Severe bleeding following off-pump coronary artery bypass grafting: predictive factors and risk model

Yu LIU1,2, Xing WANG3, Zi-Ying CHEN2, Wen-Li ZHANG2, Lin GUO4, Yong-Quan SUN2, Hong-Zhan CUI2, Ji-Qiang BU2, Jian-Hui CAI1,5,

1. Department of Surgery, Hebei Medical University, Shijiazhuang, China; 2. Department of Cardiac Surgery, the Second Hospital of Hebei Medical University, Shijiazhuang, China; 3. Department of Endocrinology, the Second Hospital of Hebei Medical University, Shijiazhuang, China; 4. School of Industrial and Systems Engineering, University of Oklahoma, Norman, USA; 5. Department of Surgery and Oncology, Hebei General Hospital, Shijiazhuang, China

✉ Correspondence to: drcrpauthor@163.com
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ABSTRACT

BACKGROUND Severe bleeding following cardiac surgery remains a troublesome complication, but to date, there is a lack of comprehensive predictive models for the risk of severe bleeding following off-pump coronary artery bypass grafting (OPCABG). This study aims to analyze relevant indicators of severe bleeding after isolated OPCABG and establish a corresponding risk assessment model.

METHODS The clinical data of 584 patients who underwent OPCABG from January 2018 to April 2020 were retrospectively analyzed. We gathered the preoperative baseline data and postoperative data immediately after intensive care unit admission and used multifactor logistic regression to screen the potential predictors of severe bleeding, upon which we established a predictive model. Using the consistency index and calibration curve, decision curve, and clinical impact curve analysis, we evaluated the performance of the model.

RESULTS This study is the first to establish a risk assessment and prediction model for severe bleeding following isolated OPCABG. Eight independent risk factors were identified: male sex, aspirin/clopidogrel withdrawal time, platelet count, fibrinogen level, C-reactive protein, serum creatinine, and total bilirubin. Among the 483 patients in the training group, 138 patients (28.6%) had severe bleeding; among the 101 patients in the verification group, 25 patients (24.8%) had severe bleeding. Receiver operating characteristic (ROC) curve analysis for the internal training group revealed a convincing performance with a concordance index (C-index) of 0.859, while the area under the ROC curve for the external validation data was 0.807. Decision curve analysis showed that the model was useful for both groups.

CONCLUSIONS Although there are some limitations, the model can effectively predict the probability of severe bleeding following isolated OPCABG and is therefore worthy of further exploration and verification.

Currently, coronary heart disease (CHD) remains a major threat to public health worldwide. Coronary artery bypass grafting (CABG) is considered to be the first choice for the treatment of CHD, especially for complex lesions.[1] To recover the blood flow of the distal coronary artery and achieve complete revascularization of the myocardium, an autologous artery or vein segment is transplanted to the distal segment of the coronary artery demonstrating the primary stenosis. Perioperative bleeding is a common complication of CABG.[2,3] Approximately 15% to 20% of patients consume more than 80% of the blood products used for cardiac surgery.[4] Excessive perioperative bleeding not only escalates the need for blood transfusion but also leads to reoperation and mortality,[5-9] and an increase in the incidence of recurrent myocardial infarction (MI) and stroke.[10] Excessive bleeding is usually associated with a variety of factors. The factors that may affect the haemostatic mechanism include the patient’s individual characteristics (inflammatory conditions,
platelet count and dysfunction, fibrinogen level, and coagulation factor abnormalities, etc.) and surgical factors (operation mode, use of cardiopulmonary bypass, etc.). In addition, the preoperative use of aspirin, clopidogrel, and other drugs in patients with CHD can affect haemostatic function and may increase postoperative bleeding. It is of great importance to predict the risk of postoperative excessive bleeding and blood transfusion and actively take appropriate preventive and therapeutic measures. However, to date, no biomarker has been able to accurately identify patients at high risk of bleeding.

In recent years, many experimental studies have investigated the possible related indicators of excessive bleeding and blood transfusion after cardiac surgery, such as platelet count, fibrinogen level, coagulation factors, and antiplatelet drugs, but none of them has been shown to predict bleeding and blood transfusion after cardiac surgery. A single indicator may not be sufficient to predict an increase in bleeding risk. In addition, due to differences in research schemes, sample sizes, and enrolled research subjects, some research designs have obvious confounding factors, so no consistent conclusion has yet been reached.

