Gastrointestinal Bleeding in Patients Admitted to Cardiology: risk factors and a new risk score

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Abstract

Background: Although the early use of a risk stratification score in gastrointestinal bleeding(GIB) is recommended, there has been no risk score for GIB in patients admitted to cardiology so far.

Objective: To describe the risk factors of GIB and develop a new risk score model in patients admitted to cardiology.

Methods: A total of 633 inpatients with GIB from January 2014 to December 2018 were recruited, 4,231 inpatients with non-GIB recruited as the control group. Multivariate logistic regression was used to describe the risk factors of GIB,A new risk score model was developed in the derivation cohort. Accuracy to predict GIB was assessed by the area under the receiver operating characteristic (AUROC) curve in the validation cohort.

Results: Male, coronary heart disease, hypertension, stroke, systolic blood pressure, hematocrit, plasma albumin and alanine aminotransferase(ALT) were associated with GIB . The model had a high predictive accuracy (AUROC 0.816; 95%CI, 0.792-0.839), which was supported by the validation cohort (AUROC 0.841; 95% CI, 0.807~0.874). Besides,the prediction of the model better than HAS-BLED score(AUROC 0.557; 95%CI, 0.513~0.602) and CRUSADE score(AUROC 0.791; 95%CI, 0.757~0.825), respectively. Among the inpatients with a score 0-3, 4-7, and ≥8 points, the incidence of GIB, the proportion of inpatients requiring suspended red blood cells transfusion, length of stay and in-hospital mortality all increased gradually(P< 0.001).

Conclusions: Male, coronary heart disease, hypertension, stroke, systolic blood pressure, hematocrit, plasma albumin and ALT are associated with GIB. The new risk score model is an accurate risk score that predicts GIB in patients admitted to cardiology.

1. Introduction

GIB is one of the complications of patients admitted to cardiology, which is common in acute myocardial infarction[1], percutaneous coronary intervention (PCI)[2]and anticoagulant or antiplatelet drugs[3]. Not only the length of stay and hospitalization expenses increased, but also lead to other organ dysfunction or even failure, and may cause death in severe cases. It is reported that among more than 300,000 hospitalized patients in the United States each year, the mortality rate of GIB is

between 2% and 15%[4]. Therefore, a risk stratification score to predict GIB in patients admitted to cardiology is required, in order to classify the grade of inpatients or early intervention so that to get better outcomes. However, the bleeding risk score related to cardiology mostly aimed at some specific diseases, such as HAS-BLED bleeding score is mainly used to estimate major bleeds in patients with atrial fibrillation on vitamin K-antagonists treatment[5], and CRUSADE bleeding score mainly used to predict bleeding patients with acute non-ST segment elevation myocardial infarction[6].Meanwhile, patients admitted to cardiology usually accompanied with comorbidities, including acute myocardial infarction, atrial fibrillation, hypertension, diabetes, hepatic and renal insufficiency, etc. Therefore, predictive clinical scores with high generalizability have not been established.

Our study aimed to develop the risk factors of GIB in patients admitted to cardiology, also in order to establish a new risk score model to predict GIB, which can help clinicians identify high-risk inpatients early so that to improve outcomes.

2. Materials And Methods

2.1. Object of study

A retrospective study was designed,which recruited 126,770 consecutive patients attended in the Department of Cardiology of The Second Hospital of Hebei Medical University from January 2014 to December 2018. During this period, a total of 633 patients diagnosed with GIB were set as the experimental group,4231 patients were recruited as the control group. Ultimately, we retrospectively identified 4,864 patients for the study. The diagnostic criteria of GIB are based on the results of symptoms, physical examination, endoscopy and laboratory examination. Inclusion criteria included: (i)symptoms of upper or lower GIB: unexplained decrease of blood pressure accompanied with increase of heart rate concomitant vomiting coffee-like substances or blood, black stool or bloody stool; (ii)unexplained hemodynamics disturbance; (iii)local bleeding focuses can be screened under endoscope. Exclusion criteria were: (i)patients confirmed GIB at the time of admission; (ii)patients with peptic ulcer, gastrointestinal tumor, cirrhosis, esophageal and gastric varices, inflammatory bowel disease; (iii)patients with black stool or vomiting coffee-like substances caused by eating based

on medical history and physical examination: such as animal blood, ferralia, etc.

