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Blood pressure variability and prognostic significance in traumatic brain injury: analysis of the eICU-CRD database

Shao-Yang Zhang[1†], Chang-Li Li[2†], Jian Yin[1], Meng Jiang[1*] and Xiao-Feng Yang[1]

Abstract

Background Preliminary evidence demonstrates that visit-to-visit systolic blood pressure (SBP) variability is a prognostic factor of TBI. However, literature regarding the impact of initial blood pressure management on the outcomes of TBI patients is limited. We aimed to further validate the clinical significance of BPV on the prognostic outcomes of patients with TBI.

Methods We performed the analysis by using individual patient-level data acquired from the eICU-CRD, which collected 200,859 ICU admissions of 139,367 patients in 2014 and 2015 from 208 US hospitals. Adult patients with traumatic intraparenchymal hemorrhage or contusion were included. The primary outcome was in-hospital mortality and the secondary outcome was discharge-home rate. Blood pressure variability (BPV) was calculated according to standard criteria: at least six measurements were taken in the first 24 h (hyperacute group) and 36 over days 2–7 (acute group). We estimated the associations between BPV and outcomes with logistic and proportional odds regression models. The key parameter for BPV was standard deviation (SD) of SBP, categorized into quintiles. We also calculated the average real variability (ARV), as well as maximum, minimum, and mean SBP for comparison in our analysis.

Results We studied 1486 patients in the hyperacute group and 857 in the acute group. SD of SBP had a significant association with the in-hospital mortality for both the hyperacute group (highest quintile adjusted OR 2.28 95% CI 1.18–4.42; p_{trend}<0.001) and the acute group (highest quintile adjusted OR 2.17, 95% CI 1.08–4.36; p_{trend}<0.001). The strongest predictors of primary outcome were SD of SBP in the hyperacute phase and minimum SBP in the acute phase. Associations were similar for the discharge-home rate (for the hyperacute group, highest quintile adjusted OR 0.58, 95% CI 0.37–0.89; p_{trend}<0.001; for the acute group OR 0.55, 95% CI 0.32–0.95; p_{trend}<0.001).

Conclusion Systolic BPV seems to predict a poor outcome in patients with TBI. The benefits of early treatment to maintain appropriate SBP level might be enhanced by smooth and sustained control.

Keywords Traumatic brain injury, Blood pressure variability, Mortality, Discharge-home rate

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Introduction

According to statistics from 2016, there were approximately 55.5 million cases of traumatic brain injury (TBI) worldwide, resulting in 8.1 million years of life lived with disability (YLDs) [1]. TBI has emerged as the leading cause of disability and neurological complications among victims of trauma [2]. It is a complex condition that results from both primary (direct external impact) and secondary injuries (inflammatory cascade) [3]. Existing literatures have demonstrated that advanced age, pre-existing comorbidities, and the initial severity of the TBI are associated with increased mortality and poorer prognosis [4–7]. However, literature regarding the impact of initial blood pressure management on the outcomes of TBI patients is limited.

Currently, there are no definitive treatments for TBI, and medical care is primarily focused on supportive measures such as monitoring intracranial pressure (ICP) and ensuring adequate oxygen delivery to the brain [3]. The guideline for the management of severe TBI [8] recommended that maintaining appropriate systolic blood pressure (SBP) level (e.g., 100 mm Hg for patients aged 50 to 69 years old) would improve the outcomes. Recent researches by Tran et al. [9, 10] have shed new light on the importance of blood pressure variability (BPV) within the first 24 h of admission. They found that high BPV was significantly associated with hematoma progression [9] and lower discharge-home rate [10] in patients with traumatic intraparenchymal hemorrhage or contusion. These results suggest that achieving stable SBP levels, rather than just targeting a specific SBP level, may play a critical role in the management of TBI.

Given the limited sample sizes in existing literatures about the effect of BPV on TBI [9–11], we utilized the comprehensive big data resource of the eICU Collaborative Research Database (eICU-CRD) [12] to investigate the clinical significance of BPV. To mitigate the influence of initial resuscitation in the first 24 h, we analyzed the impact of BPV in both the first 24 h (defined as hyperacute BPV) and during days 2–7 (defined as acute BPV).

Methods

Data description

This study utilized the eICU-CRD, a critical care database based in the United States [12]. The eICU-CRD amassed 200,859 ICU admissions from 139,367 patients across 208 US hospitals in 2014 and 2015. Physiological readings were recorded hourly at the bedside, with demographic characteristics, diagnoses, laboratory data, and other clinical information collected during routine medical care. This analysis was based on a publicly available database with pre-existing institutional review board approval, and it was reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [13].