To help clinicians effectively predict the risk of severe bleeding and blood transfusion in patients undergoing off-pump coronary artery bypass grafting (OPCABG) for the first time and rapidly identify high-risk patients at the early stage, we carried out this study. Through systematic retrospective screening of clinical characteristics and routine examination indexes of patients, a diagnostic model was constructed and verified. This model allows doctors to make clinical decisions conveniently, and it can also be used as a tool to communicate with patients or their family members.

METHODS

Study Population

Searching the electronic medical record system of the Second Hospital of Hebei Medical University from January 2018 to April 2020, we retrospectively selected 584 patients who underwent isolated OPCABG in the Department of Cardiac Surgery, the Second Hospital of Hebei Medical University, Shijiazhuang, China.

Patients who met the following criteria are eligible for the study: (1) a diagnosis of coronary angiography prior to the operation; (2) a selection of OPCABG based on the “Revascularization of coronary heart disease expert consensus in China”; (3) signed informed consents for the operation obtained from the patient and his or her immediate family members; and (4) age ≥ 60 years. Patients who met any of the following criteria will not be eligible for this study: (1) undergo emergency CABG (defined as emergency CABG class 1–4); (2) previous cardiac surgery history or who needed other cardiac surgery at the same time; (3) continuous warfarin or glucocorticoid use before surgery; (4) platelet counts (< 100 × 10^9/L or > 300 × 10^9/L) were detected in the laboratory before surgery; (5) underwent reoperation due to haemostasis within 24 h after surgery; (6) inflammatory reactions before surgery (infection, active arthritis, etc.) who were taking other anti-inflammatory and analgesic drugs; (7) other organ dysfunction; and (8) tumors or rheumatic immune diseases.

Finally, 584 patients were included in the study (Figure 1), including 483 patients in the training group and 101 patients in the validation group.

The design and protocol (No.2020-R270) of this retrospective study were approved by the Ethics Committee of the Second Hospital of Hebei Medical University, Shijiazhuang, China. The study follows the guidelines of the Helsinki Declaration.

Surgical Procedures

All patients received standardized general anaesthesia and surgical treatment. Each patient was given 1.5 mg/kg heparin before the left internal mammary artery was dissected. When the activated clotting time (ACT) reached 300 s, bypass grafting was started. After bypass grafting, protamine sulfate (0.8 mg/1 mg heparin) was administered for neutralization. The haematocrit was maintained above 25% by using a blood recovery device and transfusion of red blood cells. If bleeding continued after adequate surgical haemostasis and protamine neutralization (confirmed by the ACT), blood transfusion was performed with the consent of the anaesthesiologist and surgeon. Patients were returned to the cardiac surgery intensive care unit (ICU) for treatment based on the standard postoperative treatment procedure.
The total amount of chest tube drainage and total blood transfusion of each patient were measured within 24 h after surgery or before reoperation. Severe bleeding was defined as ≥ 1,000 mL of drainage within 24 h following the operation. The indication for blood transfusion was the haematocrit < 25%. The indications for reoperation due to excessive bleeding were as follows: (1) blood loss > 400 mL in 1 h after the operation; (2) blood loss > 200 mL/h within 4 h after the operation; (3) cardiac tamponade; or (4) sudden increase in drainage with decreased haematocrit, haemodynamic instability or cardiac arrest. The final decision for performing blood transfusion and reoperation was made by the ICU specialists and surgeons.

Clinical Outcomes

The preoperative baseline data of all patients, including demographic characteristics (sex, age, and body mass index), previous medical history (hypertension, hyperlipidaemia, diabetes mellitus, old cerebral infarction, old MI, and previous percutaneous coronary intervention history), preoperative oral antiplatelet drugs (preoperative aspirin and clopidogrel withdrawal time), and routine laboratory tests (haemoglobin, haematocrit, platelet count, alanine aminotransferase, total bilirubin, serum creatinine, prothrombin time, activated partial thromboplastin time, and fibrinogen level), were collected before the operation.

