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Associations between sepsis occurrence, hemoglobin level and mortality in patients with non-trauma hemorrhagic brain injuries: trajectory-based analysis

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Abstract

Background The impact of concurrent sepsis on the prognosis in patients with non-traumatic hemorrhagic brain injury (HBI) remains unclear, and the appropriate hemoglobin (HGB) level in HBI patients with sepsis has not been investigated. This study aimed to investigate the impact of sepsis in HBI and the prognosis of patients with different HGB trajectories with/without sepsis.

Methods The association between sepsis and prognosis (including neurologic outcome and 28-day mortality) in patients with non-trauma HBI was investigated, and multivariate logistic model, propensity score matching (PSM), and inverse-probability-weighted regression adjustment (IPWRA) were used to reach a causal relationship. Group-based trajectory analysis was adopted to explore the associations between HGB trajectories and outcomes.

Results A total of 3,040 patients were included. Compared with the HBI-without-sepsis group, the HBI-with-sepsis group had higher 28-day mortality and worse neurological outcomes. After adjusting for confounders, the association between sepsis and mortality remains significant in multivariate logistic model (OR 2.31, 95%CI 1.77–3.01), PSM analysis (212/942 vs. 130/942, $p < 0.001$) and IPWRA model (ATE 0.073, 95%CI 0.04–0.09). Based on 72-h HGB data, four HGB-trajectories were identified. In HBI-without-sepsis cohort, OR for mortality decreased from HGB-traj2 (OR: 0.56, 95% CI 0.33—0.96) to HGB-traj4 (0.26, 95% CI 0.11—0.59), referred to HGB-traj1. But this decreasing trend became non-significant in HBI-with-sepsis cohort. Sensitivity analyses showed similar results.

Conclusion In HBI, concurrent sepsis was associated with higher mortality rate. Furthermore, there was an inverse gradient relationship between HGB level and mortality in HBI patients without sepsis, while this association became non-significant in those with sepsis.

Keywords Mortality, Hemoglobin, Hemorrhagic brain injury, Sepsis

Introduction

Hemorrhagic brain injury (HBI) [1] accounts for 10 to 15% of all strokes, with high morbidity/mortality rates and limited effective therapeutic interventions to improve outcomes [2]. Sepsis, as a fatal disease characterized by organ dysfunction, is one common complication in patients with HBI [3, 4]. Previous studies [5–7] have shown that sepsis often leads to diffuse neuro-inflammation, excitotoxicity, and altered cerebral perfusion [8],

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which can contribute to sepsis-associated brain dysfunction, including cerebral edema, increased intracranial pressure, and encephalopathy. These complications are frequently observed in sepsis patients and are associated with poor outcomes. However, the specific impact of concurrent sepsis on the prognosis of patients with HBI remains poorly understood.

In addition, maintaining an appropriate hemoglobin (HGB) level is essential for ensuring adequate oxygenation and preventing secondary brain damage in HBI. Several studies have demonstrated that low HGB was associated with poor outcomes in patients with various brain injuries [9–11]. However, the cutoff values of HGB vary significantly across studies, with thresholds, such as 10 g/dL [10], 11 g/dL[12], and 12 g/dL[13], and the optimal HGB level remains unclear. Furthermore, most studies have conducted dichotomous comparisons between anemia and non-anemia groups, leaving the question of whether higher HGB levels in non-anemia patients correlate with better outcomes unanswered. Also, most previous studies focused on static HGB data. The lack of consideration of the longitudinal dynamics changes in HGB increased the risk of bias. In addition, a common consensus of a HGB threshold of 7.0 g/dL was reached in sepsis without myocardial ischemia, severe hypoxemia, or acute hemorrhage according to the sepsis guidelines [14]. However, whether this threshold applies to patients with HBI with concurrent sepsis has not been investigated.

This study has two aims: 1. Explore the impact of concurrent sepsis on the prognosis in patients with HBI, using doubly robust estimation; 2. Using group-based trajectory approach, evaluate the association between the longitudinal HGB levels and prognosis in HBI patients with/without sepsis.

Methods

Data source and Ethics

This study utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV) database [15], published by the Massachusetts Institute of Technology Computational Physiology Laboratory (https://physionet.org/content/mimiciv/2.2/). The database contains clinical data from patients admitted to the intensive care unit (ICU) at Beth Israel Deaconess Medical Center (BIDMC). The Institutional Review Board at the BIDMC granted a waiver of informed consent and approved the sharing of the research resource. Data collected at BIDMC as part of routine clinical care are deidentified, transformed, and made available to researchers who have completed training in human research and signed a data use agreement [16, 17]. The corresponding author Yanfei Shen has passed the online training course and has access to this database and was responsible for the data extraction.

Ethics

Above all, the study was exempt from our institutional review board approval because the databases used deidentified data and also carried preexisting institutional review board approval.

