Cardiothoracic Anesthesia, Respiration and Airway

Prediction of massive blood transfusion in cardiac surgery

[La prédiction d'une transfusion massive en cardiochirurgie]

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Purpose: In cardiac surgery with cardiopulmonary bypass (CPB), excessive blood loss requiring the transfusion of multiple red blood cell (RBC) units is a common complication that is associated with significant morbidity and mortality. The objective of this study was to develop a prediction rule for massive blood transfusion (MBT) that could be used to optimize the management of, and research on, at-risk patients.

Methods: Data were collected prospectively over the period from 2000 to 2005, on patients who underwent surgery with CPB at one hospital. Patients who received $\geq$ five units of RBC within one day of surgery were classified as MBT. Logistic regression was used to appropriately select and weigh perioperative variables in the prediction rule, which was developed on the initial 60% of the sample and validated on the remaining 40%.

Results: Of the 10,667 patients included, 925 (8.7%) had MBT. The clinical prediction rule included 12 variables (listed in order of predictive value: CPB duration, preoperative hemoglobin concentration, body surface area, nadir CPB hematocrit, previous sternotomy, preoperative shock, preoperative platelet count, urgency of surgery, age, surgeon, deep hypothermic circulatory arrest, and type of procedure) and was highly discriminative (c-index = 0.88). In the validation set, those classified as low-, moderate-, and high-risk by a simple risk score derived from the prediction rule had a 5%, 27%, and 58% chance of MBT, respectively.

Conclusion: A clinical prediction rule was developed that accurately identified patients at low-risk or high-risk for MBT. Studies are needed to determine the external generalizability and clinical utility of the prediction rule.

Objectif : En cardiochirurgie avec circulation extracorporelle (CEC), une perte de sang excessive exigeant la transfusion de multiples unités de culots globulaires (CG) est une complication fréquente associée à une morbidité et à une mortalité significatives. L'objectif de notre étude était d'élaborer une règle de prédiction pour la transfusion massive (TM) qui pourrait être utilisée pour optimiser la recherche sur les patients à risque, et leur traitement.

Méthode : Les données prospectives ont été recueillies sur les patients qui ont subi une opération avec CEC dans un hôpital entre 2000 et 2005. Les patients ayant reçu $\geq$ cinq unités de CG en moins d'un jour postopératoire ont été classés comme TM. La régression logistique a permis de choisir et pondérer convenablement les variables périopératoires de la règle de prédiction qui a été élaborée d'après les premiers 60 % de l'échantillon et validée sur les 40 % restant.

Résultats : Des 10 667 patients inclus, 925 (8,7 %) avaient eu une TM. La règle de prédiction clinique incluait 12 variables (présentées par ordre de valeur prédictive : durée de la CEC, concentration d'hémoglobine préopératoire, surface corporelle, hématocrite minimal de la CEC, sternotomie antérieure, choc

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préopératoire, numération plaquettaire préopératoire, urgence de l'opération, âge, chirurgien, arrêt circulatoire hypothermique profond et type d'opération) et était hautement discriminative ($c\text{-index} = 0,88$). Dans l'ensemble de validation, les patients classés à risque faible, modéré et élevé par une cote de risque simple, à partir de la règle de prédiction, présentaient respectivement 5 %, 27 % et 58 % de risque d'avoir une TM.

Conclusion : Une règle de prédiction clinique a été élaborée, qui reconnaît précisément les patients à faible ou haut risque d'un TM. D'autres études devront déterminer la généralisabilité externe et l'utilité clinique de la règle de prédiction.

EXCESSIVE blood loss necessitating the transfusion of multiple units of red blood cells (RBC) is a relatively common complication of cardiac surgery that is independently associated with serious postoperative adverse events including sepsis, acute respiratory distress syndrome, renal failure, and death.¹⁻⁴

A clinical prediction rule that could accurately estimate the probability of massive blood transfusion (MBT) after cardiac surgery would have clinical and research relevance. Such a prediction rule could be used to rationalize clinical management by, for example, limiting the use of expensive blood conservation modalities (such as aprotinin or cell salvage and washing) in patients identified as being at low-risk for MBT. It could also be used to investigate, and, if found to be appropriate, institute preventive measures (such as modifying risk factors or prophylactic administration of hemostatic agents or coagulation factors) to reduce the risk of MBT in those identified as being at high-risk for MBT.

Previous studies have identified several variables that are associated with RBC transfusion or excessive blood loss in cardiac surgery (Table I).^{2,5-21} However, no multivariable prediction rules have been developed that can be used by clinicians to accurately estimate the probability of MBT in cardiac surgical patients. Consequently, we sought to develop and validate such a prediction rule in a cohort of patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) at a single institution.

Methods

Patient population and data collection

Following institutional ethics approval, data on consecutive patients who underwent cardiac surgery with CPB at the Toronto General Hospital from January 2000 to May 2005 were obtained from prospec-

tively collected databases that have been previously described.^{4,22} Full-time research personnel blinded to the details of this current study adjudicated all patient outcomes included in the databases. Quality assurance checks of the databases have consistently revealed a missing data rate of less than 2% and an error rate of less than 2%. For this study, patients with missing data that could not be obtained from their hospital records were excluded from the analyses. For patients who underwent more than one cardiac operation with CPB at the study institution during the study period, only their first surgery was used in the analyses.