The laboratory test results (haemoglobin, haematocrit, platelet count, high sensitivity C-reactive protein, cardiac troponin I, creatine kinase isoenzyme, N-terminal pro-B-type natriuretic peptide, alanine aminotransferase, total bilirubin, serum cre-
atinine, prothrombin time, activated partial thromboplastin time, and fibrinogen level) and the total amount of drainage within 24 h after the operation were recorded. The amount of cell saver transfusion, red blood cells, and plasma transfusion during the operation were recorded as well.

The preoperative use of aspirin and clopidogrel was defined as the withdrawal time of aspirin ≤ 24 h and the withdrawal time of clopidogrel ≤ 72 h, respectively.

Statistical Analysis

The statistical analyses were performed by using the SPSS 23.0 software (SPSS Inc., Chicago, Illinois, USA) in this study. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. We represent continuous variables to a normal distribution as mean ± SD and compared them with the Student’s t-test; otherwise, we represent them as median (interquartile range) and compared them with the Mann-Whitney U test. Categorical variables are presented as percentages, and the differences between two groups were compared by the Pearson’s chi-squared test or Fisher’s exact probability test. In the training group, the occurrence of severe perioperative bleeding was set as the binary independent variable. Logistic regression analysis was used to screen the independent risk factors for severe bleeding after isolated OPCABG.

Since there were many risk factors investigated in this study, univariable logistic regression was used for preliminary screening of risk factors. To avoid omitting factors, those with a P-value < 0.2 in the univariable analysis were included in multivariable logistics regression. Factors that demonstrated statistical significance (P < 0.05) in the multivariable analysis were determined to be independent risk factors for severe bleeding. Multicollinearity among these potential variables was estimated using the variance inflation factor (VIF).

We used R software (version 4.0.3 for Windows, http://www.r-project.org/) to visualize the analyses, and programming was performed in the RStudio integrated environment (https://www.rstudio.com/). The data of the training group were analysed, and the concordance index (C-index) was obtained. The receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was measured. We quantified the predictive ability of the model with the C-index, calibration curve, decision curve and clinical impact curve. The C-index measures the probability of concordance between the predicted and observed incidence of severe bleeding. The clinical usefulness of the prediction model according to the threshold probability was evaluated by decision curve analysis. The estimated number of patients who would be declared high risk for each risk threshold and a representation of the proportion of those who were cases (true positives) were shown by clinical impact curve analysis.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 584 patients were included in the study, including 483 patients in the training group and 101 patients in the validation group. There were 138 patients (28.6%) with severe bleeding in the training group and 25 patients (24.8%) with severe bleeding in the validation group. Table 1 and Table 2 show the baseline demographic and clinical characteristics data of the training group and the validation group, respectively.

Construction of the Model and Its Performance

In the training group, eight independent risk factors were obtained by multivariable logistic regression analysis (Table 3). In accordance with the regression model, the following indicators were highly associated with the occurrence of severe bleeding: male sex (X1), aspirin (X2)/clopidogrel (X3) withdrawal time, platelet count (X4), fibrinogen level (X5), total bilirubin (X6), serum creatinine (X7), and C-reactive protein (X8); where (X2) and (X3) refer to the withdrawal time before the operation, and (X4–X8) refers to the clinical characteristics data after the patient entered the ICU. These risk factors were used to formulate the following model equation:

\[
\text{Logit } P = -0.739 - 1.308 \times (X1) + 0.581 \times (X2) + 0.545 \times (X3) - 0.245 \times (X4) - 0.619 \times (X5) + 0.538 \times (X6) + 0.461 \times (X7) - 0.546 \times (X8)
\]