2.2. Data collection

All required clinical data included baseline demographic characteristics; history of medical, such as coronary heart disease, hypertension, diabetes, stroke, heart failure, hyperlipidemia, smoke and alcohol(previous or currently); related laboratory indexes : systolic blood pressure, heart rate, hematocrit, platelet count, plasma albumin, high-sensitivity C-reactive protein, serum creatinine, aspartate aminotransferase(AST), ALT, γ glutamyltranspeptidase; Related drugs and procedures before GIB: for instance aspirin, warfarin, statins, new oral anticoagulants, non-steroidal anti-inflammatory drugs, glucocorticoids, proton pump inhibitors(PPI), and whether PCI were collected.

2.3. Risk score establishment

4,864 research objects were randomly divided into two cohorts at 7:3 : the derivation cohort (3,404) was used to establish the model, the validation cohort (1,460) was applied to validate the predictive value of the model. Multivariate logistic regression were used to identify risk factors for GIB in the study. According to the results of risk factors screened out and the odds ratio(OR) as the standard, the risk factors were assigned and scored a basis for the correlation intensity. In this study, the method of assigning the correlation degree of risk factors is as follows: $1.0 \leq OR \leq 1.1$ for non-association; $1.1 < OR \leq 2.0$ for weak association; $2.0 < OR \leq 4.0$ for medium association; $4.0 < OR \leq 10.0$ for strong association; $OR > 10.0$ for stronger association. Meanwhile, non-association = 0 points, weak association = 1 points, medium association = 2 points, strong association = 3 points, strong association = 4 points.

2.4. Risk score validation, comparison and stratification

In the validation cohort, AUROC, Youden index, sensitivity and specificity of the new risk score model, HAS-BLED score and CRUSADE score were calculated respectively. Moreover, the predictive value of the model for GIB in patients admitted to cardiology was evaluated and compared with the other two bleeding score. We assessed the validity of the three-level the model using 0–3, 4–7, and ≥ 8 points which was divided into low-risk group, medium-risk group and high-risk group respectively, and the differences in the incidence of GIB, the proportion of inpatients requiring suspended red blood cells transfusion, length of stay and in-hospital mortality were observed among those groups.

2.5.Statistical analysis

Data analysis was performed using SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL, USA) .Continuous variables were described as mean ± standard deviation (SD) or 25th (Quartile 1) and 75th (Quartile 3) percentile. Categorical variables were shown as frequencies and percentages. Continuous variables were compared using Student's t-test or the Mann–Whitney U test based on their distribution. Categorical variables were compared using chi-squared tests. A multivariate logistic regression analysis was used to analyze the independent predictors for GIB. The statistical software Medcalc 15.2.2 was used to draw the receiver operating characteristic curve(ROC), and the AUROC comparison of different risk score was performed using the Z test. The trend of changes in the incidence of GIB, the proportion of inpatients requiring suspended red blood cells transfusion, length of stay and in-hospital mortality were analyzed applying a nonparametric trend test (nptrend in Stata) or Fisher’s exact test. p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

Patients with GIB in the derivation cohort were significantly higher than the control group in male, age, previous history of coronary heart disease, hypertension, diabetes, stroke, heart rate, high-sensitivity C-reactive protein values and AST levels, and lower in previous history of heart failure, hyperlipidemia, alcohol, systolic blood pressure values, plasma albumin values, hematocrit values, estimation of glomerular filtration rate(eGFR) values, oral aspirin, new oral anticoagulants, statins before GIB and the proportion after PCI than those with non-GIB($P < 0.01$). However, there was no significant differences in the use of PPI between the two groups ($P > 0.05$) (Table 1).