Patient population

Adult patients who had experienced traumatic intracranial hemorrhage or cerebral contusion that had stayed in the ICU for a minimum of 24 h were considered eligible for the study. To minimize bias for calculating BPV, we only included patients who had at least six SBP readings per day for the first seven days until discharge or death based on earlier study [14]. BPV was calculated during the hyperacute phase (first 24 h) and the acute phase taken on days 2–7 (Fig. 1). As this was a hypothesis-generating epidemiological study, all eligible cases in the eICU-CRD database were included to maximize the statistical power.

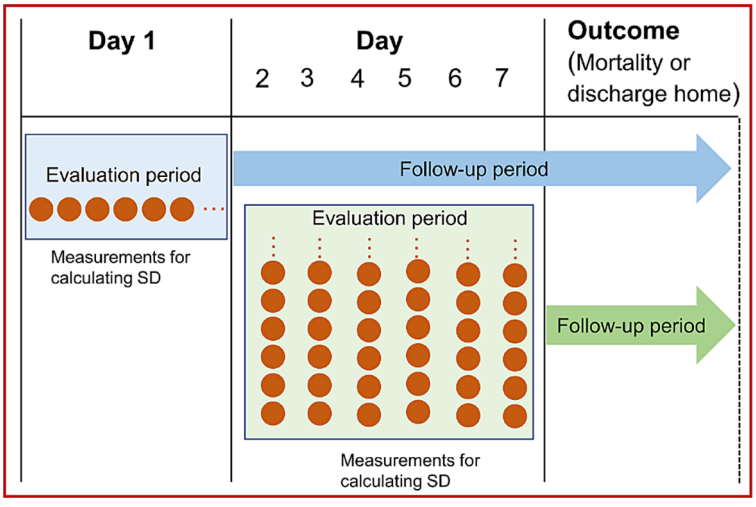

Fig. 1 Measurements used to calculate blood pressure variability. Red circles indicate number of SBP readings

Demographic and laboratory variables

We collected the following information on the first day of ICU admission: age at the time of hospital admission, gender, admission ICU type, type of TBI, comorbidities, Sequential Organ Failure Assessment (SOFA) score, Glasgow coma scale score (GCS), APACHE IV score, and the major medical management (including ICP monitoring, craniectomy, and vasopressor use). The primary outcome was in-hospital mortality. Discharge-home rate was used as a proxy for the secondary outcome, since previous researches have suggested that being discharged home is linked to better long-term neurological function for TBI patients [5, 6, 15]. It's reasonable to assume that patients who are able to be discharged home after their hospitalization have better outcomes.

Definition of blood pressure variability (BPV)

We selected the standard deviation (SD) of SBP as the primary parameter to measure BPV because it has a direct correlation with mean SBP but contains more valuable information and is straightforward and relevant to clinical practice [14]. Additionally, we calculated the average real variability (ARV), which accounts for the order of blood pressure measurements over time [16], as well as maximum, minimum, and mean SBP for comparison in our analysis.

To assess the relationship (strength and shape) between BPV and the primary and secondary outcomes, we categorized the SD of SBP into five groups (quintiles), with the lowest fifth serving as the reference for staged logistic regression models. We compared baseline characteristics between the five groups using either a χ^2 test or Kruskal-Wallis non-parametric test for categorical or continuous variables, respectively. Variables were chosen for inclusion in the regression models based on published research, clinical expertise, and their predictive power in relation to outcomes (i.e., $p<0.05$). Model 1 was adjusted for age and admission ICU type; Model 2 was adjusted for all covariables in model 1 plus ICP monitor and vasopressors use; and model 3 included all variables in model 2 plus SOFA score (not APACHE IV score because of the collinearity). We analyzed the other parameters for BPV as continuous measures in the three models. The results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). We utilized the integrated discrimination index (IDI) [17] and Akaike's information criterion (AIC) to discriminate between different parameters. To assess heterogeneity in the associations between BPV and outcomes across different ICU types (Neuro-ICU [NICU] or other ICU), we added an interaction term (ICU type*SOFA score) to model 3.

We conducted statistical analyses using STATA software (version 17.0). Statistical significance was determined by two-sided p values less than 0.05.