The VIFs of these variables were all close to 1.0 (Table 4), indicating that there was no multicollinearity among these variables. The C-index of the
| Variables                                      | Non-severe bleeding (n = 345) | Severe bleeding (n = 138) | P-value |
|-----------------------------------------------|-------------------------------|--------------------------|---------|
| Age, yrs                                      | 64.0 (61.0–71.0)*             | 63.0 (60.5–72.5)*        | 0.204   |
| Male                                          | 260 (75.4%)                   | 89 (64.5%)               | < 0.05  |
| Body mass index, kg/m²                        | 25.5 ± 4.3                    | 25.7 ± 3.9               | 0.625   |
| Hypertension                                  | 226 (65.5%)                   | 83 (60.1%)               | 0.267   |
| Hyperlipidemia                                | 57 (16.5%)                    | 26 (18.8%)               | 0.542   |
| Diabetes mellitus                             | 108 (31.3%)                   | 40 (29.0%)               | 0.618   |
| Prior myocardial infarction                   | 43 (12.5%)                    | 13 (9.4%)                | 0.345   |
| Prior percutaneous coronary intervention       | 25 (7.2%)                     | 9 (6.5%)                 | 0.779   |
| Stroke                                        | 77 (22.3%)                    | 24 (17.4%)               | 0.400   |
| Aspirin                                       | 227 (65.8%)                   | 108 (78.3%)              | < 0.05  |
| Clopidogrel                                   | 93 (27.0%)                    | 52 (37.7%)               | < 0.05  |
| Preoperative laboratory test                  |                               |                          |         |
| Hemoglobin, g/L                               | 132.1 ± 15.1                  | 134.6 ± 14.7             | 0.103   |
| Hematocrit, %                                 | 39.2 ± 4.4                    | 38.5 ± 4.1               | 0.100   |
| Platelet count, × 10⁹/L                       | 214.9 ± 67.3                  | 211.3 ± 63.9             | 0.597   |
| Alanine transaminase, U/L                     | 24.8 (15.4–40.5)*             | 29.6 (21.2–41.2)*        | 0.077   |
| Total bilirubin, μmol/L                       | 11.4 ± 4.2                    | 12.2 ± 4.4               | 0.064   |
| Serum creatinine, μmol/L                      | 71.0 (62.0–81.0)*             | 75.0 (64.5–81.5)*        | 0.183   |
| Prothrombin time, s                           | 11.3 ± 1.0                    | 11.3 ± 0.6               | 0.624   |
| Activated partial thromboplastin time, s      | 30.1 (28.4–32.2)*             | 31.2 (28.8–33.0)*        | < 0.05  |
| Fibrinogen, g/L                               | 3.4 ± 0.7                     | 3.4 ± 0.6                | 0.502   |
| Postoperative laboratory test                 |                               |                          |         |
| Hemoglobin, g/L                               | 114.1 ± 16.1                  | 114.5 ± 19.1             | 0.861   |
| Hematocrit, %                                 | 34.2 ± 4.4                    | 33.3 ± 5.2               | 0.058   |
| Platelet count, × 10⁹/L                       | 178.0 ± 48.9                  | 162.1 ± 47.6             | < 0.05  |
| Alanine transaminase, U/L                     | 25.1 (16.2–46.5)*             | 31.0 (21.4–43.3)*        | 0.260   |
| Total bilirubin, μmol/L                       | 15.2 (11.1–19.6)*             | 16.5 (12.3–22.0)*        | < 0.05  |
| Serum creatinine, μmol/L                      | 77.5 ± 18.1                   | 85.3 ± 20.3              | < 0.05  |
| C-reactive protein, mg/L                      | 17.4 (7.0–66.0)*              | 34.3 (6.5–144.8)*        | < 0.05  |
| Cardiac troponin I, ng/mL                     | 1.0 (0.5–1.8)*                | 1.2 (0.5–2.3)*           | 0.069   |
| Creatine kinase-MB isozyme, U/L               | 27.0 (22.0–33.0)*             | 25.0 (21.0–31.0)*        | 0.123   |
| Prothrombin time, s                           | 12.6 (12.1–13.3)*             | 12.6 (12.0–13.5)*        | 0.913   |
| Activated partial thromboplastin time, s      | 32.7 (29.9–36.6)*             | 32.6 (30.3–36.1)*        | 0.536   |
| Fibrinogen, g/L                               | 2.4 ± 0.5                     | 2.2 ± 0.6                | < 0.05  |
| N-terminal pro-B-type natriuretic peptide, pg/mL | 337.0 (128.0–826.0)* | 304.7 (115.0–785.0)* | 0.482   |
| Cell saver transfusion, mL                    | 450.0 (300.0–800.0)*          | 600.0 (410.0–1144.0)*    | < 0.05  |
| Red blood cells, U                            | 0                              | 0                        | 0.185   |
| Plasma, mL                                    | 400.0 (0.0–400.0)*            | 400.0 (0.0–400.0)*       | 0.302   |
| Postoperative chest drain loss, mL/24 h       | 729.0 (628.0–856.0)*          | 1202.5 (1105.0–1350.0)*  | < 0.05  |

