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Original Article

Rate Pressure Product at Admission and RBC Transfusion are Risk Factors for Acute Cerebral Infarction in Upper Gastrointestinal Bleeding Patients

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SUMMARY

Background: Acute cerebral infarction (ACI) is a complication of upper gastrointestinal bleeding (UGIB), but the risk factors for ACI in UGIB patients have not been fully explored. The purpose of the current study was to investigate the risk factors for ACI in UGIB patients.
Methods: Upper gastrointestinal bleeding patients admitted to Nanchang University Affiliated Ganzhou Hospital from January 2019 to December 2021 were included. Patients were divided into an ACI group and a non-ACI group according to whether they had a complication of ACI. Propensity score matching was used to match the data between the two groups. The risk factors for ACI in UGIB patients were analyzed by conditional multivariate logistic regression analysis, and receiver operator characteristic (ROC) curves were used to test the performance of risk factors.
Results: There were 1379 UGIB patients included in this study: 50 patients in the ACI group and 1329 patients in the non-ACI group. Forty-eight pairs were matched after propensity score matching according to sex, age, smoking, drinking, hypertension, coronary heart disease (CHD), diabetes, previous history of cerebral infarction, gout, peptic ulcer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and hepatic cirrhosis. Univariate analysis showed that RBC transfusion was a risk factor for ACI. Compared with middle rate pressure product (RPP) at admission, low RPP and high RPP were risk factors for ACI in UGIB patients. Hemoglobin, mean platelet volume (MPV) and albumin were protective factors for ACI. Conditional multivariate logistic regression showed that red blood cell (RBC) transfusion (OR 3.136, 95% CI 1.711–5.750, $p < 0.001$) was an independent risk factor for ACI. Compared with middle RPP at admission, low RPP and high RPP were independent risk factors for ACI in UGIB patients. The ROC curve analysis showed that the areas under the curve (AUCs) of the RPP at admission and after RBC transfusion were 0.625 (0.513–0.737, $p < 0.05$) and 0.688 (0.580–0.795, $p < 0.01$), respectively.
Conclusions: Compared with middle RPP at admission, low RPP and high RPP were independent risk factors for ACI in UGIB patients, and RBC transfusion was also an independent risk factor for ACI in UGIB patients.

1. Introduction

Upper gastrointestinal bleeding (UGIB) refers to gastrointestinal bleeding caused by lesions of the esophagus, stomach, duodenum, bile and pancreas above Treitz's ligament. UGIB is a common digestive tract disease, with clinical manifestations of hematemesis and/or melena, and severe cases accompanied by dizziness and syncope. The global incidence of UGIB is approximately 47/100,000.[1] In the United States, the incidence of UGIB is higher than the global level, approximately 82–96/100,000, and approximately 300,000 hospitalized patients die every year, with a mortality rate of 5%.[2–4] Peptic ulcer, esophagogastric variceal hemorrhage, acute erosive hemorrhagic gastritis and gastric cancer are the most common causes of UGIB. Endoscopy is the main method to determine the cause of UGIB. In addition, endoscopic intervention is a fast and effective method to control UGIB.

The complications of UGIB include acute coronary syndrome, acute renal insufficiency, and acute cerebral infarction (ACI). In addition, for hepatic cirrhosis patients with esophageal variceal hemorrhage, UGIB significantly increases the risk of hepatic encephalopathy. Upper gastrointestinal bleeding combined with ACI not only increases the mortality of patients but also prolongs the hospitalization time and increases the hospitalization expenditure of patients. The induction of ACI is related to a decrease in the supply of blood and oxygen caused by a decreased circulating blood volume and oxygen carrying capacity after UGIB.

The treatment of UGIB combined with ACI can be very complex. There are contradictions between the treatment of UGIB and the treatment of ACI. The treatment of UGIB requires hemostasis with drugs such as hemocoagulase. Chen B et al. found that thrombin increased nerve damage during cerebral ischemia, resulting in cogni-

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tive loss.[5] ACI needs to be treated with aspirin and clopidogrel for antiplatelet aggregation and low molecular weight heparin for anticoagulation. The use of these drugs will increase the risk of UGIB.