Table 1

Baseline characteristics analysis of patients in the derivation cohort

Variable	GIB (n = 460)	No GIB (n = 2944)	Z/X^2 Value	*P* Value
Male sex	304(66.1%)	1,580(53.7%)	34.518	<0.001
Age(y)	67(60,76)	61(53,68)	-13.173	<0.001
Previous medical history				
Coronary artery disease	238(51.8%)	1,236(42.0%)	66.825	<0.001
Hypertension	293(63.7%)	1,601(54.4%)	19.019	<0.001
Diabetes	105(22.8%)	526(17.9%)	9.262	0.002
Stroke	85(18.5%)	323(11.0%)	30.089	<0.001
Smoke	87(18.9%)	588(20.0%)	0.407	0.524
Alcohol	55(12.0%)	476(16.2%)	7.377	0.007
Heart failure	54(11.7%)	544(18.5%)	16.697	<0.001
Hyperlipidemia	78(17.0%)	766(26.0%)	23.559	<0.001
Laboratory examination on admission				
Systolic blood pressure(mmHg)	126(110,141)	134(122,147)	-9.178	<0.001
Heart rate(bpm)	78(68,91)	72(64,82)	-8.788	<0.001
Hematocrit(%)	32.3(25.6,38.9)	40.6(37.6,43.5)	-22.962	<0.001
Platelet count(10^9/L)	205(164,249)	198(165,238)	-1.930	0.054
Plasma albumin(g/L)	36.7(33.0,40.2)	41.2(38.5,43.9)	-19.976	<0.001
High-sensitivity C-reactive protein(mg/L)	5.1(1.7,17.5)	1.4(0.8,3.5)	-15.877	<0.001
eGFR(ml/min■1.73 m^2)	68.3(50.7,82.6)	99.7(79.5,121.7)	-5.266	<0.001
AST (u/L)	20.2(15.4,39.9)	18.9(15.5,24.0)	-5.127	<0.001
ALT(u/L)	16.5(11.0,30.8)	17.6(12.5,26.9)	-0.950	0.342
γ glutamyltranspeptidase(u/L)	20.4(14.0,32.8)	20.0(14.0,32.0)	-0.175	0.861
Medication and related procedures before GIB				
Aspirin	56(12.0%)	1,735(58.9%)	485.821	<0.001
Warfarin	13(2.8%)	104(3.5%)	0.715	0.398
Statins	284(61.7%)	1,976(67.1%)	7.143	0.008
New oral anticoagulant	2(0.4%)	273(9.3%)	57.381	<0.001
Glucocorticoid	2(0.4%)	5(0.2%)	0.142	0.663
PPI	138(30%)	819(27.8%)	1.345	0.246
After PCI	41(9.0%)	485(16.5%)	23.696	<0.001

GIB: Gastrointestinal bleeding; eGFR: Estimation of glomerular filtration rate; PPI: Proton pump inhibitors; PCI: Percutaneous coronary intervention; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; eGFR (mL/min/1.73 m2) = 194 × serum creatinine$^{-1.094}$×age$^{-0.287}$ (× 0.739 if female).

3.2. Risk Factors and the new risk score model for GIB

After multivariate analysis of all potential risk factors, which included a total of eight independent risk factors associated with GIB in inpatients in vasculocardiology deparment. Then, the score was assigned from the OR value of each independent risk factors: male (2 points), coronary heart disease (1 point), hypertension (1 point), stroke (1 point), systolic blood pressure (mmHg) (≤ 80, 4points;81–90, 4 points; 91–140, 1 point), hematocrit (%) (< 31, 4 points; 31-33.9, 3 points; 34-36.9, 2 points; 37-39.9, 1 point), plasma albumin (g/L) (< 20, 3 points; 20-29.9, 4 points; 30-39.9, 2 points),and the score of ALT was 0 point.The score ranged from 0 to 17(Table 2).

Table 2

Multivariate logistic regression analysis of all required clinical variables for GIB in patients admitted to Cardiology in the derivation cohort.