Clinical practice

Hemostatic and CPB management during the study period were as follows. Antifibrinolytics [tranexamic acid (Cyclokapron®, Pharmacia & UpJohn Inc., Mississauga, ON, Canada) 50 to 100 mg·kg⁻¹ or aprotinin (Trasylol®, Bayer AG, Toronto, ON, Canada) 6 x 10⁶ units] were routinely administered to all patients. Institutional guidelines recommended that aprotinin be reserved for patients who had active endocarditis, were undergoing complex procedures requiring prolonged CPB support, or had at least two previous sternotomies. Anticoagulation for CPB was achieved with heparin to maintain an activated clotting time above 480 sec. The CPB circuit (non-heparin coated; membrane, hollow fibre oxygenator; roller pump) was primed with 1.8 L of Ringer's lactate and 50 mL of 20% mannitol. Albumin (5% or 25%) and synthetic colloids (Pentaspán®, Bristol-Myers Squibb, Montreal, QC, Canada) were used at the discretion of the clinical team. Management of CPB included systemic temperature drift to 34°C, alpha-stat pH management, targeted mean perfusion pressure between 50–70 mmHg, and pump flow rates of 2.0–2.4 L·min⁻¹·m⁻². Myocardial protection was achieved with intermittent antegrade and, occasionally, retrograde blood cardioplegia. When necessary, deep hypothermic circulatory arrest (DHCA) was achieved by cooling to 20–28°C, depending on the anticipated duration of circulatory arrest. Neuroprotection was carried out with antegrade or retrograde cerebral perfusion at the discretion of the operating surgeon. When circulatory arrest was carried out for very short periods of time, cerebral perfusion was often omitted. Pericardial blood was salvaged into the cardiotomy suction reservoir and re-infused via the CPB circuit for as long as patients were anticoagulated. After separation from CPB, heparin was neutralized with protamine sulphate to a target activated clotting time within 10% of baseline.

Perioperative blood management during the study period was as follows. To guide RBC transfusions,

TABLE I Previously identified clinical variables associated with RBC transfusion or excessive blood loss in cardiac surgery

<i>Variables</i>	<i>Risk factors for excessive blood loss References</i>	<i>Risk factors for ≥ 1 RBC transfusion References</i>	<i>Analyzed in the current study</i>
Female sex	13-15	5-10	Yes
Male sex	16		Yes
Older age	2,14,15,17-20	5-11	Yes
Lower weight, body mass index, or body surface area	14,17,18,20	5,8-10	Yes
Lower baseline hemoglobin concentration	14,19-21	5-8,10	Yes
Lower RBC volume or mass	19,21	9,11,12	Yes
Renal dysfunction	2,14,20	6,7,9,10,12	Yes
Recent cardiac catheterization		6,7	Yes
Other co-morbidities (diabetes, peripheral vascular disease, left ventricular dysfunction, congestive heart failure, shock, non-smoker, NYHA classification)	14,15	6,7,9,10	Yes
Lower albumin		9	No
Coagulation defect (elevated INR, elevated bleeding time, thrombocytopenia)	14,19	6,7,12	Yes
Preoperative heparin	14,19,22		Yes
Preoperative acetylsalicylic acid	9,19		Yes
Other antiplatelet drugs	15		No
Non-elective surgery	17,20	9,10	Yes
Complex surgery	2,22	12	Yes
Previous sternotomies	9,14,19,20,22	6,7,9,10	Yes
Longer CPB duration	2,9,16,18,20-22	12	Yes
Nadir hematocrit during CPB	16		Yes
Lowest temperature during CPB	20		Yes
Protamine insufficiency/excess	9		No
Use of antifibrinolytic drugs	20		Yes
Surgeon	16		Yes
Hospital		6	Not applicable

RBC = red blood cells; NYHA = New York Heart Association; INR = international normalized ratio; CPB = cardiopulmonary bypass.

hematocrit concentrations were measured before surgery, before CPB, every 15 min during CPB, every 30 min after CPB in the operating room, upon arrival and every four hours thereafter in the intensive care unit for the first 24 hr after surgery (and more frequently in bleeding or unstable patients). Leukoreduced RBC concentrates were transfused to maintain the hematocrit concentration at or above 18–20% during CPB, and at or above 24–27% after CPB.

Platelet counts, partial thromboplastin time, prothrombin time and international normalized ratio (INR) were routinely measured before surgery and upon arrival to the intensive care unit after surgery. During surgery, these tests were performed at the discretion of the clinical team in patients with prolonged CPB or microvascular hemorrhage following termination of CPB and neutralization of heparin. Indications for platelet transfusion included a platelet count of $< 50 \times 10^9 \cdot L^{-1}$, ongoing hemorrhage after complete reversal of heparin and a platelet count of $< 80 \times 10^9 \cdot L^{-1}$, or ongoing hemorrhage after prolonged CPB (> 2 hours) was considered prolonged by most clinicians) irrespective of platelet counts. In cases where

the risk of developing a qualitative platelet disorder after CPB was deemed to be high (e.g., recent use of long-acting platelet glycoprotein IIb/IIIa receptor antagonist therapy, high-dose clopidogrel, or CPB > 3 hours), platelets were at times transfused prophylactically upon termination of CPB. All platelets (random donor or single donor) were leukoreduced by the Canadian Blood Services. Fresh frozen plasma was transfused to bleeding patients if the INR was greater than 1.5 after complete neutralization of heparin with protamine. Owing to 30 min turnaround times for coagulation tests, fresh frozen plasma and platelets were at times transfused empirically in bleeding patients. Cryoprecipitate transfusion was guided by fibrinogen levels, which were measured in bleeding patients. Patients received eight units of cryoprecipitate if their fibrinogen level was less than $1 \text{ g} \cdot L^{-1}$.