The rate pressure product (RPP) refers to the product of systolic blood pressure and heart rate and is widely used to predict the occurrence of adverse events in patients with cardiovascular diseases.[6–8] In addition, Krishnamoorthy V et al. found that the RPP was related to the mortality of patients with severe traumatic brain injury.[9] Jingwei Zhao et al. found that the RPP was a predictor of mortality in patients with aneurysmal subarachnoid hemorrhage.[10] The RPP of patients with UGIB can change significantly. We speculate that the RPP is related to the occurrence of ACI in patients with UGIB.

Therefore, this study retrospectively analyzed the data of patients with UGIB complicated with ACI and those without ACI admitted to Nanchang University Affiliated Ganzhou Hospital and explored the relationship between the RPP and ACI in UGIB patients.

2. Patients and methods

2.1. Patients

Patients with UGIB who were treated in the Emergency Department and Gastroenterology Department of Nanchang University Affiliated Ganzhou Hospital from January 2019 to December 2021 were retrospectively analyzed. The inclusion criteria were as follows: (1) patients with hematemesis and/or melena or positive stool occult blood test; and (2) patients who were diagnosed with UGIB by endoscopy. The exclusion criteria were as follows: (1) ACI within 1 month before UGIB; (2) acute cerebral infarction without brain CT or MRI; and (3) incomplete data.

2.2. Methods

Patients were divided into an ACI group and a non-ACI group according to whether they were complicated with ACI. Propensity score matching was used to match the patients in the two groups and balance the confounding factors between the two groups. Multivariate conditional logistic regression was used to explore the relationship between the RPP and ACI in UGIB patients (Figure 1).

2.3. Data collection

All patient data were collected from the electronic medical record system of Nanchang University Affiliated Ganzhou Hospital. Blood samples of patients were collected and tested within 24 hours after admission for white blood cell (WBC) count, hemoglobin, red blood cell distribution width (RBC-DW), platelet count, mean platelet volume (MPV), urea nitrogen, creatinine, activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, D-dimer, total bilirubin, and albumin. The RPP at admission and 24 hours after admission of all patients were recorded.

2.4. Propensity score matching

ACI was chosen as the dependent variable, and patient sex, age, smoking, drinking, and medical history (including hypertension, coronary heart disease, diabetes, previous history of cerebral infarction, gout, chronic kidney disease, peptic ulcer, chronic obstructive pulmonary disease, and cirrhosis) were chosen as independent variables. The propensity score (PS) of each patient was calculated by a logistic regression model; the matching method prioritized complete matching and randomly arranged the case order when extracting matching items. Furthermore, the random seed was 123456, the ACI group and non-ACI group were matched 1:1, and the matching tolerance was 0.02. Finally, 48 pairs were successfully matched.

2.5. Patient treatment

All patients were monitored for vital signs after admission, including systolic blood pressure and heart rate at admission and 24 hours after admission. The main treatment measures for patients after admission included the use of proton pump inhibitors (PPIs), fluid supplementation and nutritional support. Patients with UGIB were treated with hemagglutinin, octreotide or somatostatin and mechanical ventilation according to the condition of the patient. Patients with hemoglobin lower than 70 g/L and hemodynamic instability were treated with red blood cell (RBC) transfusion.

2.6. Definitions

ACI was defined as rapidly occurring neurological impairment confirmed by brain CT or MRI.[11] Smokers were defined as those who smoked continuously for more than 6 months.[12] Drinkers were defined as those who drank alcohol continuously for more than 6 months.[13]

2.7. Ethics approval

The study was approved by the ethics committee of Nanchang University Affiliated Ganzhou Hospital. As this study was retrospective, informed consent from patients was exempt.

