest AIS, median [IQR]	2 (1-3)	2 (1-3)	2 (1-3)	0.73
Abdominal AIS, median [IQR]	1 (1-2)	1 (1-2)	1 (1-2)	0.81
Spine AIS, median [IQR]	2 (1-2)	2 (1-2)	2 (1-2)	0.43
Extremity AIS, median [IQR]	1 (1-1)	1 (1-1)	1 (1-1)	0.52
Surgical intervention, %	51	53	46	0.12
Mechanism of injury, %				
Traffic accident	58.0	61.0	56.0	0.36
Fall	34.0	32.0	36.0	0.47
Other	8.0	7.0	8.0	0.67
Mortality, %	62.2	100.0	0.0	**<0.001**

***SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **MAP:** Mean arterial pressure, **Lac:** Lactate, **GCS:** Glasgow Coma Scale, **AIS:** Abbreviated injury scale, **SD:** Standard deviation.*

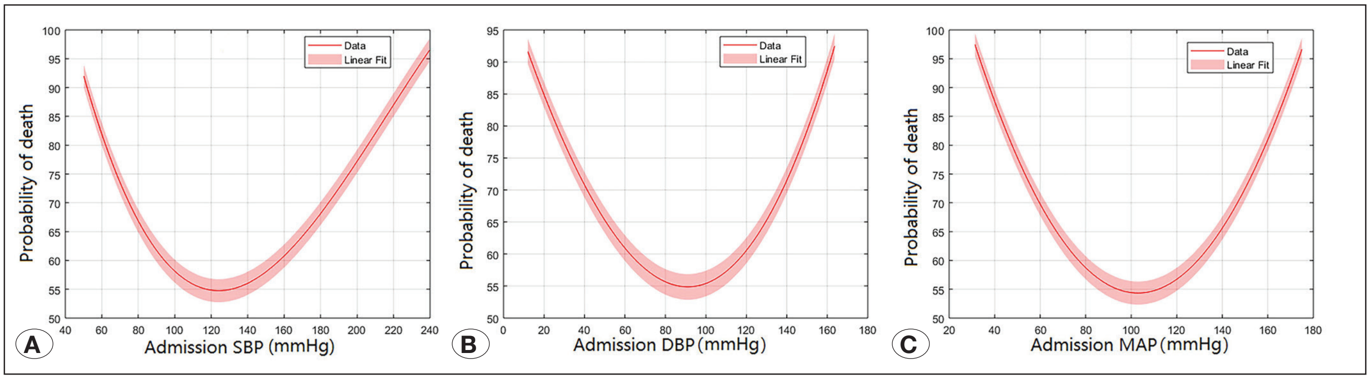

Figure 2: Associations of SBP **(A)**, DBP **(B)** and MAP **(C)** with the probability of death. The 95% confidence interval (CI) is represented by red shading.

In addition, in the complete case crude analyses, other U-shaped relationships between mortality and different BP indices were found with the multilevel random intercept logistic regression models, even after potential confounders were adjusted (Figure 3). The independent predictors of mortality in this model included older age, AIS, transport time, serum Lac level and lower GCS (Table II). In addition, adjustments were made for all three BP indices at disparate ranges, comparing SBP between 120–129 mmHg, DBP between 90–99 mmHg and MAP between 100–109 mmHg, which are the ranges with the greatest likelihood of survival. The results revealed that the following BP indices upon admission were associated with a greater chance of mortality: a SBP under 100 mmHg or above 170 mmHg, a DBP under 70 mmHg or above 130 mmHg and a MAP under 80 mmHg and above 140 mmHg. Extreme values of all the blood pressure indices were significantly associated with an increased risk of mortality according to the multivariate analysis. Hence, we performed receiver operating characteristic (ROC) analysis to evaluate the ability of different blood pressure parameters to predict one-week mortality. Although the results were very close, of the three curves, one-week mortality was more sensitive to the variation in MAP (AUC: 0.816) than to the variation in SBP (AUC: 0.797) or DBP (AUC: 0.760). These findings suggest that we should consider all three blood pressure parameters, especially the MAP, rather than just the SBP, in TBI management.