Data are presented as means ± SD or n (%). *Presented as median (interquartile range).
Table 2  Baseline demographic and clinical characteristics of patients with non-severe bleeding and severe bleeding in the validation group.

| Variables                        | Non-severe bleeding (n = 76)    | Severe bleeding (n = 25)       | P-value |
|----------------------------------|---------------------------------|--------------------------------|---------|
| Age, yrs                         | 63.0 (60.5–71.5)                | 65.0 (63.0–73.0)               | 0.051   |
| Male                             | 60 (78.9%)                      | 16 (64.0%)                     | 0.133   |
| Body mass index, kg/m²           | 26.0 ± 3.4                      | 25.1 ± 2.6                     | 0.198   |
| Hypertension                     | 49 (64.5%)                      | 16 (64.0%)                     | 0.966   |
| Hyperlipidemia                   | 11 (14.5%)                      | 4 (16.0%)                      | 1.000   |
| Diabetes mellitus                | 24 (31.6%)                      | 9 (36.0%)                      | 0.683   |
| Prior myocardial infarction      | 13 (17.1%)                      | 5 (20.0%)                      | 0.979   |
| Prior percutaneous coronary intervention | 9 (11.8%)                  | 2 (8.0%)                       | 0.869   |
| Stroke                           | 10 (13.2%)                      | 4 (16.0%)                      | 0.982   |
| Aspirin                          | 43 (56.6%)                      | 17 (68.0%)                     | 0.313   |
| Clopidogrel                      | 20 (26.3%)                      | 12 (48.0%)                     | < 0.05  |

Preoperative laboratory test

| Hemoglobin, g/L                  | 133.4 ± 14.8                    | 132.2 ± 14.1                   | 0.707   |
| Hematocrit, %                   | 39.7 ± 4.4                      | 38.2 ± 4.0                     | 0.144   |
| Platelet count, × 10⁹/L         | 213.2 ± 73.3                    | 205.0 ± 49.8                   | 0.605   |
| Alanine transaminase, U/L       | 26.4 (16.2–43.4)                | 27.0 (18.4–42.1)               | 0.850   |
| Total bilirubin, μmol/L         | 11.0 ± 3.9                      | 11.6 ± 5.0                     | 0.498   |
| Serum creatinine, μmol/L        | 74.4 ± 18.0                     | 75.0 ± 13.4                    | 0.861   |
| Prothrombin time, s             | 11.3 (10.9–11.9)                | 11.4 (11.1–11.9)               | 0.798   |
| Activated partial thromboplastin time, s | 30.0 ± 2.8                  | 30.0 ± 3.4                     | 0.945   |
| Fibrinogen, g/L                 | 3.2 (2.8–3.5)                   | 3.6 (3.0–3.8)                  | 0.105   |

Postoperative laboratory test

| Hemoglobin, g/L                  | 114.5 (105.0–125.0)             | 111.0 (96.0–125.0)             | 0.447   |
| Hematocrit, %                   | 34.3 ± 4.4                      | 32.9 ± 5.7                     | 0.178   |
| Platelet count, × 10⁹/L         | 167.5 ± 44.3                    | 150.6 ± 50.0                   | 0.111   |
| Alanine transaminase, U/L       | 24.3 (16.0–44.9)                | 38.7 (96.0–125.0)              | 0.382   |
| Total bilirubin, μmol/L         | 14.7 ± 6.1                      | 17.4 ± 6.1                     | 0.058   |
| Serum creatinine, μmol/L        | 75.5 (64.5–93.5)                | 81.7 (74.7–91.7)               | 0.207   |
| C-reactive protein, mg/L        | 17.2 (8.4–43.9)                 | 23.2 (5.1–124.2)               | 0.467   |
| Cardiac troponin I, ng/mL       | 1.1 (0.5–1.8)                   | 1.0 (0.5–2.4)                  | 0.747   |
| Creatine kinase-MB isozyme, U/L | 27.2 ± 9.3                      | 29.8 ± 10.7                    | 0.245   |
| Prothrombin time, s             | 12.7 (12.0–13.3)                | 12.8 (12.0–13.9)               | 0.447   |
| Activated partial thromboplastin time, s | 28.5 ± 3.6                  | 27.7 ± 3.8                     | 0.353   |
| Fibrinogen, g/L                 | 2.4 ± 0.5                       | 2.3 ± 0.6                      | 0.390   |
| N-terminal pro-B-type natriuretic peptide, pg/mL | 405.4 ± 199.5              | 398.2 ± 229.0                  | 0.880   |
| Cell saver transfusion, mL      | 450.0 (300.0–700.0)             | 600.0 (350.0–1150.0)           | 0.189   |
| Red blood cells, U              | 0                               | 0                               | 0.355   |
| Plasma, mL                      | 400.0 (0.0–400.0)               | 400.0 (50.0–575.0)             | 0.227   |
| Postoperative chest drain loss, mL/24 h | 660.0 (610.0–950.0)             | 1160.0 (1052.5–1420.0)         | < 0.05  |