Results

From the eICU-CRD database, 2207 adult ICU admissions with traumatic intracranial hemorrhage or cerebral contusion were initially identified. After excluding 517 patients who died within 24 h after ICU admission or ICU stays less than 24 h, 1690 patients were included for further analysis. Of these, 1486 were included in the analysis of hyperacute BPV, and 857 in the analysis of acute BPV (Fig. 2). The overall demographic characteristics of patients upon admission for hyperacute and acute groups were shown in Table 1. In the hyperacute BPV group, 182

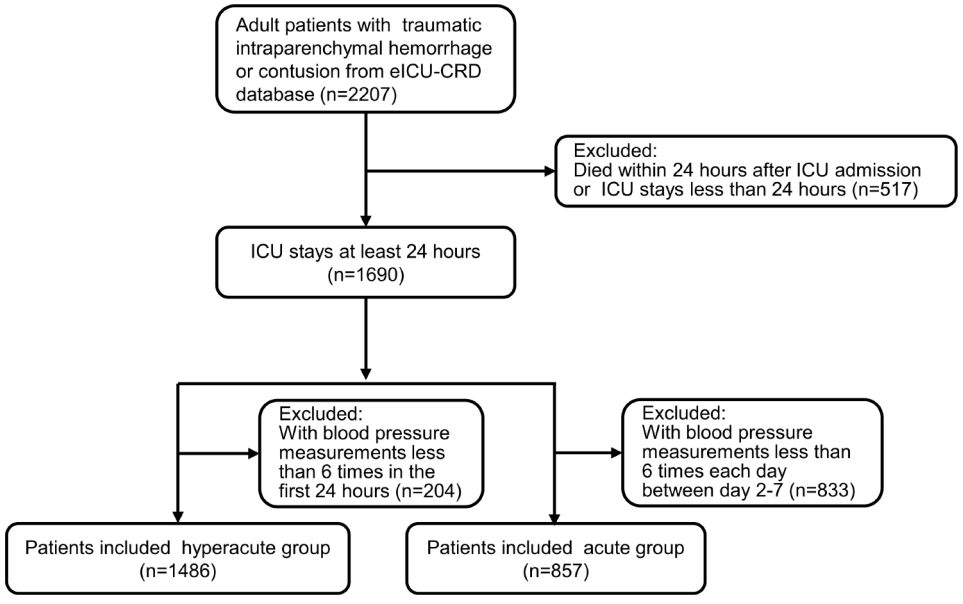

Fig. 2 Flow chart of patient selection

Table 1 Overall clinical characteristics of the study population

	Hyperacute BPV (fist 24 h; *n* = 1486)	Acute BPV (days 2–7; *n* = 857)
Demographics		
Age (years)	68.0 [56.0, 79.0]	67.0 [54.0, 79.0]
Male	824 (55.5)	501 (58.5)
Ethnicity		
White	104 (7.0)	74 (8.6)
African American	1190 (80.1)	665 (77.6)
Other	192 (12.9)	118 (13.8)
Diagnosis		
Subdural hematoma	624 (42.0)	357 (41.7)
Subarachnoid hemorrhage	417 (28.1)	233 (27.2)
Intracerebral hemorrhage	316 (21.3)	191 (22.3)
Cerebral contusion	39 (2.6)	20 (2.3)
Epidural hematoma	24 (1.6)	11 (1.3)
Intraventricular hemorrhage	66 (4.4)	45 (5.3)
Clinical features		
NICU	539 (36.3)	349 (40.7)
Diabetes	184 (12.4)	109 (12.7)
Hypertension	192 (12.9)	117 (13.7)
GCS score	14.0 [10.0, 15.0]	14.0 [8.0, 15.0]
APACHE IV score	50.0 [37.0, 67.0]	53.0 [39.0, 69.0]
SOFA score	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]
SBP measurements	25.0 [20.0, 36.0]	48.0 [20.0, 132.0]
SBP (mm Hg)	137.0 [121.0, 152.0]	133.0 [119.0, 148.0]
DBP (mm Hg)	71.0 [62.0, 82.0]	67.0 [58.0, 77.0]
SD of SBP	13.4 [10.5, 17.1]	13.9 [11.2, 17.2]
Management		
ICP monitor	110 (7.4)	101 (11.8)
Craniectomy	114 (7.7)	85 (9.9)
Vasopressor use	64 (4.3)	44 (5.1)
Outcome		
ICU length of stay, days	2.0 [1.0, 4.0]	3.7 [2.5, 7.0]
Hospital length of stay, days	5.8 [3.1, 11.2]	8.9 [5.5, 14.9]
ICU mortality	106 (7.1)	51 (6.0)
In-hospital mortality	182 (12.2)	98 (11.4)
Discharge-home rate	605 (40.7)	243 (28.4)

Data are median (IQR) for continuous variables, and n (%) for categorical variables

NICU: Neuro-ICU; GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment; SBP: systolic blood pressure; DBP: Diastolic blood pressure; SD: standard deviation; ICP: intracranial pressure; ICU: intensive care unit

(12.2%) patients died in the hospital, while in the acute BPV group, 98 (11.4%) patients died. For the second outcome, 605 (40.7%) and 243 (28.4%) patients were discharged home in the hyperacute and acute BPV groups, respectively. Regarding the type of TBI in the hyperacute BPV group, subdural hematoma, subarachnoid hemorrhage, and intracerebral hemorrhage accounted for 42.0%, 28.1%, and 21.3% of the cohort, respectively, with the remaining 8.6% accounted for the other types of TBI. The distribution of TBI type was similar for the acute BPV group (Table 1). The baseline characteristics of patients by fifths of SD-SBP in the hyperacute and acute BPV groups were shown in Supplementary file: Table S1 and S2. No significant heterogeneity of associations was detected between SD of SBP and the primary outcome (in-hospital mortality) by ICU type (Supplementary file: Table S3).