In addition, the concentration of Lac was found to be positively related to one-week mortality. The crude and adjusted odds of death for Lac levels (within one week) were 1.41 (95% CI: 1.32-1.6) and 1.54 (95% CI: 1.41-1.72), respectively, reflecting the risk factors (Table II). The median serum Lac concentration with the IQR in the group who survived for one week (480 patients) was 2.80 [1.80–4.70] mmol/L, which was lower than that in the group who died (4.8 [2.15–8.45] mmol/L, 790 patients; $p<0.001$; Figure 4A). To investigate the possible value of serum Lac levels for assessing mortality, receiver operating characteristic (ROC) curves were constructed, and area under the curve (AUC) values were computed. The results revealed that the AUC value was 0.733 (95% CI: 0.662-0.805; Figure 4D). ROC curve analysis and Youden's test provided the best area under 77% specificity and 49% sensitivity for a cutoff of 4.5. TBI patients who met this cutoff presented a greater mortality risk.

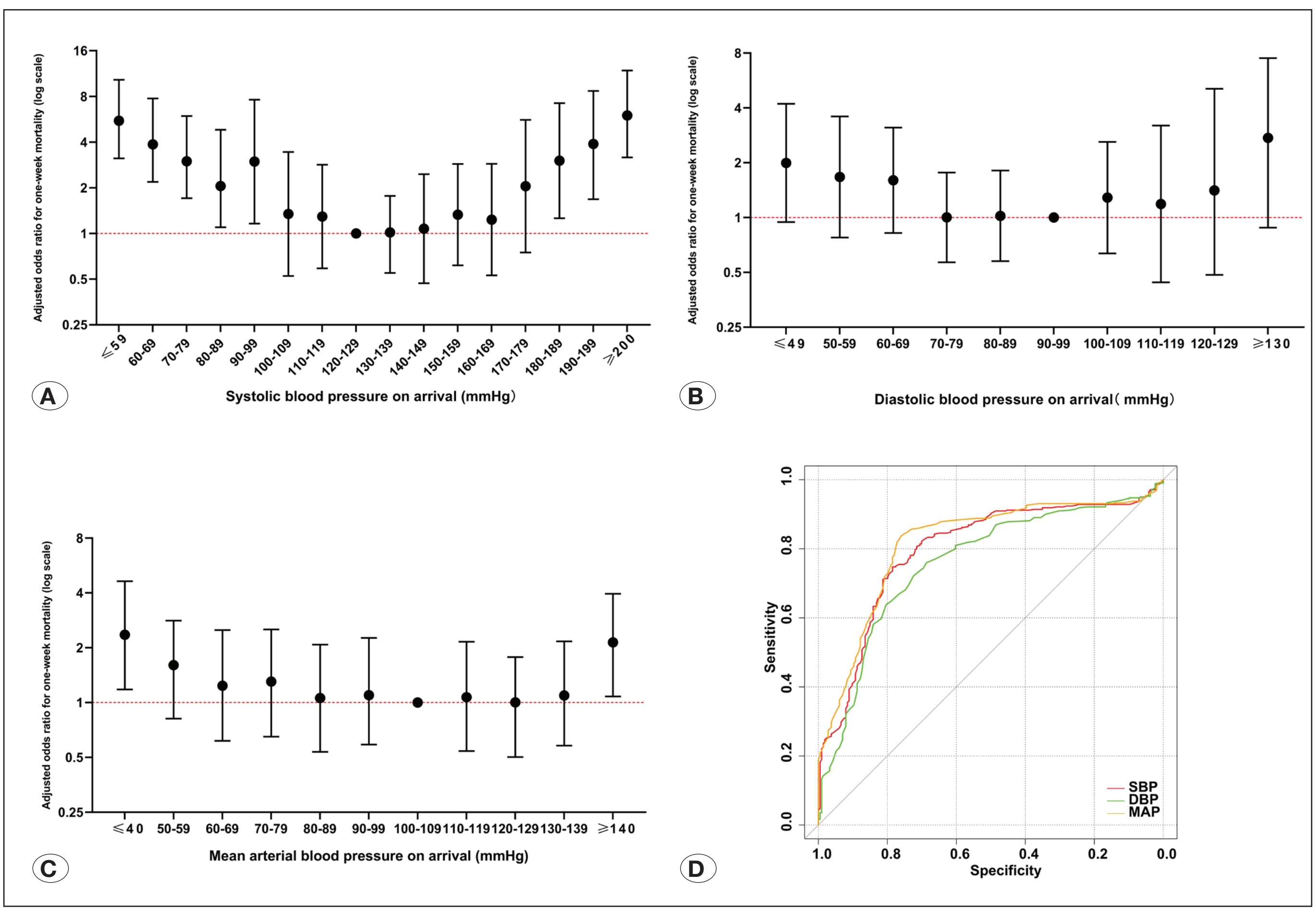

Figure 3: Associations between different categories of SBP **(A)**, DBP **(B)** and MAP **(C)** and one-week mortality according to adjusted multilevel logistic regression. (Receiver operating characteristic (ROC) curves with the area under the curve (AUC) were used to assess the ability of SBP, DBP, and MAP to predict one-week mortality **(D)**.