Changes in blood management practice during study period

In November 2002, a clinical protocol for the off-label use of activated recombinant factor VII (NiaStase®, Novo Nordisk, Mississauga, ON, Canada) in patients

with excessive, refractory hemorrhage after cardiac surgery was introduced at our institution, the details of which have been described previously.²³ In January 2003, the processing times for blood gas and hematocrit measures were reduced to two to five minutes from ten to 15 min owing to the introduction of a point-of-care system. Finally, throughout the study period there was a gradual increase in the RBC transfusion trigger during CPB, likely as a result of our observations that hematocrit concentrations below 20% were associated with increased morbidity.^{22,24}

Dependent and predictor variables

The primary definition for MBT was $\geq$ five units of RBC transfused within one day of surgery. This cutoff was based on the distribution of perioperative RBC transfusion in our patient population (corresponding to the 90th percentile) as well as on the independent relationship between the number of units of RBC transfused and adverse postoperative events.⁴ To explore the predictive value of clinical variables associated with greater blood loss, a second classification for MBT using a cutoff of $\geq$ seven units of RBC within one day of surgery (95th percentile) was also assessed.

Predictor variables included perioperative variables previously shown to be associated with perioperative blood loss (Table I), as well as several variables related to adverse postoperative outcomes.

Statistical analyses

SASTM version 8.2 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses. Categorical variables were summarized as frequencies and percentages, continuous variables as means and standard deviations if normally distributed, and medians and interquartile ranges if not normally distributed.

Patients operated on from January 2000 to December 2002 were used for model development (training set) and those operated on from January 2003 to May 2005 were used for model validation (validation set). January 2003 was used as the cutoff because it correlated with the changes of practice noted above and was therefore anticipated to result in training and validation sets that would differ from each other, allowing for a more robust test of the validity of the model. Characteristics of the two groups were compared using the t-test or Wilcoxon rank sum test for continuous variables and the Chi-square test for categorical variables.

Multivariable logistic regression was used to appropriately select and weigh the predictor variables for inclusion in the prediction rule.²⁵ Bivariate analysis

TABLE II Red blood cell transfusion within one day of surgery in the entire patient population

# of units of RBC	Frequency	%
0	4553	43
1	1681	16
2	1703	16
3	972	9
4	854	8
5	285	2.7
6	170	1.6
7	114	1.1
8	73	0.7
9	62	0.6
10	49	0.5
> 10	172	1.6

RBC = red blood cells.

(using the Chi-square test for categorical variables and the t-test or Wilcoxon rank-sum test for continuous variables) was first carried out to assess the unadjusted relationship between the predictor variables and MBT in the training set. The shape of the relationships between the continuous predictor variables and MBT (logit transformation) were assessed using restricted cubic spline functions.²⁵ Based on this analysis, some variables were either mathematically transformed or categorized for the logistic regression analysis.²⁵

Backward stepwise logistic regression modelling was then carried out to construct the model for the prediction rule. All significant ($P < 0.1$) predictor variables were considered for inclusion in the model. Variable retention in the model was guided by the variables' Wald χ^2 statistic and co-linearity and interaction issues.²⁵ For comparison, a second model was constructed using the second cutoff of $\geq$ seven units of RBC as the dependent variable, using similar modelling steps. The models' calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test (the larger the P value, the better the fit), and discriminative ability was assessed by the c-index [which is equivalent to the area under the receiver operating characteristic (ROC) curve].²⁵

Based on the performance of the primary model ($\geq$ five units of RBC) at various probability cutoffs, optimal cutoffs were identified for classifying patients as being at low, moderate, or high-risk for MBT. Since application of logistic regression models involves complex calculations, a simple risk score was developed by categorizing all continuous variables in the prediction rule based on the shape of their spline function in the logistic regression analysis, and assigning a risk derived

TABLE III Comparison of the training and validation sets (for selected covariates and outcomes)