Overall, the SD of SBP indicated a downward trend in both the survivor and non-survivor groups; however, the SD of survivors was significantly lower than that in the non-survivor group within 28 days of hospitalization (Fig. 3). Notably, for hyperacute BPV, the SD of SBP demonstrated a significant linear correlation with in-hospital mortality across all models (the highest quintile of SD of SBP in model 3 adjusted OR: 2.28, 95% CI 1.18–4.42; p_{trend}<0.001; Fig. 4A-C). Additionally, all other

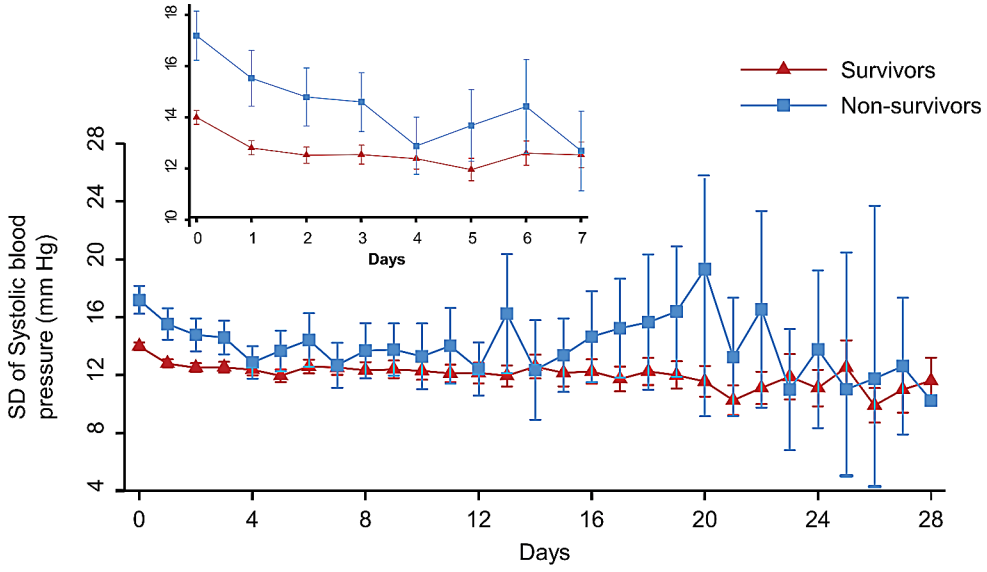

Fig. 3 Inter-group mean standard deviation of systolic blood pressure over time for survivors and non-survivors