Patient selection and grouping method

The International Classification of Diseases 9th Edition codes were used for the preliminary screening of the patients with non-trauma HBI. Exclusion criteria included age below 18 years, hospital stays of less than three days, or the absence of HGB records. Subgroup analyses were conducted on HBI patients with and without concurrent sepsis within 72 h of ICU admission.

Sepsis was defined based on previously established criteria [18]: the suspected infection was determined according to the time of bacterial culture and antibiotic use of the patient, and the diagnosis of sepsis could be obtained by combining the SOFA score. When antibiotics are first administered, a microbiological sample must be collected within 24 h. When microbial sampling is first performed, antibiotics must be administered within 72 h.

Data collection

The clinical and laboratory data of the patients during the ICU stay were extracted from the MIMIC database using a PostgreSQL tool. The extracted data included patient demographics, comorbidities, laboratory parameters, and clinical characteristics. HGB values within the first 72 h of ICU admission were collected for trajectory modeling. Vasopressor use was defined as the use of any vasopressor, including dobutamine, dopamine, epinephrine, and norepinephrine, within 72 h after ICU admission. The 28-day mortality rate was used as the primary outcome. A poor neurological outcome was the secondary outcome, defined as the Glasgow coma scale (GCS) at discharge ≤ 8 or death.

Construction of the group-based trajectory models

Group-based trajectory modeling [19] is used widely to map the progress of dynamic laboratory indexes. In this study, we used the HGB records obtained within 72 h after ICU admission to identify the HBI patients with similar HGB trajectories. The model construction process was as follows: first, the number of trajectories was determined according to the Bayesian information criterion; second, the model complexity was determined based on the log Bayes factor ($2\log_e(B_{10})$); and third, the average posterior probability (AvePP) was calculated to evaluate the posterior probability of each individual

being assigned to the corresponding HGB trajectory, with an acceptable value of 0.70.

Sensitivity analysis

Hemodynamic instability is one important risk factor for death in HBI patients, especially in those with sepsis. Therefore, sensitivity analysis was performed in a cohort without vasopressor use.

Missing data management

The frequency of the missing continuous data was < 5%. According to the distribution of these variables, the missing values were replaced by the mean or median values. For the binary data (such as gender), the missing values were replaced by the modal number.

Statistical analyses

The normally distributed continuous variables were compared using the Student's t-test and reported as the means ± standard deviations. The non-normally distributed continuous variables were reported as the medians and the interquartile ranges (IQRs) and compared using the Wilcoxon rank-sum test. The categorical variables were compared using the chi-square or Fisher's exact tests. Propensity score matching (PSM) and inverse-probability-weighted regression model (IPWRA) were used to minimize the effect of confounding factors. A propensity score (PS) was calculated based on the sepsis probability estimated using a logistic regression model. In PSM, a one-to-one nearest neighbor matching algorithm was applied using a caliper width of 0.02. Kernel density plots of the propensity score were used to examine the PSM degree. In the IPWRA, PS was used in the sepsis-assignment model (propensity score model), and the estimated average treatment effect (ATE) between sepsis and non-sepsis groups was investigated in the final model. The backward stepwise method was used for cofounder selection in the multivariable logistic regression. The variance inflation factor was used to test for multicollinearity, with the variance inflation factor ≥ 5 indicating significant multicollinearity. All the statistical analyses were performed using Stata 11.2 (College Station, TX, USA) and R 4.2.2. All the tests were two-sided, and $P < 0.05$ was used as the threshold for statistical significance.

Results

Comparisons between groups with sepsis and non-sepsis

A total of 3,040 patients were included in this study. The flowchart of patient selection was presented in Supplementary Figure S1. The comparisons of baseline characteristics are shown in Table 1. The overall mortality rate was 9.9%. Compared with the HBI without sepsis group, HBI with sepsis group had higher SAPS II (36 (28—44) vs. 29 (22—6), p < 0.001), and was more likely to receive vasopressors (9.7% vs. 1.4%, $p < 0.001$). 28-day mortality (185/1062 vs. 118/1978, p < 0.001) and poor neurological outcome rate (258/1062 vs. 149/1978, p < 0.001) were significantly higher in the HBI with sepsis group.

The association between sepsis and 28-day mortality was estimated in multivariate logistic, IPWRA, and PSM models (Table 2). In the multivariate logistic model, concurrent sepsis was significantly associated with an increased mortality rate (odds ratio (OR) 2.31, 95% confidence interval (CI) 1.77—3.01, p < 0.001) after adjusting for confounders. In the PSM analysis, confounders, including age, SOFA on ICU admission, white blood cell count, creatinine level, hypertension, diabetes, and vasopressor-use were well balanced (Fig. 1). HBI with sepsis was significantly associated with a higher poor neurological outcome rate (148/942 vs. 102/942, p < 0.001) and 28-day mortality (212/942 vs. 130/942, p < 0.001). Aiming to reach a stable result, the IPWRA model was adopted. The result showed that concurrent sepsis in HBI may increase mortality risk by 7.3% (95%CI 0.048—0.099, p < 0.001) compared to HBI without sepsis.