Table II: Multiple Logistic Regression Analysis with One-Week Mortality as the Outcome Variable

	Odds Ratio	95% CI	p-value
Age	1.019	1.009-1.029	**<0.001**
GCS	0.89	0.81-0.98	**<0.001**
Head AIS	1.36	1.20-1.55	**<0.001**
Transport time	1.052	1.012-1.55	**0.012**
Serum Lac	1.54	1.41-1.72	**<0.001**
AD SBP, mmHg			
≤ 59	5.525	3.125-10.281	**0.009**
60-69	3.866	2.184-7.763	**0.017**
70-79	2.990	1.708-5.941	**0.014**
80-89	2.052	1.098-4.816	**0.044**
90-99	2.973	1.161-7.61	**0.023**
100-109	1.344	0.525-3.442	0.18
110-119	1.293	0.589-2.839	0.52
120-129	Reference		
130-139	1.015	0.549-1.766	0.80
140-149	1.075	0.47-2.456	0.32
150-159	1.331	0.617-2.87	0.15
160-169	1.233	0.529-2.873	**0.038**
170-179	2.047	0.749-5.596	**0.014**
180-189	3.015	1.259-7220	**0.019**
190-199	3.885	1.681-8.682	**0.011**
≥ 200	5.986	3.171-11.847	**0.003**
AD DBP, mmHg			
≤49	1.995	0.945-4.209	**0.015**
50-59	1.670	0.777-3.592	**0.018**
60-69	1.602	0.823-3.116	**0.016**
70-79	1.002	0.568-1.766	0.26
80-89	1.021	0.576-1.812	0.39
90-99	Reference		
100-109	1.287	0.636-2.602	0.38
110-119	1.187	0.441-3.198	**0.027**
120-129	1.410	0.484-5.090	**0.017**
≥130	2.740	0.880-7.505	**0.013**
AD MAP, mmHg			
≤ 40	2.355	1.181-4.632	**0.003**
50-59	1.605	0.816-2.817	**0.013**
60-69	1.237	0.616-2.502	**0.037**
70-79	1.304	0.649-2.518	**0.025**
80-89	1.057	0.536-2.081	0.43
90-99	1.098	0.588-2.266	0.68
100-109	Reference		
110-119	1.07	0.542-2.156	0.34
120-129	1.003	0.502-1.778	0.12
130-139	1.093	0.581-2.166	**0.007**
≥ 140	2.14	1.08-3.955	**0.002**

***AD:** Admission, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **MAP:** Mean arterial pressure, **GCS:** Glasgow Coma Scale, **AIS:** Abbreviated injury scale, **CI:** Confidence interval.*

Table III: Delong Test for ROC Comparison

	Difference in AUC	D	df	p-value
One-week vs.Two-week	0.093	-1.711	366.13	**0.038**
One-week vs. 24-hour	0.043	0.860	369.16	0.390
Two-week vs. 24-hour	0.137	-2.560	361.87	**0.010**

***ROC:** Receiver operating characteristic curve, **AUC:** Area under curve.*

Moreover, the level of serum lactate commonly decreases after good resuscitation in trauma patients. As a result, to test the diagnostic ability of mortality analysis on the basis of the Lac levels, we conducted a sensitivity analysis of two-week mortality and 24-hour mortality and performed a DeLong test for receiver operating characteristic (ROC) comparisons. The results were as follows. The median serum Lac concentration with IQR in the group who survived for two weeks (410 patients) was 3.0 [1.92–5.14] mmol/L, which was also lower than that of the group who died within two weeks (4.65 [2.72–8.05] mmol/L, 860 patients, $p<0.001$; Figure 4B). Moreover, the median serum Lac concentration with the IQR in the group who survived for 24 hours (816 patients) was 2.65 [1.70-4.28], which was also lower than that of the group who died within 24 hrs (6.40 [3.50-9.10] mmol/L, 454 patients; $p<0.001$; Figure 4C). Hence, patients with poor outcomes demonstrated greater change in Lac levels upon arrival. Moreover, the DeLong test for ROC comparison suggested that Lac levels may have a better predictive ability for mortality in the shorter period (the AUCs of one-week mortality and 24-hour mortality were significantly different from that of two-week mortality, whereas the differences between the AUCs of one-week mortality and 24-hour mortality were insignificant; Figure 4D & Table III).