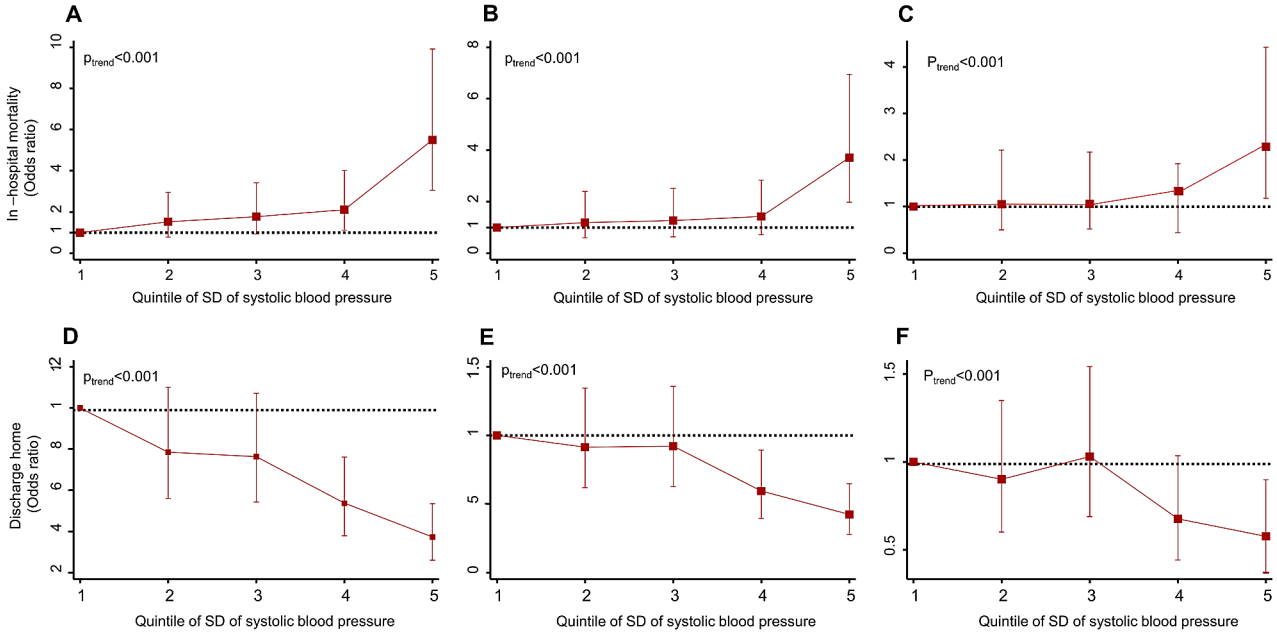

Fig. 4 Association between quintiles of standard deviation of systolic blood pressure and in-hospital mortality (**A**-**C**) and discharge-home rate (**D**-**E**) for the hyperacute phase BPV. Lowest quintile is reference

parameters of systolic BPV, except for mean SBP, were also significantly linked to in-hospital mortality in the fully adjusted model (Table 2). The validity of our results was reinforced by the likelihood ratio tests, as evidenced by the improved fitting of model 3's variables contrasted with model 2 (Supplementary file: Table S4 and S5).

The SD of SBP during the hyperacute phase exhibited a negative association with the discharge-home rate, with the highest quintile in model 3 displaying an adjusted OR of 0.58 and a 95% CI of 0.37–0.89 (p_{trend}<0.001; Fig. 4D-F). Similarly, all other indicators of hyperacute systolic BPV (except for minimum SBP and ARV) demonstrated a significant correlation with the secondary outcome, as summarized in Table 2.

Regarding acute BPV, the SD of SBP was found to be significantly associated with in-hospital mortality across all models, particularly within the highest quintile of SD of SBP (model 3 OR: 2.17, 95% CI 1.08–4.36; p_{trend}<0.001; Fig. 5A-C). Moreover, a negative nonlinear association with the secondary outcome was also detected across all models, with the highest quintile of SD of SBP showing evidence of association (model 3 OR: 0.55, 95% CI

Table 2 Effects of one standard deviation increment of systolic blood pressure variability in the first 24 h on in-hospital mortality and discharge-home rate

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
	In-hospital mortality					
SD	1.12 (1.09–1.15)	< 0.001	1.10 (1.07–1.13)	< 0.001	1.07 (1.04–1.10)	< 0.001
Minimum	0.96 (0.95–0.97)	< 0.001	0.97 (0.96–0.98)	< 0.001	0.98 (0.97–0.99)	0.002
Maximum	1.01 (1.00-1.02)	0.001	1.01 (1.00-1.02)	0.019	1.01 (1.00-1.02)	0.035
Mean	0.97 (0.96–0.98)	< 0.001	0.97 (0.96–0.99)	< 0.001	0.99 (0.98-1.00)	0.124
ARV	0.85 (0.77–0.94)	0.001	0.82 (0.74–0.91)	< 0.001	0.83 (0.75–0.93)	0.001
SV	1.08 (1.03–1.11)	0.002	1.05 (1.02–1.09)	< 0.001	1.04 (1.01–1.07)	< 0.001
CV	1.11 (1.05–1.16)	< 0.001	1.09 (1.03–1.14)	< 0.001	1.07 (1.02–0.13)	< 0.001
	Discharge home					
SD	0.93 (0.91–0.95)	< 0.001	0.94 (0.92–0.96)	< 0.001	0.96 (0.94–0.98)	< 0.001
Minimum	1.01 (1.01–1.02)	< 0.001	1.01 (1.00-1.02)	0.003	1.00 (0.99–1.01)	0.988
Maximum	0.99 (0.98–0.99)	< 0.001	0.99 (0.98–0.99)	< 0.001	0.99 (0.98–0.99)	< 0.001
Mean	1.00 (0.99-1.00)	0.554	1.00 (0.99-1.00)	0.383	0.99 (0.98-1.00)	0.001
ARV	0.95 (0.88–1.03)	0.196	0.97 (0.90–1.05)	0.418	0.95 (0.88–1.03)	0.234
SV	0.95 (0.89–0.98)	< 0.001	0.95 (0.90–0.98)	< 0.001	0.97 (0.93–0.99)	< 0.001
CV	0.98 (0.93–1.01)	0.134	0.99 (0.96–1.06)	0.253	1.01 (0.98–1.09)	0.419