Construction of the hemoglobin-based trajectory model

According to the Bayesian information criterion and the statistical significance, four similar HGB trajectories were identified in HBI with/without sepsis cohorts (Fig. 2). HBI without sepsis cohort: HGB-traj1, patients with HGB trajectories of approximately 9 g/dL; HGB-traj2, patients with HGB trajectories of approximately 11 g/dL; HGB-traj3, patients with HGB trajectories of approximately 13 g/dL; and HGB-traj4, patients with HGB trajectories of approximately 15 g/dL. HBI with sepsis cohort: HGB-traj1, patients with HGB trajectories of approximately 8 g/dL; HGB-traj2, patients with HGB trajectories of approximately 10 g/dL; HGB-traj3, patients with HGB trajectories of approximately 12 g/dL; and HGB-traj4, patients with HGB trajectories of approximately 14 g/dL. According to the logarithmic Bayes factor, each trajectory was a unique quadratic equation describing the HGB as a function of time (Supplementary Table S1). The comparisons within four HGB trajectories were presented in Supplementary Tables S2 and S3.

Clinical outcomes according to the hemoglobin trajectory

A stepwise increase of the initial and maximum HGB values from HGB-traj1 to HGB-traj4 was observed in HBI patients with/without sepsis (Fig. 3). The poor neurological outcome and 28-day mortality rates decreased gradually from the HGB-traj1 to HGB-traj4 in the HBI without sepsis cohort (Fig. 3, right panel). However, in the HBI with sepsis cohort, less significant decreasing trend was

Table 1 Baseline comparisons between non-trauma HBI patients with and without sepsis

Demographics	HBI without sepsis (*n* = 1978)	HBI with sepsis (*n* = 1062)	p
Age (years)	67.1 ± 15.9	66.3 ± 15.4	0.050
Male [*n* (%)]	1281 (64.76)	683 (64.31)	0.836
Weight (kg)	78.9 ± 21.0	79.5 ± 21.2	0.481
Comorbidities			
Hypertension [*n* (%)]	1184 (59.86)	613 (57.72)	0.270
Diabetes mellitus [*n* (%)]	405 (20.48)	263 (24.76)	0.007
Coronary diseases [*n* (%)]	266 (13.45)	137 (12.90)	0.712
Subarachnoid hemorrhage [*n* (%)]	489 (24.7)	312 (29.4)	0.006
Cirrhosis (%)	29 (1.5)	43 (4.0)	< 0.001
Laboratory indexes			
Initial white blood cell count (10^9/L)	10.1 ± 3.6	11.9 ± 4.9	< 0.001
Initial hemoglobin level (g/dl)	12.3 ± 1.9	11.9 ± 2.1	< 0.001
Initial platelet count (10^9/L)	221.7 ± 75.9	213.4 ± 91.3	0.008
Initial serum creatinine (mg/dl)	1.0 ± 0.8	1.1 ± 0.9	0.129
Treatments			
Vasopressor-use [*n* (%)]	29 (1.47)	104 (9.79)	< 0.001
RBC Transfusion [*n* (%)]	47 (2.43)	90 (8.47)	< 0.001
Clinical evaluation			
GCS at ICU admission [median (IQR)]	15(13–15)	13(8- 14)	< 0.001
Maximum GCS [median (IQR)]	15(15–15)	15(14–15)	< 0.001
GCS at ICU discharge [median (IQR)]	15(14–15)	14(9- 15)	< 0.001
SAPS II at ICU admission [median (IQR)]	29(22–36)	36(28–44)	< 0.001
Maximum SOFA [median (IQR)]	2(1– 4)	4(3–6)	< 0.001
ICU LOS (days)	**3.3 (1.8–6.3)**	**8.5 (4.2–15.1)**	**< 0.001**
Hospital LOS (days)	**11.0 (4.9–12.1)**	**15.3(8.7–23.8)**	**< 0.001**
Poor neurologic outcome [*n* (%)]	**149 (7.53)**	**258 (24.29)**	**< 0.001**
28-day mortality [*n* (%)]	**118 (5.97)**	**185 (17.42)**	**< 0.001**

HBI hemorrhagic brain injury, *SOFA* sequential organ failure assessment, *GCS* Glasgow Coma Score, *ASP III* Simplified acute physiology score II, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay

observed in the mortality or poor neurological outcome rate (Fig. 3, right panel).