Variable	OR	95%CI	*P* Value	Score (points)
Male sex	3.530	2.480–5.024	<0.001	2
Coronary artery disease	1.736	1.226–2.458	0.002	1
Hypertension	1.481	1.027–2.136	0.035	1
Stroke	1.776	1.153–2.735	0.009	1
Systolic blood pressure (mmHg) ≤ 80 81–90 91–140 ≥ 141	59.381 23.753 1.305 Ref	7.243–486.840 8.406–67.190 1.171–1.636 Ref	<0.001 <0.001 0.021 Ref	4 4 1 0
Hematocrit(%) <31 31-33.9 34-36.9 37-39.9 ≥ 40	39.380 4.940 2.440 1.127 Ref	28.326–54.747 3.292–7.414 1.735–3.431 1.077–1.634 Ref	<0.001 <0.001 <0.001 <0.001 Ref	4 3 2 1 0
Plasma albumin(g/L) <20 20-29.9 30-39.9 ≥ 40	6.153 32.816 3.648 Ref	1.608–23.539 18.950-56.825 2.860–4.653 Ref	0.008 <0.001 <0.001 Ref	3 4 2 0
ALT (u/L)	1.005	1.001–1.010	0.027	0

OR: Odds ratio; CI: Confidence interval; Ref: Reference; ALT: Alanine aminotransferase.

3.3. The predictive value of the new risk score model

The new risk score model was suitable which was validated by the AUROC curves for the derivation and validation cohorts (0.816 [95%CI, 0.792–0.839] and 0.841 [95% CI, 0.807 ~ 0.874],respectively).In addition, the AUROC of the model in the validation cohort, was the highest compared with HAS-BLED score(0.557; 95%CI, 0.513 ~ 0.602) and CRUSADE score(0.791; 95%CI, 0.757 ~ 0.825). ROC results showed that a cut-off score of 6.5 points of the model had a sensitivity of 65.3% and specificity of 89.1%. Therefore, the model had the highest specificity, but it was slightly lower for sensitivity than CRUSADE score (Table 3 and Fig. 1).

Table 3

Comparison of predictive value of the new risk score model with other risk score for GIB in patients admitted to Cardiology in the validation cohort.

Risk score	AUROC	95%CI	Youden index	cut-off score	Sensitivity (%)	Specificity (%)
The new risk score model	0.841	0.807–0.874	0.544	6.5	0.653	0.891
HAS-BLED	0.557	0.513–0.602	0.087	2.5	0.358	0.729
CRUSADE	0.791	0.757–0.825	0.456	29.5	0.658	0.798

CI: Confidence interval; AUROC: the area under the receiver operating characteristic curve.

3.4 GIB and secondary outcomes under the risk stratification of the new risk score model in the validation cohort

The incidence of GIB with 0-3, 4-7, and ≥8 points were 2.2% (12/547),9.7%(75/771), and 61%

(99/162), respectively(P<0.001,trend) (Figure 2A). Among the patients with 0-3, 4-7, and ≥8 points, the rates of suspended red blood cells transfusion requirements were 0.18%(1/547), 2.20%(17/771), and 24.07%(39/162), respectively(P<0.001, trend) (Figure 2B).The length of stay were 9.4, 10.4 and 12.3 days(P<0.05,trend) (Figure 2C).The in-hospital mortality with 0-3, 4-7, and ≥8 points were 0% (0/547), 0.78%(6/771), and 4.32% (7/162), respectively(P<0.001,trend) (Figure 2D).

4. Discussion

In our study, male, coronary heart disease, hypertension, stroke, systolic blood pressure, hematocrit, plasma albumin and ALT were associated with the incidence of GIB in patients admitted to cardiology. Previously, some studies had investigated that male and previous history of diabetes were independent risk factors for non-varicose upper gastrointestinal bleeding in patients taking aspirin or other non-steroidal anti-inflammatory drugs[7–10]. It had been demonstrated that multiple comorbidities (such as hypertension, diabetes) were associated with the occurrence of GIB in elderly inpatients, rather than only a single organ failure or the combined use of multiple drugs[11]. Mora et al. [12] confirmed that hematocrit is a risk factor for GIB and a predictor of poor prognosis. Jiménez et al. [13] found that low plasma albumin level was a risk factor for GIB and death in hospitalized patients. Moreover, several studies had mentioned that serum ALT is a risk factor for upper GIB and death within 60 days[14]. The results of the above studies were consistent with our study.