Model 1 was adjusted for age and admission ICU type; model 2 was adjusted for all variables in model 1 plus intracranial pressure monitor and vasopressor use; model 3 was adjusted for all variables in model 2 and SOFA score

SD: standard deviation; ARV: average real variability; SV: successive variation; CV: coefficient variation

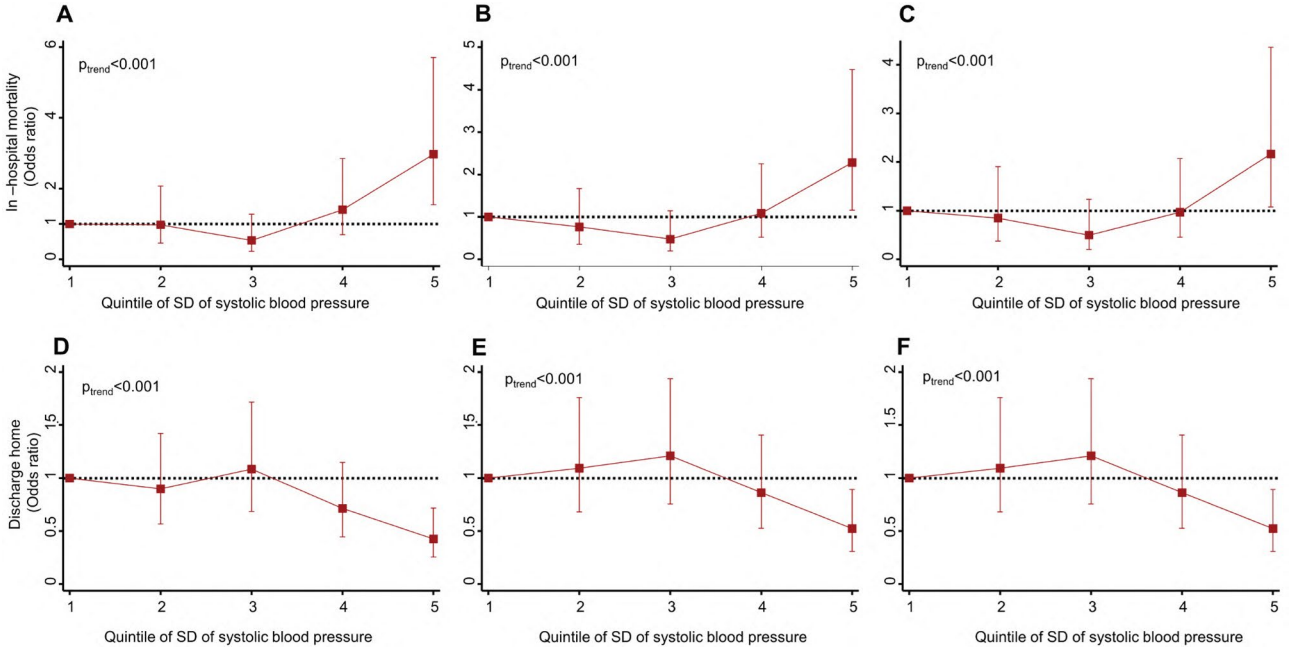

Fig. 5 Association between quintiles of standard deviation of systolic blood pressure and in-hospital mortality (**A**-**C**) and discharge-home rate (**D**-**E**) for the acute phase BPV. Lowest quintile is reference

0.32–0.95; p_{trend}<0.001; Fig. 5D-F). As for other parameters of SBP variability, only minimum SBP was significantly related to in-hospital mortality in model 3 (OR 0.98, 95% CI 0.96–0.99; p_{trend}=0.001); and only maximum SBP was significantly associated with discharge-home rate in model 3 (OR 0.99, 95% CI 0.98–0.99; p_{trend}=0.002) (Table 3). Furthermore, likelihood ratio tests supported the robustness of our outcomes, as the variables for model 3 demonstrated improved fitting versus model 2 (Supplementary file: Table S4 and S5).

Although the ORs overlapped for SD and the other parameters of BPV in model 3, results for the IDI and AIC indicated that the best predictors of in-hospital

Table 3 Effects of one standard deviation increment of systolic blood pressure variability in the 2–7 days on in-hospital mortality and discharge-home rate

	Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
	In-hospital mortality					
SD	1.37 (1.16–1.60)	< 0.001	1.30 (1.10–1.53)	0.002	1.25 (1.05–1.48)	0.01
Minimum	0.96 (0.95–0.98)	< 0.001	0.97 (0.96–0.98)	< 0.001	0.98 (0.96–0.99)	0.001
Maximum	1.01 (1.00-1.02)	0.081	1.00 (0.99–1.01)	0.508	1.00 (0.99–1.02)	0.365
Mean	0.98 (0.97-1.00)	0.04	0.98 (0.97-1.00)	0.018	0.99 (0.97-1.00)	0.178
ARV	0.87 (0.75–1.02)	0.086	0.87 (0.74–1.03)	0.111	0.86 (0.71–1.04)	0.114
SV	0.98 (0.96–1.07)	0.103	0.96 (0.92–1.03)	0.133	0.93 (0.87–1.01)	0.201
CV	1.21 (1.11–1.31)	< 0.001	1.18 (1.09–1.26)	< 0.001	1.15 (1.03–1.23)	< 0.001
	Discharge home					
SD	0.84 (0.75–0.93)	0.001	0.87 (0.78–0.97)	0.016	0.89 (0.79-1.00)	0.044
Minimum	1.02 (1.01–1.02)	0.001	1.01 (1.00-1.02)	0.008	1.01 (1.00-1.02)	0.109
Maximum	0.99 (0.98–0.99)	< 0.001	0.99 (0.98-1.00)	0.002	0.99 (0.98–0.99)	0.002
Mean	0.99 (0.98-1.00)	0.248	1.00 (0.99–1.01)	0.469	0.99 (0.98-1.00)	0.194
ARV	1.09 (0.96–1.22)	0.174	1.07 (0.95–1.21)	0.261	1.08 (0.95–1.21)	0.233
SV	1.05 (0.93–1.10)	0.136	1.03 (0.91–1.09)	0.214	1.02 (0.89–1.07)	0.323
CV	0.91 (0.81–0.98)	0.006	0.93 (0.84–0.98)	0.032	0.94 (0.87–0.99)	0.041

Model 1 was adjusted for age and admission ICU type; model 2 was adjusted for all variables in model 1 plus intracranial pressure monitor and vasopressor use; model 3 was adjusted for all variables in model 2 and SOFA score

SD: standard deviation; ARV: average real variability; SV: successive variation; CV: coefficient variation

Table 4 Discrimination between indices of systolic blood pressure variability and odds of in-hospital mortality

	Hyperacute BPV (first 24 h)		Acute BPV (days 2–7)	
	IDI (%)	AIC	IDI (%)	AIC
Mean	0.28	573.97	0.68	367.27
SD	2.28	551.02	1.93	358.17
Minimum	1.17	563.81	2.31	356.99
Maximum	0.59	572.09	0.02	369.31
ARV	1.07	562.15	0.40	367.35
SV	1.03	596.21	0.63	382.46
CV	1.12	587.93	0.57	379.38

Adjusted for age, admission ICU type, intracranial pressure monitor, vasopressor use, and SOFA score at baseline. The IDI is the percentage improvement in the average sensitivity and specificity of the fitted model when the index variable is added to the prediction model (higher scores are better). A low value for AIC indicates a close fit of the model to the true odds

IDI: relative integrated discrimination index; AIC: Akaike's information criteria; SD: standard deviation; ARV: average real variability; SV: successive variation; CV: coefficient variation

mortality was SD of SBP in the hyperacute phase and minimum SBP in the acute phase (Table 4).

Discussion

Our study has shown that the within-patient variation in SBP from visit to visit is a crucial factor in predicting the prognosis of patients with traumatic intraparenchymal hemorrhage or contusion, in both the hyperacute and acute periods after TBI. We found that greater variation in SBP is strongly associated with a poor outcome, defined either by in-hospital mortality or discharge-home rate. Out of the different parameters used to measure BPV, the SD of SBP is likely the most practical and the most significant predictor of a poor outcome. Our findings suggest that it is essential not only to rapidly achieve the appropriate SBP level soon after the onset of TBI, but also to ensure that blood pressure is maintained smoothly for several days after admission.

Our results support a recent small-scale, retrospective observational study, which found that SBP variability measured by successive variations (SV) was independently associated with hematoma progression among TBI patients who required an external ventricular drain [9]. In another analysis of the same cohort among patients with traumatic intraparenchymal hemorrhagic contusion, increased SV of SBP within the first 24 h is associated with lower rates of discharge home after initial hospitalization [10]. Currently, the evidence on the impact of SBP variability on TBI patients is limited. Our findings based on a larger cohort have contributed to the accumulating evidence that variation in SBP during early hospitalization is associated with poor clinical outcomes among patients with TBI.