2.8. Statistical analysis

SPSS 26.0 was used for the statistical analysis. Continuous variables are presented as the mean ± standard deviation and were assessed using Student's t test or the rank sum test, as appropriate. Categorical variables are presented as frequencies and were as-

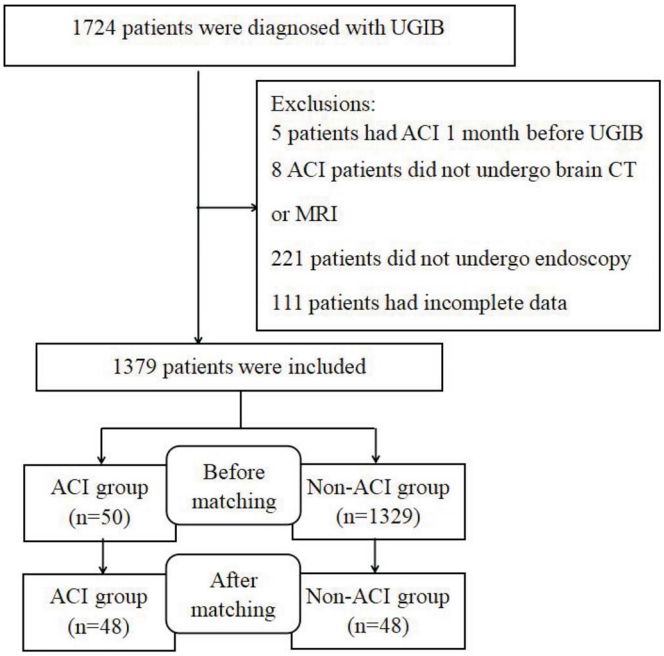

Figure 1. Flowchart of the patients included in this study. ACI: acute cerebral infarction; CT: computer tomography; MRI: magnetic resonance imaging; UGIB: upper gastrointestinal bleeding.

sessed using the chi-square test. Factors with a p value < 0.1 were included in the conditional multivariate logistic regression analysis. An ROC curve was used to test the sensitivity and specificity of the factors. p < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

There were 1379 UGIB patients in the study; among them, 1077 were male, 302 were female, 1000 were younger than 65 years of age, and 379 were older than 65 years of age (Table 1).

3.2. Propensity score matching

There were 50 patients in the ACI group and 1329 patients in the non-ACI group before matching. There were significant differences in age, hypertension, coronary heart disease (CHD), diabetes, previous history of cerebral infarction, chronic obstructive pulmonary disease (COPD) and hepatic cirrhosis between the two groups before matching (p < 0.05). Patient sex, age, smoking, drinking, hypertension, CHD, diabetes, previous history of cerebral infarction, gout, chronic kidney disease (CKD), peptic ulcer, COPD and hepatic cirrhosis were used as independent variables for propensity score matching, and 48 pairs of patients were successfully matched. After matching, there was no significant difference in matching factors between the two groups (Table 2).

Table 1
Baseline patient characteristics.

Baseline characteristics	N = 1379	Percentage (%)
Gender (male)	1077	78.1%
Age (> 65 years)	379	27.5%
Smoking	371	26.9%
Drinking	299	21.7%
Hypertension	303	22.0%
CHD	73	5.3%
Diabetes	122	8.8%
Previous history of ACI	84	6.1%
Gout	58	4.2%
Peptic ulcer	220	16.0%
COPD	19	1.4%
CKD	30	2.2%
Hepatic cirrhosis	260	18.9%
RBC transfusion	405	29.4%
Hemagglutinin	484	35.1%
Octreotide	646	46.8%
Somatostatin	332	24.1%

ACI: acute cerebral infarction; CHD: coronary heart disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; RBC: red blood cell.

3.3. Comparison of laboratory results, treatment and the RPP after matching

After matching, hemoglobin, MPV and albumin in the ACI group were significantly lower than those in the non-ACI group. The percentages of low and high RPP at admission in the ACI group were much higher than those in the non-ACI group, and the percentage of middle RPP at admission in the ACI group was much lower than that in the non-ACI group. The percentage of RBC transfusion was much higher in the ACI group than in the non-ACI group. There were no significant differences in WBC, RBC-DW, platelet count, urea nitrogen, creatinine, APTT, PT, fibrinogen, D-dimer, total bilirubin, RPP 24 hours after admission, hemagglutinin, octreotide, or somatostatin between the two groups (Table 3).