Meanwhile, we found that there was no significant differences in PPI between the two groups and had no protective effect on the incidence of GIB. Similarly, previous studies had reported that PPI could not decrease the incidence of GIB in patients after anticoagulant therapy with dabigatran[15]. It was noteworthy that a study that 46,301 patients with dual antiplatelet therapy after myocardial infarction were recruited, reported PPI could reduce the risk of GIB, However, long-term outcomes needed to be further observed [16]. Ray et al.[17]demonstrated that oral PPI could decrease the incidence of upper GIB in hospitalized patients treated with oral anticoagulants.

Early detection of high-risk patients with GIB was helpful to timely surveillance and take related preventive treatment, so as to decrease the incidence and mortality. Nowadays some clinical bleeding risk score systems related to cardiology were almost established for a certain disease in some specific

population. For example, HAS-BLED was a simple and practical score for predicting the major bleeding(such as GIB, decreased hemoglobin > 2 g/L or requiring blood transfusion, etc.) in patients with atrial fibrillation, especially in cases of GIB without any antithrombotic drugs or only with single antiplatelet therapy[18]. Of course, with the further expansion of the application of HAS-BLED score, it has also been proved to be effective in predicting bleeding events in patients with non-atrial fibrillation, including venous thrombosis[5], acute coronary syndrome, after PCI or coronary artery bypass grafting[19, 20]. CRUSADE score was initially used only for major bleeding risk assessment during hospitalization in patients with acute non-ST segment elevation myocardial infarction[6]. Likewise, subsequent studies have confirmed that it can evaluate the risk of bleeding within 30 days after discharge, or even within 1 year, and the study population has been extended to all patients receiving dual antiplatelet therapy after PCI[21]. Systolic blood pressure[22], plasma albumin[13, 22], hematocrit[12, 23]and ALT[14]included in the model were applied as predictors of death because of GIB by other risk score, so the model may also has a certain ability to predict the mortality of GIB. Recently, it had been reported that the AIMS65 bleeding score could well predict the in-hospital mortality, length of stay and expenses of patients with upper GIB[22, 24, 25]. In particular, Robertson et al. [26] found that the AIMS65 bleeding score had a good ability to predict the death of upper GIB(AUROC: 0.84). However, due to the limitation of sample size in our study, more data are needed to verify the predictive value of the new risk score model on mortality.

Considering the types of diseases, comorbidities, the use of various drugs and the diversity and complexity of related operations of patients admitted to cardiology, the current bleeding risk score could not fully evaluate the risk of GIB, thus the new risk score model was established in this study. Although the sensitivity of the model (0.653) was slightly lower than that of CRUSADE score(0.658), the model was the best among the three risk score in terms of specificity and ability to predict GIB. We found that although the whole incidence of GIB in patients admitted to cardiology was not high(0.5%, 633/126770), the incidence of GIB in the high-risk inpatients (a score ≥ 8 points)reached 61% (99/162),and only 2.2% (12/547) and 9.7%(75/771) for low-and medium-risk inpatients respectively. Similarly, in-hospital mortality of GIB patients could reach 4.32% (7/162) in high-risk

inpatients (a score ≥ 8 points).Meanwhile, we also noted that the length of stay and the proportion of inpatients requiring suspended red blood cells transfusion of high-risk inpatients were higher, undoubtedly,which would directly increase the expenses of them and the burden of social medical resources. Therefore, the results of our study shows that when patients admitted to cardiology are stratified into the high-risk(a score ≥ 8 points) by the model, clinicians should pay high attention to and closely monitor any bleeding tendency of them, taking appropriate preventive measures, detecting and actively conducting relevant treatment as soon as possible, so as to decrease the incidence and mortality of GIB.

5. Limitations

There were some limitations in our study that should be mentioned.Due to human and material resources and many other limitations, we failed to collect data of non-GIB in inpatients of whole department of cardiology from January 2014 to December 2018 as the control group, resulting in a relative shortage of sample size in the control group. In addition, this was a retrospective, single-center study, with a small number of cases, limited by time and region, so the accuracy and clinical significance of the new risk score model still required further multicenter, large sample study.