Similar phenomenon was also observed among spontaneous intracerebral haemorrhage that systolic BPV seems to be associated with poor outcomes [14, 18]. Based on a post-hoc analysis of the INTERACT2 trial, SBP variability in the early hospital stays was associated with death or major disability in patients with acute intracerebral haemorrhage [14]. Besides, Tanaka et al. found that both increased SBP_{SD} and SBP_{SV} were associated with neurologic deterioration during the initial 24 h after spontaneous intracranial hemorrhage [19]. The exact mechanism

by which SBP variability affects the outcomes of TBI is unknown. Prior literature demonstrated that for acute intracerebral hemorrhage, large fluctuations in SBP could impair cerebral baroreflex sensitivity and that BPV leads to brain edema or hematoma enlargement in the perihematomal region, which may cause secondary brain injury [20]. Impairment of cerebral autoregulation has been proved to be correlated with cerebral edema in patients with intracerebral haemorrhage [21]. We deemed that for both traumatic and spontaneous intracranial haemorrhage, the decreased cerebral autoregulation might be the key pathophysiological process that impaired by the SBP variability.

Unlike other predictors of neurologic outcomes among TBI patients, BPV is a modifiable risk factor that might be directly impacted by medical care. Prior evidence have demonstrated that close control of BPV using intravenous agents may improve the outcomes among patients with spontaneous intracerebral haemorrhage [22]. Our findings further support that management of traumatic intracranial haemorrhage should also emphasize steady maintain of blood pressure and avoids rapid swings [11].

Limitations and strengths

Our study has some limitations that should be considered. First, although we included GCS, APACHE IV and SOFA scores in the analysis, more specific assessment scales for the background of traumatic patients such as injury severity score for all injured area and abbreviated injury scale for severity of TBI were not available in the eICU-CRD database. This might impair the generalization of our findings, and it need to be verified by future well designed prospective study. Second, despite adjusting for several variables, the possibility of reverse causality or residual confounding cannot be completely ruled out, particularly for patients with severe neurological deficits who may have high systolic BPV. Third, the variability in treatment strategies employed across different ICUs may have introduced uncertainty into the analysis of BPV. Fourth, the lack of data of neurological outcomes hampered our ability to comprehensively evaluate the BPV on the TBI patients' prognosis, even though discharge home was used as a proxy for this. Fifth, due to the limitation of data availability, we couldn't confirm the association between BPV and long-term mortality of TBI; we couldn't obtain higher-resolution and more frequent data than hourly recordings for SBP to offer a more accurate depiction of patients' hemodynamic status; and we couldn't get the medication history before admission and the indication for ICU admission. Sixth, we found that the ARV has an inverse effect on mortality in the acute phase, which seems to be a paradox. We didn't know how to explain this phenomenon, this should be confirmed in the future. Moreover, we were unable to compare ICP between patients who required external ventricular drainage, which might have provided additional information on the relationship between BPV and patient outcomes. Lastly, the lack of CT scan data in the eICU-CRD database prevented us from further investigating the impact of BPV on hemorrhage progression.

This study also has several strengths. First, the large sample size and numerous blood pressure measurements allowed for a more accurate assessment of the significance of BPV on clinical outcomes. Second, our use of a staged approach to develop multivariable models provides confidence in the reliability of our association estimates. We constructed three models based on adjusting for different covariates, and we used the results of model 3 as the final data. In order to test weather adding new covariates would improve the results, we applied the likelihood ratio tests to confirm the robustness of our data. Additionally, our results were consistent across subgroup analyses, including different types of TBI (as shown in Supplementary file: Table S6). The generalizability of the results is strengthened by the wide range of patients who were included from a variety of ICUs, along with the different background treatment.

Conclusions

In conclusion, our study demonstrates that visit-to-visit variability in SBP is a significant predictor of in-hospital mortality and discharge-home rate in patients with traumatic intracranial hemorrhage or contusion. The prognostic value of BPV is independent of mean SBP and other major risk factors. These findings, along with the evidence by Tran and colleagues [9, 10] (Supplementary file: Table S7), suggest that further investigation of the therapeutic effects of targeting BPV in patients with intracranial hemorrhage or contusion is warranted.

Abbreviations

AIC	Akaike's information criteria
ARV	Average real variability
BPV	Blood pressure variability
DBP	Diastolic blood pressure
GCS	Glasgow Coma Scale
IDI	Relative integrated discrimination index
ICP	Intracranial pressure
ICU	Intensive care unit
NICU	Neuro-ICU
SOFA	Sequential Organ Failure Assessment
SBP	Systolic blood pressure
SD	Standard deviation

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
M.J., C.L.L and X.F.Y conceived the study idea and design, drafted the manuscript. M.J. obtained funding. M.J. performed acquisition of data. C.L.L and S.Y.Z performed analysis and interpretation of data. J.Y. and C.L.L performed critical revision of the manuscript for important intellectual content and statistical analysis. M.J. and X.F.Y took administrative, technical, or material support tasks. M.J. wrote the main manuscript text and prepared Figs. 1, 2, 3, 4 and 5. All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files. Data were fully available at https://physionet.org/content/eicu-crd-demo/2.0/. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was an analysis based on the publicly available database with pre-existing institutional review board approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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