<i>Variables</i>	<i>Training set (n= 6,651)</i> <i>Mean ± SD or n (%)</i>	<i>Validation set (n= 4016)</i> <i>Mean ± SD or n (%)</i>	<i>Comparisons</i> <i>(P value)</i>
<i>Patient related covariates</i>			
Age (yr)	62 ± 12	62 ± 13	0.3
Female	1662 (25)	1117 (28)	< 0.01
Body surface area (m ²)	1.91 ± 0.22	1.89 ± 0.23	0.05
Hypertension	3642 (55)	2366 (59)	< 0.01
Diabetes mellitus (type I or II)	1713 (26)	1096 (27)	0.07
Peripheral vascular disease (history of aortoiliac, femoropopliteal, or carotid artery disease)	980 (15)	598 (15)	0.8
Cerebrovascular disease (history of stroke or transient ischemic attacks)	617 (9)	345 (9)	0.2
Atrial fibrillation	420 (6)	293 (7)	0.06
Left ventricular ejection fraction < 20%	230 (3)	150 (4)	0.5
Congestive heart failure	1488 (22)	909 (23)	0.7
Unstable angina (within 30 days of surgery)	2776 (42)	1351 (34)	< 0.01
Recent myocardial infarction (within 30 days of surgery)	1042 (16)	605 (15)	0.4
Recent cardiac catheterization (within 2 days of surgery)	679 (10)	413 (10)	0.9
Endocarditis (at time of surgery)	59 (0.9)	41 (1.0)	0.5
Shock (intra-aortic balloon pump or inotropes at time of surgery)	233 (3.5)	113 (2.8)	0.04
Abnormal preoperative renal function (creatinine > 100 µmol·L ⁻¹ in women; > 110 µmol·L ⁻¹ in men; or on dialysis)	1345 (20)	671 (17)	< 0.01
Preoperative thrombocytopenia (platelet count < 150 × 10 ⁹ ·L ⁻¹)	490 (7)	358 (9)	< 0.01
Preoperative international normalized ratio > 1.5	208 (3)	122 (3)	0.8
Preoperative hemoglobin (g·L ⁻¹)	134 ± 15	134 ± 16	0.1
Acetylsalicylic acid within one week of surgery	668 (10)	721 (18)	< 0.01
On heparin (<i>iv</i> or low molecular weight) before surgery	1355 (20)	938 (23)	< 0.01
<i>Surgery related covariates</i>			
Procedure other than isolated CABG or single valve	1690 (25)	1357 (34)	< 0.01
Non-elective surgery	547 (8)	322 (8)	0.7
Redo sternotomy	513 (8)	394 (10)	< 0.01
Deep hypothermic circulatory arrest	237 (3.6)	163 (4.1)	0.2
Received aprotinin instead of tranexamic acid	312 (5)	421 (10)	< 0.01
CPB-duration (min)	102 ± 38	103 ± 39	0.4
Nadir hematocrit during CPB < 20%	1192 (18%)	529 (13%)	< 0.01
Lowest temperature during CPB (°C) (excluding circulatory arrest patients)	33.8 ± 2.4	33.9 ± 1.9	< 0.01
<i>Outcomes</i>			
Discharge hemoglobin (g·L ⁻¹)	101 ± 13	101 ± 13	0.1
Re-exploration	405 (6)	281 (7)	0.06
In-hospital death	123 (1.8)	73 (1.8)	0.8
≥ 5 RBC units within one day of surgery	476 (7%)	449 (11%)	< 0.01
≥ 7 RBC units within one day of surgery	243 (4%)	219 (5%)	< 0.01

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; RBC = red blood cells.

from the β coefficients of the variables in the logistic regression model. The predictive accuracy of the prediction rule and the simplified risk score were assessed in the validation set.

Data and medical records of a sample (identified randomly based on date of surgery) of patients who had MBT, but were misclassified by the prediction rule as low-risk, were reviewed to obtain the reasons for excessive blood loss.

Results

A total of 10,667 patients who underwent cardiac surgery with CPB during the study period were included in the analysis (< 1% of cases were deleted due to missing variables). Overall, 925 (8.7%) and 470 (4.4%) patients received ≥ five and ≥ seven RBC units within one day of surgery, respectively (Table II). A total of 6,651 consecutive patients were assigned to the training set and the remaining 4,016 patients were assigned to the validation set. The training and valida-

TABLE IV Unadjusted (bivariate) relationship of covariates and outcomes with massive blood transfusion (≥ 5 U of RBC within one day of surgery) in the training set

<i>Variables*</i>	<i>MBT patients</i> (<i>n</i> = 476) <i>Mean $\pm$ SD or n (%)</i>	<i>Others</i> (<i>n</i> = 6175) <i>Mean $\pm$ SD or n (%)</i>	<i>Comparisons</i> (<i>P</i> value)
<i>Patient related covariates</i>			
Age (yr)	65 $\pm$ 13	62 $\pm$ 12	< 0.0001
Female	202 (42)	1460 (24)	< 0.0001
BSA (m ²)	1.8 $\pm$ 0.2	1.9 $\pm$ 0.2	< 0.0001
Hypertension	265 (56)	3377 (55)	0.7
Diabetes mellitus	113 (24)	1600 (26)	0.3
Peripheral vascular disease	87 (18)	893 (14)	0.02
Cerebrovascular disease	60 (13)	557 (9)	0.01
Left ventricular ejection fraction < 20%	36 (8)	194 (3)	< 0.0001
Congestive heart failure	220 (46)	1268 (21)	< 0.0001
Unstable angina	202 (42)	2574 (42)	0.7
Recent myocardial infarction	112 (24)	930 (15)	< 0.0001
Recent cardiac catheterization	87 (18)	592 (10)	< 0.0001
Endocarditis	22 (5)	37 (0.6)	< 0.0001
Preoperative shock	56 (12)	177 (3)	< 0.0001
Preoperative renal dysfunction	155 (33)	1190 (19)	< 0.0001
Preoperative thrombocytopenia	69 (15)	421 (7)	< 0.0001
Preoperative international normalized ratio > 1.5	24 (5)	184 (3)	0.02
Preoperative hemoglobin (g·L ⁻¹)	122 $\pm$ 17	135 $\pm$ 15	< 0.0001
Acetylsalicylic acid within one week of surgery	79 (17)	589 (10)	< 0.0001
On heparin before surgery	159 (33)	1196 (19)	< 0.0001
<i>Surgery related covariates</i>			
Procedure other than isolated CABG or single valve	243 (51)	1447 (23)	< 0.0001
High blood loss surgeon (relative to surgeons' median rate of MBT)	211 (44)	1941 (31)	< 0.0001
Non-elective surgery	104 (22)	443 (7)	< 0.0001
Redo sternotomy	104 (22)	409 (7)	< 0.0001
Received aprotinin instead of tranexamic acid	88 (18)	224 (4)	< 0.0001
Deep hypothermic circulatory arrest	53 (11)	184 (3)	< 0.0001
CPB-duration (min)	144 $\pm$ 68	98 $\pm$ 33	< 0.0001
Nadir hematocrit during CPB < 20%	230 (48)	962 (16)	< 0.0001
Lowest temperature during CPB (Celsius)	33.1 $\pm$ 3.6	33.8 $\pm$ 2.2	< 0.0001
<i>Outcomes</i>			
Discharge hemoglobin (g·L ⁻¹)	100 $\pm$ 19	101 $\pm$ 12	0.34
Re-exploration	187 (39)	218 (4)	< 0.0001
In-hospital death	59 (12)	64 (1)	< 0.0001

RBC = red blood cells; MBT = massive blood transfusion; BSA = body surface area; CABG – coronary artery bypass grafting; CPB = cardiopulmonary bypass.

tion sets had important differences including a higher incidence of MBT (≥ 5 U: 11% *vs* 7%; $P < 0.0001$) and procedures other than isolated coronary artery bypass grafting or single valve (34% *vs* 25%; $P < 0.0001$) in the validation set (Table III).