In the multivariable logistic regression model (Table 3), the odds ratio (OR) for the 28-day mortality relative to the HGB-traj1 decreased stepwise from HGB-traj2 (OR: 0.56, 95% CI 0.33—0.96) to HGB-traj4 (OR: 0.26, 95% CI 0.11—0.59) in HBI without sepsis cohort. Similarly, the odds ratio (OR) for the poor neurologic outcome decreased stepwise from HGB-traj2 (OR: 0.52, 95% CI 0.32—0.84) to HGB-traj4 (OR: 0.25, 95% CI 0.12—0.52) in HBI without sepsis cohort, referred to HGB-traj1. However, these decreasing trends in mortality or poor neurologic outcome were not significant in the HBI with sepsis cohort (Table 3). The detailed results were presented in Table S4. Also, the interaction between RBC transfusion and HGB trajectories was evaluated and no significant interaction was detected (Supplementary Table S5).

Sensitivity analyses

Sensitivity analyses were performed in patients without vasopressor use. Similar HGB trajectories were identified (Supplementary Figure S2). The results in the multivariable logistic regression models (Supplementary Table S6) remained stable in the HBI without sepsis and HBI with sepsis cohorts.

In addition, survival analysis was also performed to reach a stable conclusion. In multivariate Cox regression (Supplementary Table S7), the odds ratio (HR) for the 28-day mortality relative to the HGB-traj1 decreased stepwise from HGB-traj2 to HGB-traj4 in HBI without sepsis cohort, but became non-significant in the HBI with sepsis cohort. The KM curves also showed similar results (Supplementary Figure S3 and S4).

Discussion

The current study has two significant findings: 1. Concurrent sepsis in HBI is significantly associated with poor prognosis. 2. High HGB level (9–15 g/dL) was

Table 2 Estimated associations between sepsis and mortality in multivariate logistic, IPWRA and PSM models

Multivariate logistic model		
Variables	**OR (95%CI)**	**p**
Sepsis	2.31 (1.77—3.01)	< 0.001
SOFA on ICU admission	1.12 (1.03—1.21)	0.010
Hypertension	1.31 (1.001—1.713)	0.049
Cirrhosis	2.78 (1.56—4.95)	0.001
Initial WBC count	1.08 (1.05—1.11)	< 0.001
Initial Serum creatinine level	1.39 (1.24—1.55)	< 0.001
Initial Platelet count	0.996 (0.994—0.997)	< 0.001
Vasopressor usage in 3 days	2.28 (1.63—3.19)	< 0.001
Propensity score matching		
Outcomes	**HBI with sepsis (*n* = 942) vs. HBI without sepsis (*n* = 942)**	**p**
Poor neurologic outcome [*n* (%)]	148/942 vs. 102/942	< 0.001
28-day mortality [*n* (%)]	212/942 vs. 130/942	< 0.001
IPWRA model (ATE on 28-day mortality)		
Variables	**ATE (95% CI)**	**p**
No sepsis	Ref	
Sepsis	0.073 (0.048 to 0.099)	< 0.001

In the PSM model, the imbalanced variables including Age over 65, initial white blood cell count, creatinine level, SOFA on ICU admission, Hypertension, Diabetes and vasopressor use in first 3 days were included in the sepsis assignment model (propensity score model), and confounders including Age over 65, initial white blood cell count, creatinine level, SOFA on ICU admission, Hypertension, Diabetes and vasopressor use in first 3 days were included in the inverse probability weighted regression model.

IPWRA inverse probability weighted regression model, *PSM* Propensity score matching, *ATE* estimate average treatment effect, *OR* odds ratio, 95% CI 95% confidence interval

associated with stepwise decreased poor neurological outcome and mortality rate in HBI patients without sepsis, while this association became non-significant in those with sepsis. The strength of the current study was that to reach a potential causal relationship, multivariable logistic regression, PSM, and IPWRA were adopted in exploring the association between concurrent sepsis and mortality. Additionally, longitudinal HGB data, rather than static values, were used to assess the relationship between HGB and prognosis, minimizing potential bias through group-based trajectory modeling.

Earlier research [20, 21] has identified various factors influencing HBI prognosis, such as age, injury severity, and concurrent medical conditions. However, whether secondary sepsis in HBI has a negative impact on functional prognosis or mortality remains controversial. In a retrospective study [22] including 201 ICH patients, Ali et al. reported that the overall infection rate was 11%, and infection was not associated with functional prognosis after ICH. However, another study [23] with 800 ICH patients reported otherwise, that the infections were higher (31%) and were associated with poor prognosis. However, these studies were limited by small sample size, and only multivariate logistic regression models were used to explore the relationship.