3.4. Univariate analysis assessing risk factors for ACI in UGIB patients

The univariate analysis showed that RBC transfusion was a risk factor for ACI in UGIB patients. Compared with middle RPP at admission, low RPP and high RPP were risk factors for ACI in UGIB patients. Hemoglobin, MPV and albumin were protective factors for ACI in UGIB patients (Table 4).

3.5. Conditional multivariate logistic regression analysis assessing independent risk factors for ACI in UGIB patients

Factors with a p value < 0.1 were included in the conditional multivariate logistic regression analysis. The results showed that RBC transfusion was an independent risk factor for ACI in UGIB patients. Compared with middle RPP at admission, low RPP and high RPP were independent risk factors for ACI in UGIB patients (Table 5).

3.6. ROC curve analysis

An ROC curve was drawn to assess the discriminative power of the RPP at admission and RBC transfusion, and the results showed that the areas under the curve (AUCs) of the RPP at admission and RBC transfusion were 0.625 and 0.688, respectively (Figure 2).

Table 2
Baseline patient characteristics before and after matching.

Baseline characteristics	Before matching		p value	After matching		p value
	ACI group (n = 50)	Non-ACI group (n = 1329)		ACI group (n = 48)	Non-ACI group (n = 48)	
Gender (male)	36 (72.0%)	1041 (78.3%)	0.288	34 (70.8%)	33 (68.8%)	0.824
Age (> 65 years)	30 (60.0%)	349 (26.3%)	0.000	28 (58.3%)	31 (64.6%)	0.529
Smoking	11 (22.0%)	360 (27.1%)	0.426	11 (22.9%)	11 (22.9%)	1.000
Drinking	11 (22.0%)	288 (21.7%)	0.956	10 (20.8%)	9 (18.8%)	0.798
Hypertension	34 (68.0%)	269 (20.2%)	0.000	32 (66.7%)	33 (68.8%)	0.827
CHD	9 (18.0%)	64 (4.8%)	0.000	9 (18.8%)	8 (16.7%)	0.789
Diabetes	17 (34.0%)	105 (7.9%)	0.000	16 (33.3%)	11 (22.9%)	0.256
Previous history of ACI	13 (26.0%)	71 (5.3%)	0.000	12 (25.0%)	13 (27.1%)	0.816
Gout	3 (6.0%)	55 (4.1%)	0.520	3 (6.3%)	3 (6.3%)	1.000
Peptic ulcer	7 (14.0%)	213 (16.0%)	0.701	6 (12.5%)	4 (8.3%)	0.504
COPD	4 (8.0%)	15 (1.1%)	0.000	2 (4.2%)	3 (6.3%)	0.646
CKD	3 (6.0%)	27 (2.0%)	0.059	3 (6.3%)	4 (8.3%)	0.695
Hepatic cirrhosis	2 (4.0%)	258 (19.4%)	0.006	2 (4.2%)	2 (4.2%)	1.000

ACI: acute cerebral infarction; CHD: coronary heart disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

Table 3
Comparison of laboratory results, treatment and the RPP after matching.

Laboratory results, treatment and RPP	ACI group (n = 48)	Non-ACI group (n = 48)	p value
WBC (10^9/L)	9.75 ± 4.87	9.17 ± 5.49	0.584
Hemoglobin (g/L)	70.67 ± 22.82	88.98 ± 33.49	0.012
RBC-DW (%)	15.56 ± 3.35	14.84 ± 3.32	0.295
Platelet (10^9/L)	204.27 ± 96.25	225.04 ± 83.71	0.262
MPV (fL)	9.50 ± 1.12	10.11 ± 1.50	0.027
Urea nitrogen (mmol/L)	11.15 ± 6.49	11.10 ± 7.86	0.969
Creatinine (umol/L)	144.78 ± 140.67	115.53 ± 94.73	0.235
APTT (s)	27.74 ± 6.61	26.75 ± 10.14	0.486
PT (s)	12.59 ± 1.66	12.03 ± 1.47	0.088
Fibrinogen (mg/L)	2.64 ± 1.55	2.72 ± 1.12	0.227
D-dimer (mg/L)	3.04 ± 5.14	2.97 ± 10.14	0.963
Total bilirubin (umol/L)	12.53 ± 9.51	11.67 ± 7.21	0.620
Albumin (g/L)	30.19 ± 5.60	34.50 ± 6.45	0.001
RBC transfusion	32 (66.7%)	14 (29.2%)	0.000
Hemagglutinin	9 (18.8%)	7 (14.6%)	0.584
Octreotide	21 (43.8%)	23 (47.9%)	0.682
Somatostatin	8 (16.7%)	13 (27.1%)	0.217
RPP at admission			0.018
Low (< 8000)	9 (18.8%)	3 (6.3%)	
Middle (8000–15000)	30 (62.5%)	42 (87.5%)	
High (> 15000)	9 (18.8%)	3 (6.3%)	
RPP 24 hours after admission			0.055
Low (< 8000)	8 (16.7%)	12 (25%)	
Middle (8000–15000)	35 (72.9%)	36 (75%)	
High (> 15000)	5 (10.4%)	0	