The bivariate (unadjusted) relationships between the predictor variables and MBT ($\geq$ five units) in the training set are shown in Table IV. The shapes of the relationships between some of the continuous variables and MBT are shown in Figure 1. Several continuous variables were categorized to conform to the linearity assumption of logistic regression or to simplify the model. The logistic regression model for MBT ($\geq$

five units) is shown in Table Va. The model was well calibrated (Hosmer-Lemeshow goodness-of-fit $P = 0.2$) and discriminative (c-index = 0.88) when tested on the patients in the training set. Table Vb shows the model for the secondary MBT definition (≥ 7 U). The second model was also well calibrated (Hosmer-Lemeshow goodness-of-fit $P = 0.3$) and discriminative (c-index = 0.90) when tested on the patients in the training set. Moreover, the same variables were retained in the two models with little change in their predictive odds ratios. Notably, variables related to perioperative hemodilution (body surface area, preoperative hemoglobin, and nadir CPB hematocrit)

FIGURE 1 Spline function graph of the unadjusted relationships between some of the continuous predictor variables and logit probability of massive blood transfusion (MBT; $\geq$ five units of red blood cells within one day of surgery). The probability of MBT [$P(\text{MBT})$] can be calculated from the logit probability of MBT [$\text{logit } P(\text{MBT})$] by solving the following equation: $P(\text{MBT}) = 1 / (1 + e^{-\text{logit } P(\text{MBT})})$

remained in this second model, albeit their predictive value (as measured by their Wald χ^2) was reduced.

Table VI lists the sensitivity, specificity, and positive and negative predictive values of the primary model when it was re-applied to the patients in the training set using various probability cutoffs. The same data are provided as a ROC curve in Figure 2. The 0.10 and 0.35 probability levels were selected as the optimal

probability cutoffs for classifying patients into low-, moderate-, and high-risk groups.

Table VII shows the risk score that was developed based on the β coefficients of the variables in the primary model. The risk score is additive and can range from 0 to 14. Risk classification cutoffs were based on the 75th percentile (2.5) and 95th percentile (4.5) scores to correspond with the cutoffs of the predic-

FIGURE 2 Receiver operating characteristic of the logistic regression model's discriminative ability for massive blood transfusion ($\geq$ five units of red blood cells within one day of surgery) in the training set. Area under curve = 0.88 (equivalent to the model's c-index).

tion rule: ≤ 2.5 denotes low-risk, between 2.5 to 4.5 denotes moderate-risk, and ≥ 4.5 denotes high-risk for MBT.

Table VIII shows the performance of the prediction rule and the risk score in the validation set. For comparison, the predictive accuracies of three clinical variables known to be important predictors for excessive blood loss are also shown in Table VIII.

Of the 74 patients in the validation set misclassified as high-risk by the prediction rule, 41 received four units, 16 received three units, and the remainder received less than three units of RBC within one day of surgery. Of the 157 misclassified low-risk patients, 62 received five units, 24 received six units, 19 received seven units, and the remainder received more than seven units of RBC within one day of surgery. To identify the reasons for misclassification of low-risk patients, 50 of them were randomly selected and reviewed in detail. Of these 50 patients, 15 (30%) had surgical bleeding, eight (16%) had received antiplatelet or anticoagulant medications up to the time of surgery, and 27 (54%) had no identifiable reasons for MBT.

Discussion

Although the definition of excessive blood loss varies from study to study,²⁶ a consistent finding amongst studies is that cardiac surgical patients who bleed excessively and require MBT are at increased risk for serious adverse events.^{2,4,15-17,21,26} The clinical pre-

diction rule developed in this study provides several opportunities for improving the outcome of patients at risk for MBT. First, having identified the relative importance of predictors of MBT, some of which are modifiable, it may be possible to reduce patients' underlying risk by altering these variables. Second, by providing accurate risk estimates for MBT before termination of CPB, the prediction rule can be used to prepare for and institute early and aggressive therapy for bleeding in those identified as being at high-risk. Third, the prediction rule can be used to investigate, and, if found to be appropriate, institute prophylactic therapies (such as hemostatic agents)²⁷ to reduce the risk of MBT in high-risk patients.

Definition of MBT

The primary definition of MBT in this study was the transfusion of at least five units of RBC within one day of surgery. We have previously shown that this threshold, which occurs in only about 10% of our patients, is independently associated with significant increase in mortality.⁴ A second threshold of $\geq$ seven units of RBC within one day of surgery, corresponding to the 95th percentile in our patient population, was also analyzed. That the logistic regression models for the two outcomes were very similar supports the robustness of the prediction rule.

As a surrogate measure for perioperative blood loss, there are limitations with using units of RBC transfused perioperatively. Since RBC transfusions are based on factors other than perioperative blood loss, such as patients' baseline red blood cell volume and clinicians' transfusion practice, one cannot assume that every patient who was categorized as MBT had excessive perioperative blood loss. Owing to the high RBC transfusion thresholds used for defining MBT, however, it is reasonable to assume that few patients categorized as having had MBT did not have excessive perioperative blood loss.