Different from these studies, sepsis instead of infection was used as the concurrent factor in this study, as it incorporated organ dysfunction, which may be more relevant to the prognosis of patients with HBI. In addition, the current study adopted causal inference methods, such as PSM and IPWRA, to reach a potential causal relationship between sepsis and prognosis. The results suggested a detrimental impact of sepsis on the prognosis of patients with HBI (ATE on mortality 7.3%), highlighting the need for vigilant monitoring and management of infection in this vulnerable population. However, the potential mechanism remains unclear. Previous studies indicated that HBI initiated a cascade of neuro-inflammatory responses that can exacerbate brain damage and worsen patient outcomes. Whether concurrent sepsis [5] introduces an additional systemic inflammatory burden, potentially amplifying the inflammatory response initiated by HBI, still needs further investigation.

Anemia is a common complication in patients with brain injury [24, 25], with the reported prevalence ranging from 30 to 50% [26, 27]. Previous studies have shown that a low HGB level is associated with various adverse

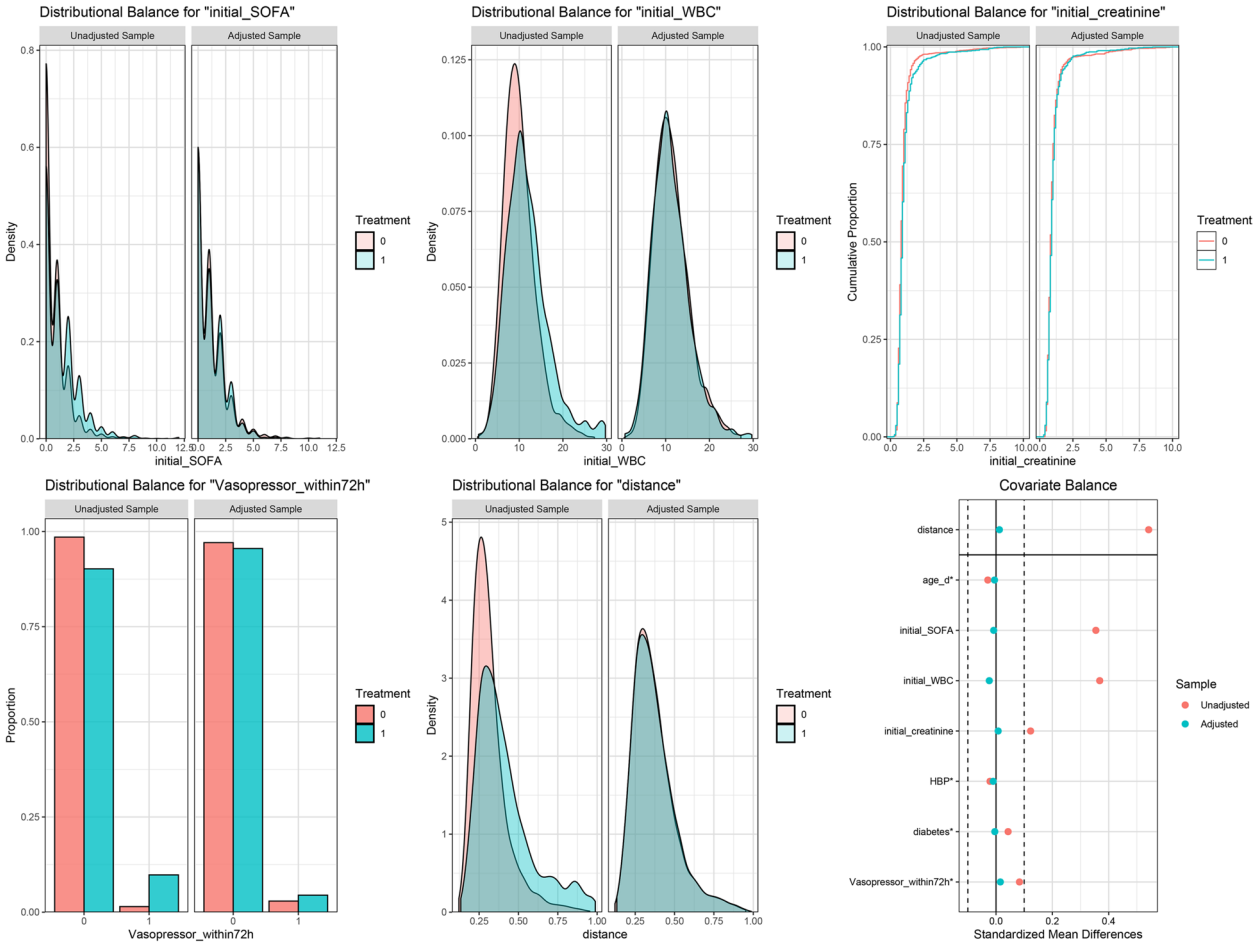

Fig. 1 Propensity score matching of key factors between HBI with and without sepsis in the PSM analysis, confounders, including age, SOFA on ICU admission, white blood cell count, creatinine level, hypertension, diabetes, and vasopressor-use were included. Kernel density plots of the propensity score showed that all these variables were well matched after propensity score matching