Data are presented as means ± SD or n (%). *Presented as median (interquartile range).
model established with the data from the training group was 0.859; and the AUC was also 0.859 (95% CI: 0.823–0.896), which consistent with the value of the C-index. Calibration of the model revealed an R² of 0.464, a Brier score of 0.128 and an unreliability test P-value of 0.910, with a curve slope of 1.0 and an intercept of 0. The cut-off value was 0.216, with a sensitivity and specificity of 88.4% and 67.8%, respectively (Figures 2–5).

Model Validation

With the data from the validation group, the C-index was 0.807, and the cut-off value was 0.165, with a sensitivity and specificity of 88.0% and 67.1%, respectively. The curve slope was 1.0, and the intercept was 0 (Figures 2–5).

DISCUSSION

Coronary atherosclerotic heart disease is one of the main diseases threatening human health. The strategy for coronary revascularization often depends on the degree of coronary artery stenosis. With the ageing of society and the continued progress in medical coronary intervention technology, the number of elderly patients with severe coronary artery disease and complicated complications who require CABG is continuously increasing. Especially for patients with SYNTAX scores greater than 32, coronary artery bypass grafts are more suitable.[16] Although the perioperative blood management strategy has been used to considerable success, it still needs to be further explored and strengthened.

As perioperative blood loss and transfusion are impacted by many factors and mechanisms, previous studies on risk prediction that involved stratification of a single factor have been unable to meet clinicians’ demands. Therefore, a risk score or model composed of various indicators would be more conducive to a relatively accurate detection and diagnosis. In this study, an easy-to-perform prediction model was constructed to estimate the individualized probability of severe perioperative blood loss in OPCABG.

Based on historical research and clinical experience, the potential factors selected were tested in the training group for their possible correlation with severe perioperative blood loss. Logistic multivariable analysis showed that male sex, aspirin/clopidogrel

| Table 3  | Multivariate analysis of logistic regression model. |
|---------|-----------------------------------------------|
| Variables     | β    | SE  | Wald $\chi^2$ value | $P$-value | Odds ratio (95% CI) |
| Male           | -1.308 | 0.314 | 17.351 | 0 | 0.270 (0.146–0.500) |
| Aspirin        | 0.581  | 0.260 | 4.982  | 0.026 | 1.787 (1.073–2.976) |
| Clopidogrel    | 0.545  | 0.237 | 5.307  | 0.021 | 1.725 (1.085–2.745) |
| Postoperative platelet | -0.245 | 0.064 | 14.840 | 0 | 0.783 (0.691–0.887) |
| Postoperative total bilirubin | 0.538 | 0.102 | 27.837 | 0 | 1.712 (1.402–2.091) |
| Postoperative fibrinogen    | -0.619 | 0.213 | 8.469  | 0.004 | 0.539 (0.355–0.817) |
| Postoperative C-reactive protein | -0.546 | 0.262 | 4.344  | 0.037 | 0.579 (0.347–0.968) |
| Postoperative serum creatinine | 0.461 | 0.215 | 4.616  | 0.032 | 1.586 (1.041–2.415) |
| Constant term | -0.739 | 0.869 | 0.723  | 0.395 | |

| Table 4  | Multicollinearity analysis of related factors. |
|---------|-----------------------------------------------|
| Model                                | Collinearity statistics |
|                                  | Tolerance | Variance inflation factor |
| Male                          | 0.660 | 1.515 |
| Aspirin                        | 0.948 | 1.055 |
| Clopidogrel                     | 0.977 | 1.023 |
| Postoperative platelet         | 0.978 | 1.023 |
| Postoperative total bilirubin  | 0.665 | 1.503 |
| Postoperative fibrinogen       | 0.938 | 1.066 |
| Postoperative C-reactive protein | 0.851 | 1.175 |
| Postoperative serum creatinine | 0.981 | 1.019 |
withdrawal time, platelet count, fibrinogen level, C-reactive protein, serum creatinine, and total bilirubin were independent risk factors for severe blood loss.