Other measures of perioperative blood loss have their own limitations. Clinical estimates of blood loss are inherently unreliable, even under controlled conditions.²⁸ Others have used surgical re-exploration as the criteria for excessive blood loss.^{2,16,17,21} Many patients with excessive blood loss, however, never require re-exploration, and some patients undergo re-exploration for causes other than bleeding. In cardiac surgery, the amount of blood in mediastinal tubes can also be used to identify excessive blood loss.¹⁵ This method, however, does not capture the significant proportion of patients who bleed excessively in the operating room after termination of CPB.

TABLE Va Details of the logistic regression model for the primary definition of massive blood transfusion (≥ 5 U of RBC within one day of surgery)

Variable	Unit or classification	Coefficient (β)	Standard error	Wald χ^2	P value	Odds ratio	95% CI
Intercept		-0.6655	0.8171	0.66			
Age	Continuous (yr)	0.0212	0.0049	18.94	< 0.0001	1.02	1.01 – 1.03
BSA	Continuous (m ²)	-1.7601	0.2826	38.80	< 0.0001	0.17	0.10 – 0.30
Pre-op shock	1 – Inotropes or IABP	1.1878	0.2214	28.80	< 0.0001	3.28	2.12 – 5.06
Pre-op thrombocytopenia	0 – Platelet count ($\times 10^9 \cdot L^{-1}$) ≥ 150 ; 1 – Between 100 and 150; 2 – ≤ 100			24.01	< 0.0001		
	2	1.8203	0.4212			6.17	2.70 – 14.09
	1	0.4720	0.1895			1.60	1.11 – 2.32
Pre-op hemoglobin	Continuous (g·L ⁻¹)	-0.0268	0.0040	46.20	< 0.0001	0.97	0.96 – 0.98
Procedure	1 – Other than isolated CABG or single valve	0.3112	0.1389	5.02	0.03	1.36	1.04 – 1.79
Surgeon	1- Greater than median MBT rate	0.4973	0.1147	18.81	< 0.0001	1.64	1.31 – 2.06
Redo surgery	1 – ≥ 1 previous sternotomies	0.8737	0.1611	29.43	< 0.0001	2.40	1.75 – 3.28
Urgency	0 – Elective; 1 – Semi-urgent; 2 – Urgent or Emergent			21.25	< 0.0001		
	2	0.7137	0.1870			2.04	1.42 – 2.94
	1	0.5047	0.1294			1.66	1.29 – 2.13
Circulatory arrest	0 – No; 1 – ≤ 30 min; 2 – > 30 min			17.64	0.0001		
	2	2.0096	0.4793			7.46	2.92 – 19.09
	1	0.1409	0.2413			1.15	0.72 – 1.85
CPB duration	Continuous (min)	0.0203	0.0014	204.09	< 0.0001	1.02	1.02 – 1.02
Low nadir CPB hematocrit	1 – Hematocrit < 20%	0.7937	0.1326	35.81	< 0.0001	2.21	1.71 – 2.87

RBC = red blood cells; CI = confidence interval; BSA = body surface area; IABP = intra-aortic balloon pump; CABG = coronary artery bypass grafting; MBT = massive blood transfusion; CPB = cardiopulmonary bypass.

Hosmer-Lemeshow goodness-of-fit test $P = 0.3$; area under ROC curve (c-index) = 0.90

Intercept = A mathematical constant; no clinical interpretation.

Coefficient (β) = The mathematical weighting of each variable in the model.

Standard error = The estimated error of the mathematical weighting.

Wald $\chi^2 = |\text{coefficient}| / \text{standard error}$. The higher the value, the higher the predictive value of the variable.

P value = The probability value obtained by comparing the Wald χ^2 with the chi-square distribution with 1 df.

Odds ratio = The change in odds of transfusion for each unit change of the variable while controlling for other variables in the model.

95% CI = The 95% confidence interval for the estimated odds ratio.

MBT = Massive blood transfusion.

BSA = Body surface area.

IABP = Intra-aortic balloon pump.

CPB = Cardiopulmonary bypass.

CABG = Coronary artery bypass grafting.

The models can be used to calculate the probability of MBT ($P(\text{MBT})$) for each patient as follows:

$P(\text{MBT}) = 1/[1 + \exp.(-LP)]$, where linear predictor (LP) = 'intercept' + $[\beta_1 \times \text{variable}_1] + [\beta_2 \times \text{variable}_2] + \dots + [\beta_i \times \text{variable}_i]$

Independent predictors of MBT as identified by the prediction rule and risk modification opportunities

Massive blood transfusion after cardiac surgery can be due to surgical or non-surgical (i.e., coagulopathy) causes. Surgical bleeding is estimated to account for about 50% of cases that require re-exploration.²⁹ In our sample, about one-third of patients with MBT required re-exploration (344/925). Although surgical bleeding is often unpredictable, the prediction rule included several variables that may be associated with increased risk of surgical bleeding owing to increased surgical complexity. These were type of procedure, urgency of procedure, previous sternotomy, CPB

duration, and DHCA. Interestingly, when the surgeon was analyzed as a dichotomous variable based on the MBT median rate, it only had a moderate influence on the risk of MBT. Analyzing each surgeon separately increased the overall importance of the variable in the model but did not alter the discriminative ability or predictive performance of the model (results not shown).