outcomes in patients with HBI, such as increased risks of hematoma expansion [28], worse neurological outcomes, and higher mortality rates [13, 29–31]. In a recent meta-analysis [32] that included seven cohort studies, the pooled results showed that anemia on admission was associated with higher mortality and a poor neurological outcome rates. However, most previous studies [12, 13, 32, 33] divided patients into anemic and non-anemic groups based on static data, with inconsistent cutoff values, such as 10 g/dL[10], 11 g/dL[12], and 12 g/dL[13]. These different definitions of anemia increased the difficulty of applying these study results to clinical practice, and whether a higher HGB level than these cutoff values can further improve prognosis remains unclear. Also, HGB changes dynamically in clinical practice. Simply using a static value to represent the total HGB status may increase the risk of bias.

Different from previous studies, we investigated the impact of HGB based on longitudinal HGB data within 72 h. We found that higher HGB levels (11 to 15 g/dL) were dose-correlated with better neurological outcomes and 28-day mortality compared to lower HGB levels (9 g/dL). This finding is an important addition to the current consensus that recognizes anemia as an important risk factor for the poor prognosis of patients with HBI but does not recognize that there is a benefit gradient between the HGB levels and the outcomes in non-anemic patients. For instance, in a recent web-based survey that included 868 societies of ICU physicians who managed their patients according to their HBI levels, almost all these physicians used an HGB threshold of 7–9 g/dl for RBC transfusions in patients with HBI. However, it is important to note that although several statistical methods have been used to draw a causal conclusion, the dose-dependent effect

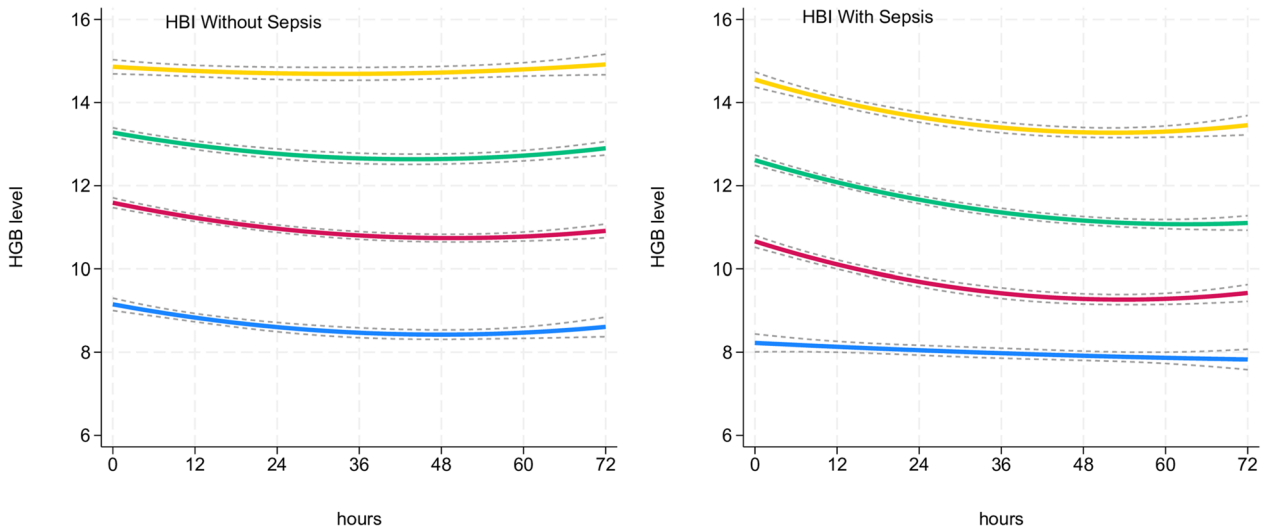

Fig. 2 Hemoglobin-based trajectories of patients with hemorrhagic brain injury In the HBI-without-sepsis cohort: HGB-traj-1 ($n=215$), patients with a HGB trajectory around 9 g/dL; HGB-traj-2 ($n=697$), patients with a HGB trajectory around 11 g/dL; HGB-traj-3 ($n=783$), patients with a HGB trajectory around 13 g/dL; and HGB-traj-4 ($n=283$), patients with a HGB trajectory around 15 g/dL. In the HBI-with-sepsis cohort: HGB-traj-1 ($n=102$), patients with a HGB trajectory around 8 g/dL; HGB-traj-2 ($n=276$), patients with a HGB trajectory around 10 g/dL; HGB-traj-3 ($n=464$), patients with a HGB trajectory around 12 g/dL; and HGB-traj-4 ($n=220$), patients with a HGB trajectory around 14 g/dL. *HGB* hemoglobin

between HGB and improved prognosis still needs to be validated in prospective studies.