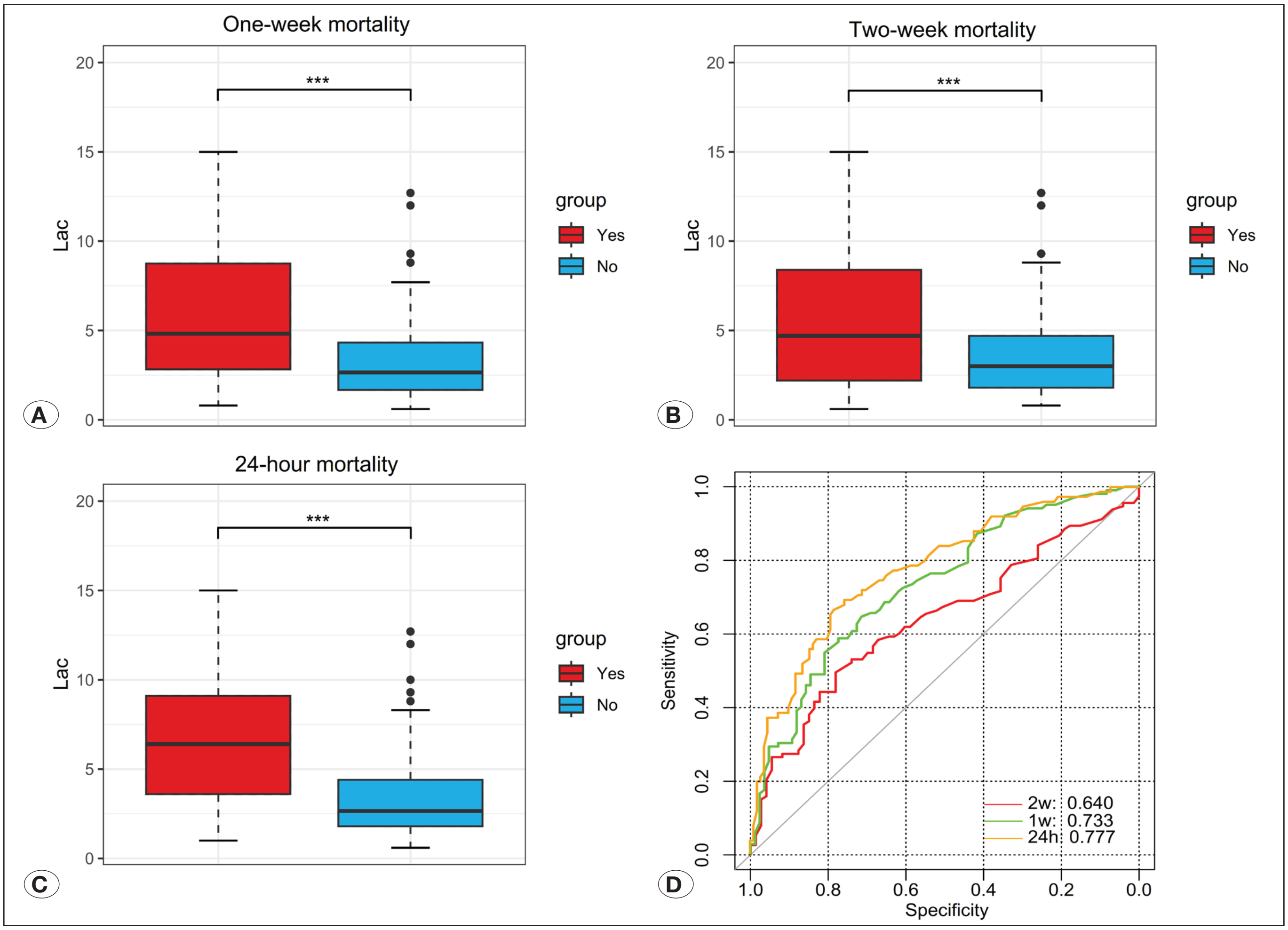

Figure 4: The level of serum Lac in the groups who survived or died within one week **(A)**, two weeks **(B)**, and 24 hours **(C)**. ROC curve analysis of the specificity and sensitivity of Lac as a biomarker for one-week mortality, two-week mortality and 24-hour mortality in sTBI patients **(D)**. Abbreviations: sTBI: severe traumatic brain injury; ***p<0.001.