APTT: activated partial thromboplastin time; MPV: mean platelet volume; PT: prothrombin time; RBC: red blood cell; RBC-DW: red blood cell distribution width; RPP: rate pressure product; WBC: white blood cell.

Table 4
Univariate analysis assessing the risk factors for ACI in UGIB patients.

Variates	p value	Coefficient	OR	95% CI
Hemoglobin	0.004	-0.671	0.511	0.324–0.805
MPV	0.034	-0.513	0.599	0.372–0.963
PT	0.092	0.366	1.442	0.941–2.210
Albumin	0.002	-0.787	0.455	0.278–0.747
RBC transfusion	0.000	1.580	4.857	2.046–11.531
RPP at admission				
Middle (8000–15000)	0.025	-	-	
Low (< 8000)	0.043	1.435	4.200	1.048–16.830
High (> 15000)	0.043	1.435	4.200	1.048–16.830

MPV: mean platelet volume; PT: prothrombin time; RBC: red blood cell; RPP: rate pressure product.

4. Discussion

UGIB is a life-threatening digestive tract disease. The mortality rate of UGIB is approximately 3–14%.[14] UGIB can be divided into variceal bleeding and nonvariceal bleeding, and the former is often more serious than the latter.[15] ACI is a serious complication of UGIB. The most common causes of ACI are atherosclerosis, smoking, hypertension, diabetes, and hyperlipidemia.[16,17] Therefore, are the risk factors for ACI secondary to UGIB the same or different? At present, the scoring systems of UGIB include the Rockall score, the Glasgow-Blatchford score and the AIMS score. These scoring systems have significant value in predicting the mortality and rebleeding rate of patients, but they are not applicable to assessing the risk of ACI in UGIB patients.[18–22] Presently, few scholars have studied the

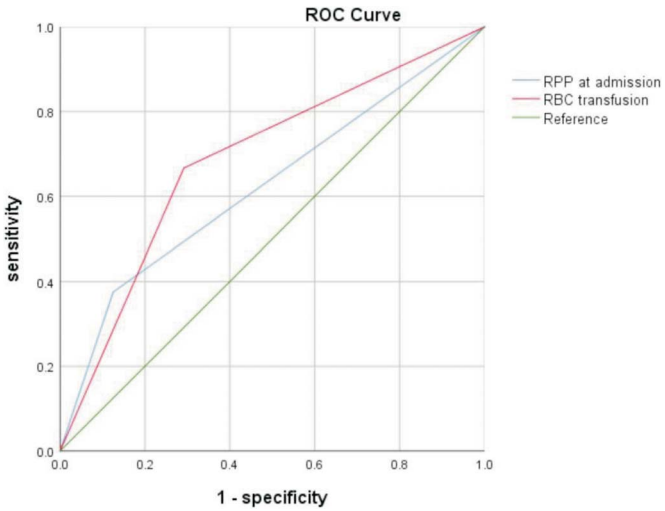

Figure 2. ROC curve analysis of the RPP at admission and RBC transfusion. RBC: red blood cell; ROC: receiver operating characteristics; RPP: rate pressure product.