On the other hand, the HGB thresholds used for sepsis and HBI differed significantly. According to the latest guidelines [14], an HGB level of 7.0 g/dL is recommended in sepsis to maintain an adequate oxygen supply. Currently, many intensivists initiate RBC transfusions in mixed sepsis patients with HGB < 7 g/dL [34]. Although HGB levels as low as 7 g/dL are well tolerated in most critically ill patients, the optimal transfusion threshold in HBI with sepsis patients remains unclear. In the current study, we found that maintaining the HGB at a high level (> 8 g/dL) within 72 h is not beneficial in HBI patients with sepsis. This finding is consistent with the result from a landmark trial [35], which found that a high level of HGB provided no benefit in mixed sepsis patients. Several factors may help explain this non-significant association. First, in sepsis, elevated hemoglobin levels can contribute to oxidative stress and exacerbate nitric oxide consumption, potentially disrupting microcirculation and increasing mortality risk [36–38]. Additionally, red blood cell morphological changes in sepsis may impair oxygen-carrying capacity, which may diminish the benefits of higher HGB levels [36, 37]. Furthermore, clinical studies have suggested a non-linear relationship between HGB levels and 28-day mortality in sepsis patients [39], which is consistent with our findings.Noteworthy, the lowest HGB trajectory was 8 g/dL in the current study, and whether there is a benefit gradient in the influence of HGB levels in the range of 7–8 g/dL is unclear, and further research is needed.

Our study had several limitations. First, it was a retrospective study. Although many potential confounders were considered, data on some potential confounders, such as intracranial pressure, were unavailable; therefore, there may have been residual confounding. Second, the association between HGB and 28-day mortality was investigated. However, the impact of HGB on long-term neurological outcomes, such as the Modified Rankin Scale and Glasgow Outcome Scale, was not analyzed due to a lack of data, which needs further investigation. Third, our study focused mainly on the longitudinal HGB level. Factors regarding transfusion, such as the timing or the transfusion volume, were not analyzed in the current study. Further studies are needed to investigate whether transfusion with a high HGB threshold can improve prognosis in these patients. Fourth, due to the nature of the retrospective study, there are certain inaccuracies in the diagnosis. For instance, the diagnosis of sepsis was based on logical inference instead of the ICD diagnosis code mentioned in the method section.

Conclusions

In patients with HBI, concurrent sepsis increases the 28-day mortality rate and promotes poor neurologic outcome occurrence. Increased HGB levels (within the range, 9–15 g/dL) was associated with a decreased mortality rate. However, in HBI patients with concurrent sepsis, maintaining HGB at a high level was not associated