Negative and significant relationships were found between Lac levels and all three BP indices by linear regression analysis, whereby MAP demonstrated the strongest association with serum Lac (Table IV).

DISCUSSION

The study was performed as a means of investigating the optimal lower thresholds of different BP indices and serum Lac levels among patients suffering from sTBI through the collection of multicenter clinical data. Greater possibilities of higher one-week mortality were found in sTBI patients with a SBP<100 mmHg, a DBP<70 mmHg or a MAP<80 mmHg and a Lac>4.5, suggesting that the definition of hypotension and the function of Lac in sTBI may need to be reconsidered. Moreover, the MAP has the strongest ability to predict one-week mortality in sTBI patients, and it also has the strongest negative correlation with Lac.

In the latest guidelines for the management of TBI, the definition of hypotension is an SBP<90 mmHg, which is based on a study in which the proportion of patients with sTBI was less than 30% (27). Moreover, the SBP upon admission in this study demonstrated a continuous relationship with mortality in the U-shaped plot of adjusted odds rather than a dichotomous relationship. Therefore, in the treatment of sTBI patients, there is no physiological threshold for SBP, and this should be acknowledged by future guidelines. As is widely known, a lower SBP during secondary injury is a powerful predictor of mortality, as sTBI patients often also experience extracranial injury and massive blood loss, which may result in hypoxia or hypotension worsening SBI (11). Importantly, the finding that higher SBP in patients with sTBI may be strongly associated with one-week mortality, which was not previously fully confirmed, is worthy of further discussion. Contrary to the findings of Butcher and Suttipongkaset, who reported that the relationship between hypertension and poor outcomes largely weakens after adjusted analysis (5,32), most hypertensive patients in this study exhibited increased mortality even after adjustment. Research by Johnson et al. and Asmar et al. also showed the same results (2,16). The mechanism may involve

Table IV: Linear Regression Between Different Blood Pressure Indices and Serum Lac

Coefficients[a]						
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	9.020	0.914		9.874	0.000
	SBP	**-0.045**	0.007	**-0.435**	-4.819	**0.000**

a. Dependent Variable: Lac

Coefficients[a]						
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	8.695	0.856		10.159	0.000
	DBP	**-0.043**	0.011	**-0.433**	-4.774	**0.000**

a. Dependent Variable: Lac

Coefficients[a]						
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	9.265	0.917		10.101	0.000
	MAP	**-0.048**	0.010	**-0.450**	-5.072	**0.000**

a. Dependent Variable: Lac

SBP: *Systolic blood pressure,* ***DBP:*** *Diastolic blood pressure,* ***MAP:*** *Mean arterial pressure,* ***Lac:*** *Lactate.*

increased SBP triggering hyperperfusion injury and cellular edema, which contributes to damage to the blood-brain barrier and autoregulation failure (10). Therefore, a higher admission SBP could translate into increased intracranial pressure and aggravated ischemic injury.

All evidence suggests that there may be a bimodal relationship between one-week mortality and SBP upon admission, which highlights the importance of maintaining the SBP spectrum within a specific section rather than beyond a threshold of hypotension for optimal prognosis in sTBI patients. A cohort study by Shibahashi et al. and another study conducted by Huang et al. found that extreme SBP upon admission was associated with higher mortality, thereby strengthening the credibility of the study's findings (14,27).

Moreover, only SBP has been analyzed in most previous studies, whereas few sTBI studies have examined all three BP indices. However, when assessing tissue perfusion pressure, the MAP is a more important determinant and better indicator of noncardiac organ perfusion than SBP (9). Therefore, the MAP has been emphasized as a crucial factor in critical patients by several landmark studies (12,19). The basic principles in the management of sTBI patients are maintaining and optimizing cerebral perfusion pressure (CPP), which is achieved by reducing intracranial pressure (ICP) or elevating MAP (25). A previous study revealed that extreme MAP values upon admission are associated with increased mortality in patients with TBI, and this association largely disappeared in the adjusted analysis (10). While the relationship still existed in this study, the results suggest that the MAP may play an underlying role in the prediction of poor outcomes.