Among all the possible factors, the preoperative withdrawal time of aspirin and clopidogrel had the exact impact on the probability of severe bleeding. As one of the cornerstones of the treatment of CHD, aspirin and clopidogrel have been indicated to be effective in reducing mortality, MI, and stroke,[17] significantly reducing the risk of major cardiovascular adverse events,[18] effectively improving the patency rate of the venous bridge,[19–21] and increasing the risk of perioperative bleeding. However, platelet transfusion can reverse the effect of aspirin on the platelet inhibition of aggregation.[22,23] Nevertheless, clinically, all patients who need CABG, regardless of whether they need emergency or selective surgery, are treated with aspirin and/or clopidogrel. Because it can be almost impossible to predict the individual differences between patients, whenever patients who are taking these drugs need CABG surgery, both they and their doctors have to confront this dilemma. According to European guidelines,[24] patients at low risk of perioperative bleeding can continue taking aspirin, as there is no need to stop taking it before surgery.[25–27] For clopidogrel, the exact percentage increase in the of bleeding following CABG performed one to four days after drug discontinuation is not clear. In one study, the individual differences were large, but the percentage of patients with fatal bleeding did not increase significantly, only the percentage who underwent blood transfusion was shown to have increased.[28] There-

Figure 2  Receiver operating characteristic curves of the model to predict the probability of severe bleeding in the training group (A) and validation group (B). AUC: area under the curve.

Figure 3  Calibration curves of the model to predict the probability of severe bleeding in the training group (A) and validation group (B).
fore, from the perspective of reducing the bleeding risk, elective CABG should be performed five days after stopping clopidogrel; while for patients who need CABG as soon as possible, surgery should take place 24 h after stopping clopidogrel to reduce severe bleeding complications.\(^\text{29}\) In conclusion, the risk of perioperative thromboembolism and bleeding complications should be taken into account in emergency situations. This shows the importance of exploring prediction models of perioperative severe bleeding.

This study also analysed the correlation between severe bleeding and preoperative and postoperative haemoglobin, haematocrit, platelet count, fibrinogen level, and coagulation indicators (prothrombin time, activated partial thromboplastin time). Logistic regression analysis showed that compared with their preoperative counterparts, postoperative platelet count and fibrinogen level had a higher correlation with severe bleeding, which contributed to their being independent indexes predicting severe postoperative blood loss. Previous studies confirmed that there was no significant correlation between preoperative or postoperative haematocrit, haemoglobin, prothrombin time, and activated partial thromboplastin time and perioperative blood loss or transfusion demand.\(^\text{30–32}\) To date, the common risk factor for postoperative bleeding has been low fibrinogen level.\(^\text{33,34}\) This may be because fibrinogen level is the first to be depleted in massive haemorrhage and haemodilution.\(^\text{35}\) However, despite the association with bleeding, the positive pre-

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**Figure 4** Decision curve analysis curves of the model to predict the probability of severe bleeding in the training group (A) and validation group (B).

**Figure 5** Clinical impact curves of the model to predict the probability of severe bleeding in the training group (A) and validation group (B). Clinical impact curve for the biomarker-based risk model. Of 1,000 patients, the heavy red solid line shows the total number who would be deemed high risk for each risk threshold. The blue dashed line shows how many of those would be true positives (cases).
predictive value of low fibrinogen level remains poor.\cite{24,33} This again proves that the risk of severe perioperative blood loss cannot be effectively predicted using any single factor. Because both the preoperative fibrinogen level < 1.5 g/L\cite{36} and postoperative hypofibrinogenemia\cite{37} are associated with increased postoperative bleeding, some scholars have proposed that fibrinogen supplementation can be used as a treatment measure for patients with postoperative bleeding after cardiac surgery.\cite{38} However, there is no consensus on whether fibrinogen supplementation can ease perioperative bleeding and reduce the need for blood transfusion. The latest European guidelines\cite{24} do not recommend preventively using fibrinogen level to reduce the risk of postoperative bleeding and blood transfusion.