The causes of coagulopathy after cardiac surgery with CPB include platelet-related abnormalities owing to thrombocytopenia or platelet dysfunction, reduction in plasma coagulation factors owing to hemodilution, excessive primary or secondary [due to disseminated

TABLE Vb Details of the logistic regression model for the secondary massive blood transfusion definition (≥ 7 U of RBC within one day of surgery)

Variable	Unit or classification	Coefficient (β)	Standard error	Wald χ^2	P value	Odds ratio	95% CI
Intercept		-3.0932	1.0996	7.91			
Age	Continuous (yr)	0.0191	0.0066	8.40	0.004	1.02	1.01 – 1.03
BSA	Continuous (m ²)	-1.5024	0.3799	15.64	< 0.0001	0.22	0.11 – 0.47
Pre-op shock	1 – Inotropes or IABP	1.1751	0.2812	17.46	< 0.0001	3.24	1.87 – 5.62
Pre-op thrombocytopenia	0 – Platelet count ($\times 10^9 \cdot L^{-1}$) ≥ 150 ;						
	1 – between 100 and 150; 2 – ≤ 100			27.86	< 0.0001		
	2	2.1772	0.4541			8.82	3.62 – 21.48
	1	0.6062	0.2439			1.83	1.14 – 2.96
Pre-op hemoglobin	Continuous (g·L ⁻¹)	-0.0208	0.0053	15.73	< 0.0001	0.98	0.97 – 0.99
Procedure	1 – Other than isolated CABG or single valve			Did not remain in the model			
Surgeon	1 – Greater than median MBT rate	0.4074	0.1584	6.61	0.01	1.50	1.10 – 2.05
Redo surgery	1 – ≥ 1 previous sternotomies	0.7584	0.2100	13.04	0.0003	2.13	1.42 – 3.22
Urgency	0 – Elective; 1 – semi-urgent;			15.77	0.0004		
	2 – Urgent or Emergent						
	2	0.9288	0.2435			2.53	1.57 – 4.08
	1	0.4857	0.1829			1.62	1.14 – 2.33
Circulatory arrest	0 – No; 1 – ≤ 30 min; 2 – > 30 min			17.91	0.0001		
	2	2.1395	0.5138			8.50	3.10 – 23.25
	1	0.3140	0.2928			1.37	0.77 – 2.43
CPB duration	Continuous (min)	0.0247	0.0016	249.58	< 0.0001	1.03	1.02 – 1.03
Low nadir CPB hematocrit	1 – hematocrit < 20%	0.6609	0.1824	13.13	0.0003	1.94	1.36 – 2.77

RBC = red blood cells; ROC = receiver operator characteristic

Hosmer-Lemeshow goodness-of-fit test $P = 0.3$; area under ROC curve (c-index) = 0.90

Intercept = A mathematical constant; no clinical interpretation.

Coefficient (β) = The mathematical weighting of each variable in the model.

Standard error = The estimated error of the mathematical weighting.

Wald χ^2 = |coefficient| / standard error. The higher the value, the higher the predictive value of the variable.

P value = The probability value obtained by comparing the Wald χ^2 with the chi-square distribution with 1 df.

Odds ratio = The change in odds of transfusion for each unit change of the variable while controlling for other variables in the model.

95% CI = The 95% confidence interval for the estimated odds ratio.

MBT = Massive blood transfusion.

BSA = Body surface area.

IABP = Intra-aortic balloon pump.

CPB = Cardiopulmonary bypass.

CABG = Coronary artery bypass grafting.

The models can be used to calculate the probability of MBT ($P(\text{MBT})$) for each patient as follows:

$P(\text{MBT}) = 1/[1 + \exp.(-LP)]$, where linear predictor (LP) = 'intercept' + [$\beta_1 \times \text{variable}_1$] + [$\beta_2 \times \text{variable}_2$] + ... + [$\beta_i \times \text{variable}_i$]

intravascular coagulation (DIC)] fibrinolysis, and relative protamine deficiency or excess.^{26,30} Excessive primary fibrinolysis is unlikely to be a factor in subjects in this study due to the routine use of antifibrinolytics in nearly all patients. Since heparin and protamine doses were not captured in the databases, their predictive value could not be assessed. Not surprisingly, variables associated with platelet-related coagulopathy were the most predictive variables in the prediction rule. Of these, the most important was CPB duration, which is known to cause a progressive impairment in platelet function.^{29,31} Consistent with this, we found a linear relationship between CPB duration and risk

of MBT (Figure 1). Deep hypothermic circulatory arrest, which not only prolongs CPB duration but also has detrimental effects on platelet function that are additive to those of CPB,³² was also an important predictor of MBT. Another important predictor was pre-existing thrombocytopenia, with the risk most pronounced when platelet counts were less than $100 \times 10^9 \cdot L^{-1}$. Low platelet count has been found to be associated with MBT after cardiac surgery in some,³³ but not all,³⁰ previous studies. Our findings support the opinion of some experts that cardiac surgical patients at high-risk for MBT may benefit from platelet transfusions if their platelet count is less than 100

TABLE VI Performance of the primary logistic regression model at different probability cutoffs in the training set for identification of MBT (≥ 5 U RBC within one day of surgery)*

Cutoff probability	Sensitivity	Specificity	Positive predictive value	Negative predictive value
≥ 0.05	86%	72%	19%	98%
≥ 0.1	69%	86%	28%	97%
≥ 0.15	58%	92%	35%	97%
≥ 0.2	50%	95%	41%	96%
≥ 0.3	40%	97%	52%	95%
≥ 0.35	33%	98%	55%	95%
≥ 0.4	29%	98%	57%	95%
≥ 0.5	22%	99%	64%	94%
≥ 0.6	16%	99%	65%	94%

* Highlighted rows identify the values selected as the cutoffs for classifying patients into low risk, moderate risk, and high risk for massive blood transfusion (MBT); RBC = red blood cells.