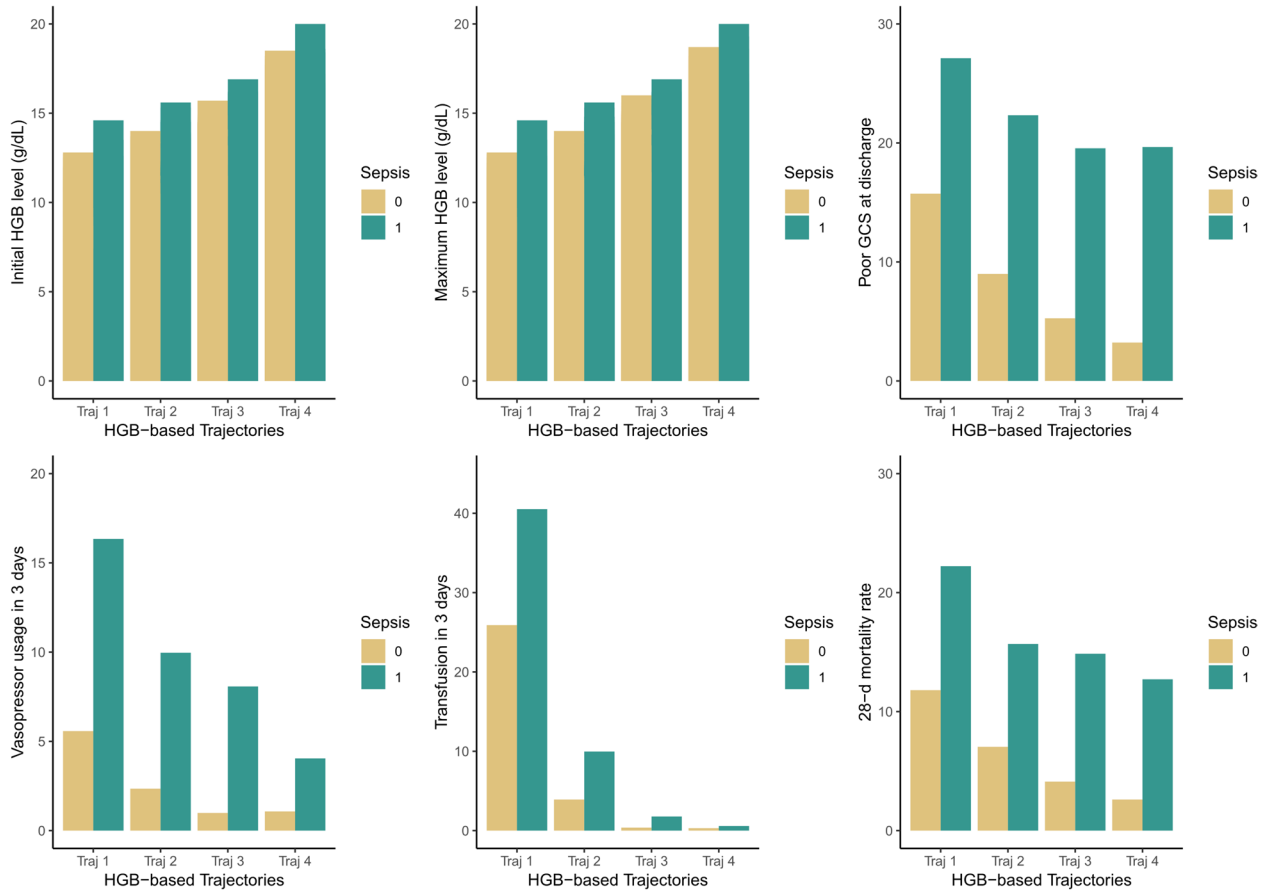

Fig. 3 Comparisons of hemoglobin levels and clinical outcomes within four hemoglobin trajectories: There was a stepwise increase of the initial and maximum HGB level from Traj-1 to Traj-4. The vasopressor use and RBC transfusion percentage, GCS score and the 28-day survival rate decreased gradually from HGB-traj-1 to HGB-traj-4 in HBI-without-sepsis cohort, but 28-day survival rate not significant in patients with HBI-with-sepsis cohort. *GCS* Glasgow Coma Scale, *HGB* hemoglobin, *HBI* hemorrhagic brain injury

with an improved prognosis. Rigorously designed studies are needed to determine whether there is a causal relationship and determine the potential mechanisms.

Table 3 Estimated associations between HGB trajectories and mortality and poor neurologic outcome in multivariate logistic model

28-d Mortality as the independent variable					
Multivariate logistic model (HBI without sepsis cohort)			**Multivariate logistic model (HBI with sepsis cohort)**		
Variables	**Adjusted OR (95% CI)**	**p**	**Variables**	**Adjusted OR (95% CI)**	**p**
Traj-1	Ref	–	Traj-1	Ref	–
Traj-2	0.56 (0.33—0.96)	0.035	Traj-2	1.06 (0.59—1.90)	0.855
Traj-3	0.33 (0.18—0.59)	< 0.001	Traj-3	0.82 (0.47—1.45)	0.504
Traj-4	0.26 (0.11—0.59)	0.001	Traj-4	0.78 (0.41—1.47)	0.437
Poor Neurologic Outcome as the independent variable					
Multivariate logistic model (HBI without sepsis cohort)			**Multivariate logistic model (HBI without sepsis cohort)**		
Variables	**Adjusted OR (95% CI)**	**p**	**Variables**	**Adjusted OR (95% CI)**	**p**
Traj-1	Ref	–	Traj-1	Ref	–
Traj-2	0.52 (0.32—0.84)	0.008	Traj-2	1.04 (0.61—1.77)	0.885
Traj-3	0.28 (0.16—0.48)	< 0.001	Traj-3	0.82 (0.49—1.37)	0.446
Traj-4	0.25 (0.12—0.52)	< 0.001	Traj-4	0.74 (0.42—1.31)	0.303

In the multivariate logistic model, confounders including initial white blood cell count, creatinine level, platelet, SOFA on ICU admission, Hypertension, Cirrhosis and vasopressor use in first 3 days were included in the HGB trajectory assignment model

HGB hemoglobin, *HBI* hemorrhagic brain injury, *GCS Scores* Glasgow Coma Scale Scores, CI 95% confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02417-6.

Supplementary materials 1

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None.

Author contributions
Y.S., X.D. and G.C. drafted the manuscript and performed the statistical analysis; S.C. and C.Z. revised the manuscript; Y.S. examined the integrity and accuracy of the data. All authors have read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
As stated in the Data source and Ethics section, this study used data from the Medical Information Mart for Intensive Care (MIMIC-IV) database, which means this study was exempt from our institutional review board approval because the databases used deidentified data and also carried preexisting institutional review board approval.

Competing interests
The authors declare no competing interests.

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