Table 5
Conditional multivariate logistic regression analysis assessing independent risk factors for ACI in UGIB patients.

Variates	p value	Coefficient	Wald	S.E.	OR	95% CI
RBC transfusion	0.000	1.143	13.665	0.309	3.136	1.711–5.750
RPP at admission						
Middle (8000–15000)	0.004	-			-	
Low (< 8000)	0.032	0.823	4.578	0.385	2.278	1.072–4.841
High (> 15000)	0.001	1.248	10.544	0.384	3.484	1.640–7.401

RBC: red blood cell; RPP: rate pressure product.

risk factors for ACI in UGIB patients. In our study, we found that RBC transfusion was a risk factor for ACI in UGIB patients. Compared with middle RPP at admission, low RPP and high RPP were risk factors for ACI in UGIB patients.

The RPP is a noninvasive indicator of myocardial oxygen consumption, which can not only predict cardiac function[8] but also predict the morbidity and mortality of the population.[23] Wenling Zheng et al. found that RPP trajectories were identifiable from childhood and were associated with left ventricular hypertrophy in midlife.[24] Verma AK et al. found that the RPP was related to the mortality of acute heart failure patients.[8] Krishnamoorthy V et al. found that low RPP and high RPP increased the mortality of patients with traumatic brain injury.[9] In a study by Jingwei Zhao et al., RPP < 10000 was defined as low RPP, 10000–15000 as middle RPP, and > 15000 as high RPP.[10] Jingwei Zhao et al. found that the RPP was a factor predicting the death of patients with aneurysmal craniocerebral hemorrhage, and the RPP was U-shaped correlated with the death of patients; low RPP and high RPP increased the mortality of patients.[10] However, there is no standard for the upper and lower limits of the RPP.[25] In our study, we defined RPP < 8000 as low RPP, 8000–15000 as middle RPP, and > 15000 as high RPP. We found that compared with middle RPP at admission, low RPP and high RPP were risk factors for ACI in UGIB patients.

Low RPP in UGIB patients increases the risk of ACI, which is related to the decrease in systolic blood pressure caused by a large amount of blood loss in patients, leading to insufficient blood supply to the brain. A high RPP would also increase the risk of ACI. In traumatic brain injury patients, the possible mechanism of high RPP increasing mortality is that brain injury induces a "catecholamine excess" state, which is characterized by increased blood pressure and heart rate, resulting in an increased RPP and cardiac insufficiency and finally leading to insufficient blood supply to the brain.[9] After blood volume loss caused by UGIB, catecholamine is produced in large quantities,[26] and a catecholamine excess state may occur. Cruickshank JM et al. studied the relationship between smoking and cerebral arterial blood supply and believed that smoking may lead to increased blood pressure and heart rate, increased cerebral arterial blood flow and decreased cerebral arterial blood supply by inducing catecholamine release.[27] Therefore, we believe that UGIB might lead to a decrease in the cerebral arterial blood supply and increase the incidence of ACI by inducing a catecholamine excess state.

Several studies have found that transfusion is a risk factor for stroke.[28–30] Our study also found that RBC transfusion was a risk factor for ACI in UGIB patients. The need for transfusion of red blood cells indicates that a patient has severe anemia, which will aggravate ischemic brain injury. During cardiopulmonary bypass surgery, the decrease in hemoglobin increases the risk of stroke.[31] In our study, the hemoglobin level in the ACI group was significantly lower than that in the non-ACI group (70.67 ± 22.82 vs. 88.98 ± 33.49), which also showed that RBC transfusion could indirectly reflect anemia. In addition, RBC transfusion may increase the aggregation of coagulant in blood vessels, which is one of the reasons why RBC transfusion increases the risk of ACI.[32,33]

4.1. Limitations

There were some limitations to the present study. First, this was a single-center retrospective study, and there were only 48 patients in the ACI group after matching, which affects the reliability of the results. Second, the RPP at admission was the systolic blood pressure and heart rate measured at the time of admission, but the time from the onset of UGIB symptoms to admission was different for each patient, which also impacts the results. Third, in this study, we did not monitor the blood flow velocity or blood flow volume of the cerebral artery, nor did we detect the blood catecholamine level. Therefore, we do not know the exact mechanism of ACI caused by UGIB.