6. Conclusion

In summary, male, coronary heart disease, hypertension, stroke, systolic blood pressure, hematocrit, plasma albumin and ALT are associated with GIB in patients admitted to cardiology. The new risk score model is an accurate risk score that predicts GIB. In addition, when inpatients are stratified at high-risk(a score ≥ 8 points), clinicians should be highly alert to the possibility of GIB.

Abbreviations

GIB: gastrointestinal bleeding; AUROC: the area under the receiver operating characteristic; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PCI: percutaneous coronary intervention; OR: odds ratio; eGFR: estimation of glomerular filtration rate; ROC: the receiver operating characteristic curve.

Declarations

Ethics approval and consent to participate

The ethics committee of The Second Hospital of Hebei Medical University approved the study, and all patients gave written informed consent for participating in the study.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MZ acquired, analyzed and interpreted data, wrote the manuscript. DML revised the manuscript, QW revised the manuscript, XG revised the manuscript, GQG revised the manuscript, RQX revised the manuscript. WC designed the study, acquired, analyzed and interpreted the data, revised the manuscript. All authors read and approved the final manuscript.

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Figures

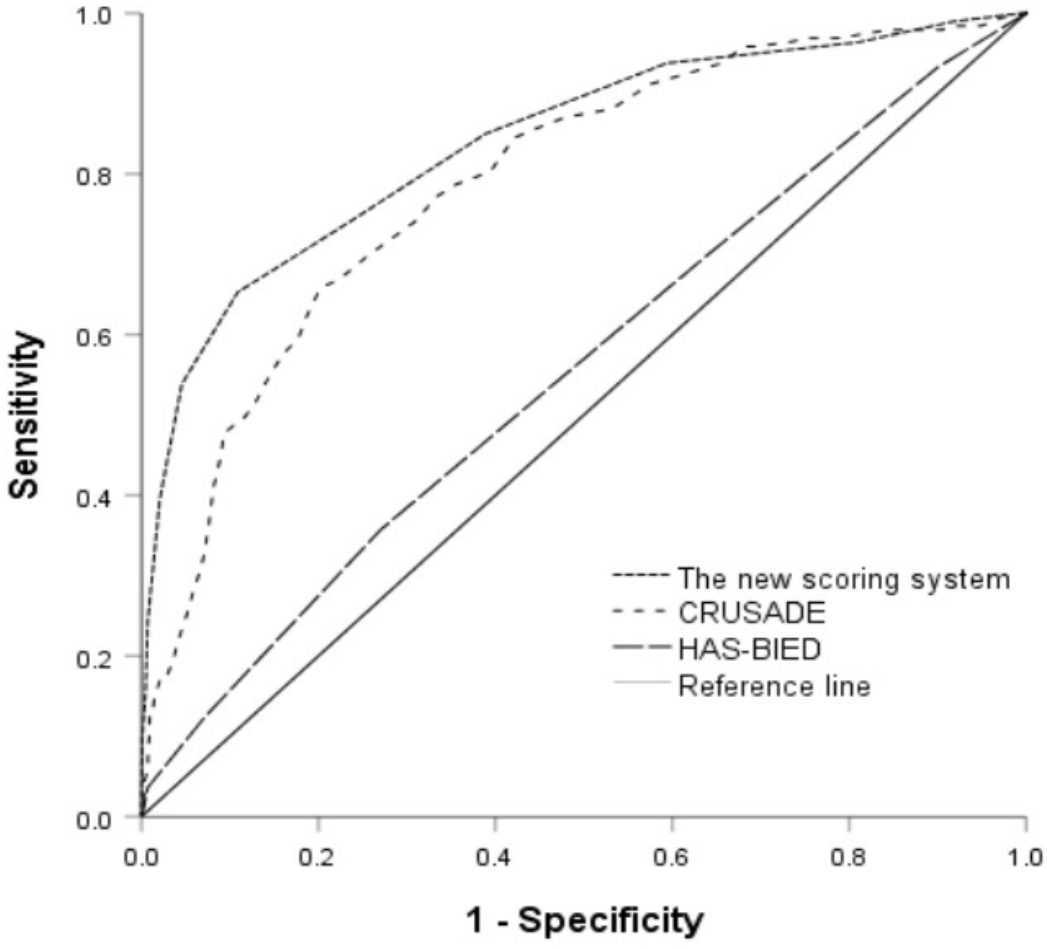

Figure 1

The receiver operating characteristic curve for the new risk score model, HAS-BLED score and CRUSADE score in the validation cohort.