In addition, DBP serves as an essential part of MAP, and low DBP values will compromise regional cerebral perfusion. Therefore, both DBP and MAP must be considered possible hemodynamic targets in sTBI management on the basis of this physiological concept. The insertion of intra-arterial lines is not always successful, particularly in some departments that lack intensively trained health care workers and robust critical care equipment, and DBP may be a better choice for the evaluation of brain perfusion due to its availability. After adjusting for confounders, both diastolic hypotension and hypertension were found to be strongly associated with poor outcomes. Therefore, similar to SBP, the results revealed the same relationships with DBP and MAP, which highlights the point that sufficient and suitable blood pressure should be maintained in all different indices during early treatment. Moreover, on the basis of the ROC analysis results in Figure 3, the best indicator of one-week mortality in sTBI patients is MAP, rather than systolic blood pressure and diastolic blood pressure. This further suggested that all blood pressure parameters should be considered, not only the single systolic blood pressure parameter, when developing guidelines for managing TBI.

In addition, in comparison to hypotension, which is a surrogate for cellular hypoperfusion, Lac levels were reported to peak on the first day after injury and to have better predictive ability for mortality among TBI patients (21,33). Lac levels in the cerebrospinal fluid (CSF) of severe TBI patients reflect the metabolic state of the damaged brain (29) and has been shown to be associated with sTBI mortality within 3 days of admission (30). However, the monitoring of CSF Lac levels cannot be routinely performed, but serum Lac levels are steadier, and monitoring them is easier. In this study, Lac was found to be an independent risk factor for sTBI, with a definite ability to predict mortality. Moreover, the sensitivity analysis and DeLong test results indicated that Lac may have better ability to predict mortality in a shorter period. The underlying negative relationships between Lac and different BP indices were also revealed. It is assumed that lower blood pressure leads to tissue hypoperfusion, which contributes to higher Lac levels. Among the three BP indices, the MAP best reflects noncardiac organ perfusion; therefore, it is most closely associated with Lac levels (4,28). This may explain why it has the strongest ability to predict one-week mortality (compared with DBP and SBP).

The sTBI patients who simultaneously had a SBP upon admission between 120–129 mmHg, a DBP between 90–99 mmHg, a MAP between 100–109 mmHg and a Lac level less than 4.5 demonstrated the greatest survival probability. Therefore, the reference indicator for sTBI treatment should not be limited to SBP, and both the optimal range of different BP indices and serum Lac levels should be considered in clinical management because of the close relationships between them.

However, this study had some limitations. First, the retrospective cohort study had inherent biases, which could only be partly solved following adjustment for confounding factors via a mathematical model. In addition, not all underlying confounding factors were included, and data, including coagulopathy and cerebral oxygen saturation, were not recorded on admission. Moreover, the reference range of different BP indices may be influenced by age, which other studies have focused on. However, in this study, the subgroup analysis based on age may not have been valid and significant because of the small sample size. Hence, large and more rigorous studies are needed to address these issues.

CONCLUSION

One-week mortality among sTBI patients was found to be associated with all three BP indices (bimodal relationships) and the serum lactic acid level (negative relationship). Among these parameters, MAP, not SBP, has the strongest ability to predict one-week mortality. In the development of guidelines for the management of TBI, the definition of hypotension (simply SBP <90 mmHg) must be reconsidered. Furthermore, variables related to hemodynamics, including SBP, DBP, MAP and Lac, could interact with each other. Among these variables, MAP had the strongest negative correlation with Lac levels, which may explain why it had the strongest ability to predict one-week mortality. Therefore, all these parameters should be considered in future TBI management rather than the hypotensive value of SBP alone.

Declarations

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AUTHORSHIP CONTRIBUTION

Study conception and design: AP, YP
Data collection: WZ
Analysis and interpretation of results: HJ, WZ, XZ. LD
Draft manuscript preparation: HJ, WZ, XZ
Critical revision of the article: AP, YP
Other (study supervision, fundings, materials, etc...): LD
All authors (HJ, WZ, XZ, LD, YP, AP) reviewed the results and approved the final version of the manuscript.

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