In conclusion, compared with middle RPP at admission, low RPP and high RPP were independent risk factors for ACI in UGIB patients, and RBC transfusion was also an independent risk factor for ACI in UGIB patients.

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Authors' contributions

Jiaming Huang collected the data, analyzed the relevant information, and drafted the manuscript. Foqiang Liao clinically managed the patient. Xu Shu designed the article and approved the final submission.

Conflict of interest and source of funding

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References

1. Oakland K. Changing epidemiology and etiology of upper and lower gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol*. 2019;42–43:101610. doi:10.1016/j.bpg.2019.04.003
2. Abougergi MS, Travis AC, Saltzman JR. The in-hospital mortality rate for upper GI hemorrhage has decreased over 2 decades in the United States: a nationwide analysis. *Gastrointest Endosc.* 2015;81(4):882–8.e1. doi:10.1016/j.gie.2014.09.027
3. Rotondano G. Epidemiology and diagnosis of acute nonvariceal upper gastrointestinal bleeding. *Gastroenterol Clin North Am*. 2014;43(4):643–663. doi:10.1016/j.gtc.2014.08.001
4. Chi T, Zhao Q, Wang P. Risk factors for acute coronary syndrome in upper gastrointestinal bleeding patients. *Gastroenterol Res Pract.* 2021;2021:8816805. doi:10.1155/2021/8816805
5. Chen B, Friedman B, Whitney MA, et al. Thrombin activity associated with neuronal damage during acute focal ischemia. *J Neurosci*. 2012;32(22):7622–7631. doi:10.1523/JNEUROSCI.0369-12.2012
6. Hagel JA, Sperotto F, Laussen PC, Salvin JW, Bachu A, Kheir JN. Shock Index, coronary perfusion pressure, and rate pressure product as predictors of adverse outcome after pediatric cardiac surgery. *Pediatr Crit Care Med*. 2021;22(1):e67–e78. doi:10.1097/PCC.0000000000002524
7. Kiviniemi AM, Kenttä TV, Lepojärvi S, et al. Recovery of rate-pressure product and cardiac mortality in coronary artery disease patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2019;150:150–157. doi:10.1016/j.diabres.2019.03.007
8. Verma AK, Sun JL, Hernandez A, et al. Rate pressure product and the components of heart rate and systolic blood pressure in hospitalized heart failure patients with preserved ejection fraction: Insights from ASCEND-HF. *Clin Cardiol*. 2018;41(7):945–952. doi:10.1002/clc.22981
9. Krishnamoorthy V, Vavilala MS, Chaikittisilpa N, et al. Association of early myocardial workload and mortality following severe traumatic brain injury. *Crit Care Med*. 2018;46(6):965–971. doi:10.1097/CCM.0000000000003052
10. Zhao J, Zhang S, Ma J, Shi G, Zhou J. Admission rate-pressure product as an early predictor for in-hospital mortality after aneurysmal subarachnoid hemorrhage. *Neurosurg Rev*. 2022;45(4):2811–2822. doi:10.1007/s10143-022-01795-3
11. Jia JP, Chen SD. *Neurology*. People's Medical Publishing House; 2018:195.
12. Zheng W, Mu J, Chu C, et al. Association of blood pressure trajectories in early life with subclinical renal damage in middle age. *J Am Soc Nephrol*. 2018;29(12):2835–2846. doi:10.1681/ASN.2018030263