In addition, platelet count < 100 × 10⁹/L has also been associated with bleeding risk and an increased need for blood transfusion.\cite{12} In the 2017 European guidelines for blood management for adult patients undergoing cardiac surgery, it is recommended that patients with platelet counts less than 50 × 10⁹/L or antiplatelet therapy with bleeding complications should receive a blood transfusion. Nonetheless, platelet transfusion increases the risk of recurrence of MI in patients after CABG.\cite{39} Additionally, platelet function has an impact on bleeding and coagulation. Preoperative detection of platelet function can help assess thrombosis and bleeding risk and guide blood transfusion treatment.\cite{40} However, the evidence level in existing studies is low. Hence, the latest guidelines in China, Europe, and the United States do not recommend platelet function tests as routine in the perioperative period.\cite{24,29,41}

Studies have shown that ageing and female sex are risk factors for postoperative bleeding.\cite{42} In our multivariable logistic regression analysis, male sex was a protective factor for postoperative bleeding, but we could not show the direct effect of advanced age on postoperative bleeding, and there was no significant difference in age between the two groups.

Chronic kidney disease is another independent risk factor for coronary artery disease and is associated with a significant increase in adverse consequences.\cite{43} As an important indicator of liver metabolic disorder, abnormal total bilirubin is associated with arrhythmia and heart failure.\cite{44} It is also an independent risk factor for death after CABG.\cite{45–47} Patel, et al.\cite{45} believes that an increase in serum creatinine and total bilirubin after the operation is an independent risk factor for mortality. Lopes, et al.\cite{42} and Lutz, et al.\cite{48} suggest that renal insufficiency and elevated preoperative serum creatinine levels are important predictors of massive haemorrhage. However, others have different opinions. Gunertem, et al.\cite{49} believes that an increase in serum creatinine before the operation has no direct effect on postoperative bleeding. By comparing preoperative and postoperative serum creatinine with total bilirubin, we identified that the former can predict the risk of severe bleeding more effectively. Total bilirubin after cardiac surgery may be related to preoperative cardiac function, liver function, cardiopulmonary bypass and blood transfusion. Correlation analysis showed that intraoperative blood transfusion and postoperative total bilirubin were not significantly correlated (r = −0.035, P = 0.442).

Inflammation activation is also related with CHD. The perioperative inflammatory response has been a consistent focus of clinicians. Inflammation can cause coagulation and damage the fibrinolytic system.\cite{50} High sensitivity C-reactive protein is a commonly used inflammatory index in clinical practice. As a risk factor for atherosclerosis, it is related to the occurrence of adverse cardiovascular events.\cite{51,52} Surgical trauma may lead the body to produce a large amount of C-reactive protein\cite{53,54} and then stimulate fibrin deposition.\cite{55} In mouse carotid artery experiments, Wu, et al.\cite{56} found that C-reactive protein can increase the expression of tissue factor (TF) in vascular smooth muscle cells in vitro and in vivo, which then forms TF-VIIa factor complex with coagulation factor VIIa (FVIIa), activating coagulation factor VIII (FVIII), upregulating its activity, and initiating the coagulation cascade. This is consistent with our study; that is, a higher postoperative C-reactive protein concentration was correlated with less postoperative blood loss.

**LIMITATIONS**

This study has the following limitations. Firstly, this is a single-centre retrospective study, lacking external data sets for validation. The sample size was relatively small, and multi-centre, prospective
validation of the risk model may be required. Secondly, the model was developed for the patients who underwent isolated OPCAB for the first time. The sample homogeneity was good and targeted, but the generalizability is limited. Last but not least, our study aimed to predict severe bleeding within 24 h following OPCAB, but in most cases, there will still be blood loss after 24 h. However, clinicians can implement targeted measures in the early postoperative period, and the amount of blood loss after 24 h is related to the medication and other factors. Regardless, we expect to develop better performing models to predict the risk of severe bleeding following OPCAB in the future.

CONCLUSIONS

In summary, our model provides a platform for surgeons to comprehensively evaluate the above predictors. Despite some limitations, this model can still accurately predict the probability of severe bleeding after OPCAB and is worthy of further exploration and validation.

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