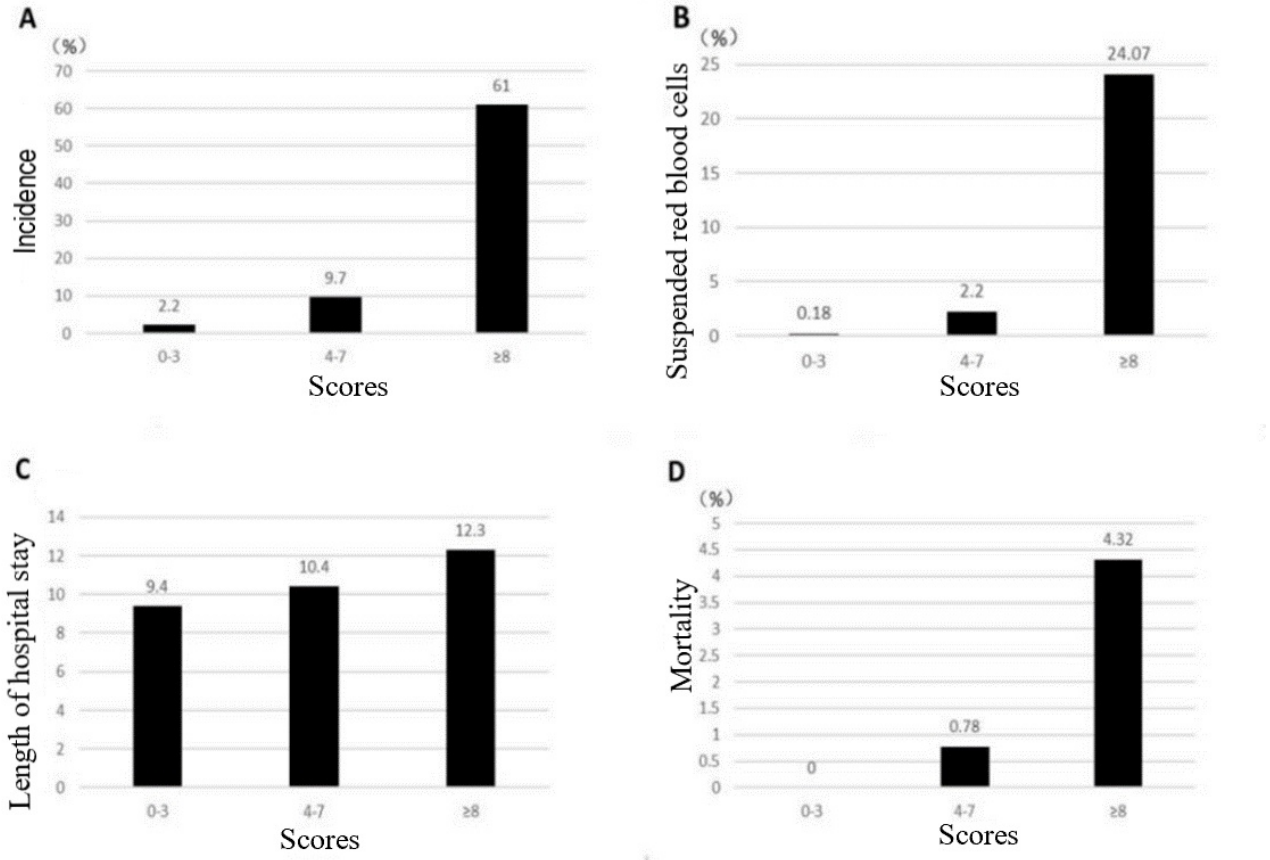

Figure 2

Changes in the incidence of GIB, the proportion of inpatients requiring suspended red blood cells transfusion, length of stay and in-hospital mortality of the patients with 0-3, 4-7, and ≥8 points in the validation cohort.