13. Li XX, Zhao Y, Huang LX, et al. Effects of smoking and alcohol consumption on lipid profile in male adults in northwest rural China. *Public Health*. 2018;157:7–13. doi:10.1016/j.puhe.2018.01.003
14. van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol.* 2008;22(2):209–224. doi:10.1016/j.bpg.2007.10.011
15. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood.* 2010;116(6):878–885. doi:10.1182/blood-2010-02-261891
16. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388(10046):761–775. doi:10.1016/S0140-6736(16)30506-2
17. Joseph P, Leong D, McKee M, et al. Reducing the global burden of cardiovascular disease, part 1: The epidemiology and risk factors. *Circ Res.* 2017;121(6):677–694. doi:10.1161/CIRCRESAHA.117.308903
18. Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. *BMJ*. 2017;356:i6432. doi:10.1136/bmj.i6432
19. Robertson M, Majumdar A, Boyapati R, et al. Risk stratification in acute upper GI bleeding: comparison of the AIMS65 score with the lasgow-Blatchford and Rockall scoring systems. *Gastrointest Endosc*. 2016;83(6):1151–1160. doi:10.1016/j.gie.2015.10.021
20. Lu M, Sun G, Huang H, et al. Comparison of the Glasgow-Blatchford and Rockall Scores for prediction of nonvariceal upper gastrointestinal bleeding outcomes in Chinese patients. *Medicine* (*Baltimore*). 2019;98(21):e15716. doi:10.1097/MD.0000000000015716
21. Custovic N, Husic-Selimovic A, Srsen N, Prohic D. Comparison of Glasgow-Blatchford Score and Rockall Score in patients with upper gastrointestinal bleeding. *Med Arch*. 2020;74(4):270–274. doi:10.5455/medarh.2020.74.270-274
22. Gu L, Xu F, Yuan J. Comparison of AIMS65, Glasgow-Blatchford and Rockall scoring approaches in predicting the risk of in-hospital death among emergency hospitalized patients with upper gastrointestinal bleeding: a retrospective observational study in Nanjing, China. *BMC Gastroenterol*. 2018,18(1):98. doi:10.1186/s12876-018-0828-5
23. Atkinson G, Leary AC, George KP, Murphy MB, Jones H. 24-hour variation in the reactivity of rate-pressure-product to everyday physical activity in patients attending a hypertension clinic. *Chronobiol Int*. 2009;26(5):958–973. doi:10.1080/07420520903044455
24. Zheng W, Mu J, Yan Y, et al. Association of rate pressure product trajectories at an early age with left ventricular hypertrophy in midlife: a prospective cohort study. *Hypertens Res*. 2023;46(2):321–329. doi:10.1038/s41440-022-01076-y
25. Stoschitzky K. Blood pressure, heart rate, or the rate pressure product: what is the best predictor of clinical outcome? *Eur Heart J Open*. 2022;2(5):oeac063. doi:10.1093/ehjopen/oeac063
26. Speranza V, Basso N. Progress in the treatment of acute gastroduodenal mucosal lesions (AGML). *World J Surg*. 1977;1(1):35–44. doi:10.1007/BF01654729
27. Cruickshank JM, Neil-Dwyer G, Dorrance DE, Hayes Y, Patel S. Acute effects of smoking on blood pressure and cerebral blood flow. *J Hum Hypertens*. 1989;3(6):443–449.
28. Kinnunen EM, Juvonen T, Biancari F. Use of blood products and diseased ascending aorta are determinants of stroke after off-pump coronary artery bypass grafting. *J Cardiothorac Vasc Anesth*. 2015;29(5):1180–1186. doi:10.1053/j.jvca.2015.02.021
29. Mikkola R, Gunn J, Heikkinen J, et al. Use of blood products and risk of stroke after coronary artery bypass surgery. *Blood Transfus*. 2012;10(4):490–501. doi:10.2450/2012.0119-11
30. Paone G, Likosky DS, Brewer R, et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg*. 2014;97(1):87–94. doi:10.1016/j.athoracsur.2013.07.020
31. Karkouti K, Djaiani G, Borger MA, et al. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg*. 2005;80(4):1381–1387. doi:10.1016/j.athoracsur.2005.03.137
32. Reynolds JD, Ahearn GS, Angelo M, Zhang J, Cobb F, Stamler JS. S-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. *Proc Natl Acad Sci U S A.* 2007;104(43):17058–17062. doi:10.1073/pnas.0707958104
33. Zallen G, Moore EE, Ciesla DJ, Brown M, Biffl WL, Silliman CC. Stored red blood cells selectively activate human neutrophils to release IL-8 and secretory PLA2. *Shock*. 2000;13(1):29–33. doi:10.1097/00024382-200013010-00006