TABLE VII The simplified risk score derived from the logistic regression model*

Variable	Score
Age ≥ 80 (yr)	1
Age 70 – 80 (yr)	0.5
BSA ≤ 1.5 (m ²)	1
BSA 1.5 – 1.9 (m ²)	0.5
Preoperative shock	1.0
Preoperative platelet count ≤ 100 ($\times 10^9 \cdot L^{-1}$)	2
Preoperative platelet count 100 – 150 ($\times 10^9 \cdot L^{-1}$)	0.5
Preoperative hemoglobin ≤ 110 (g·L ⁻¹)	1
Preoperative hemoglobin 110 – 130 (g·L ⁻¹)	0.5
Complex procedure	0.5
High-blood-loss surgeon	0.5
Redo surgery	1.0
Non-elective surgery	0.5
Circulatory arrest > 30 (min)	2.0
Circulatory arrest 0 – 30 (min)	0.5
CPB duration ≥ 180 (min)	2.5
CPB duration 120 – 180 (min)	1.0
Nadir CPB hematocrit ≤ 18 (%)	1.0
Nadir CPB hematocrit 18 – 22 (%)	0.5

* To calculate the risk, simply add all appropriate scores. Patients with scores ≤ 2.5 are at low-risk for massive blood transfusion (MBT), those with scores ≥ 4.5 are at high-risk for MBT, and all others are at moderate-risk for MBT. BSA = body surface area; CPB = cardiopulmonary bypass.

$\times 10^9 \cdot L^{-1}$.³⁴ Of note, preoperative acetylsalicylic acid (ASA) use did not remain in the model, suggesting that in patients with MBT, its effect on bleeding may be overshadowed by other factors that cause platelet-related coagulopathy. Since the databases did not contain information on the use of other drugs that may increase perioperative blood loss (such as clopidogrel and glycoprotein IIb/IIIa receptor blockers),³⁵ their effects on MBT could not be assessed. Our limited

chart review of misclassified patients indicates that such drugs may account for about one-fifth of the 5% of patients who were misclassified in the low-risk group. Their effect in the other groups, however, was not determined, and their inclusion may have improved the accuracy of the prediction rule, particularly in the moderate-risk group.

As in previous studies (Table I), this study found that variables associated with low blood volume are independently associated with MBT. Preoperative hemoglobin and body surface area were inversely related to the risk of MBT, and age was directly related to the risk of MBT. Although patients with low baseline blood volume are more likely to require RBC transfusions in response to perioperative blood loss, this alone cannot account for the strong relationship between these variables and the transfusion of more than five or seven units of RBC within one day of surgery. Another plausible explanation relates to dilutional coagulopathy that can occur in patients with small blood volume after initiation of CPB. Since the amount of CPB prime is for the most part constant, coagulation factors are more likely to drop below levels required for normal hemostasis in patients with low blood volumes. This explanation is supported by the observed strong inverse relationship between nadir hematocrit during CPB and risk of MBT in both models. Thus, interventions that limit the amount of hemodilution, such as use of smaller CPB circuits or retrograde priming of the circuit, may reduce the risk of MBT in patients with low baseline blood volume.

Another etiology for excessive blood loss in cardiac surgery is DIC.³⁰ Our prediction rule included preoperative shock, which may predispose patients to DIC.³⁶

Predictive ability of the prediction rule or the risk score

Both the prediction rule and the simplified risk score were highly accurate in identifying patients at low-risk and at high-risk for MBT (Table VIII). In the low-risk group, their negative predictive value was 95%, and in the high-risk group, their positive predictive value was around 60%. These two categories represented over 80% of the population. This compares favourably to the predictive ability of known clinical predictors of bleeding risk, such as CPB duration, urgency of procedure, and history of previous sternotomies (Table VIII). In the moderate-risk category, however, the prediction rule and the risk score did not perform well and were no better than the clinical predictors.

Thus, the prediction rule or the risk score can be applied clinically to accurately stratify about 80% of patients undergoing cardiac surgery to low- or high-

TABLE VIII Performance of the prediction rule and the risk score in the validation set at the selected cutoffs, and comparison to predictions by clinical predictors

Classification	Prediction rule		Risk score		CPB duration*		Urgent, redo surgery†	
	MBT	Total	MBT	Total	MBT	Total	MBT	Total
High-risk	117 (61%)	191	126 (58%)	218	153 (38%)	399	79 (25%)	322
Moderate-risk	175 (28%)	631	167 (27%)	625	91 (15%)	617	80 (22%)	367
Low-risk	157 (5%)	3194	156 (5%)	3173	205 (7%)	3000	290 (9%)	3327

* CPB < 120 min = low-risk; 120 – 150 min = moderate-risk; and > 150 min = high-risk †first-time + (elective or semi-urgent) = low-risk; redo + (elective or semi-urgent) = moderate-risk; urgent or emergent = high-risk. CPB = cardiopulmonary bypass; MBT = massive blood transfusion.

risk for MBT. This information can then be used to reduce costs in the low-risk group by, for example, limiting the use of expensive blood conservation modalities (such as aprotinin or cell salvage and washing), and to reduce the risk of MBT in the high-risk group by, for example, instituting preventive measures (such as reducing hemodilution or prophylactic administration of hemostatic agents).

Limitations of the prediction rule and future direction

Owing to lack of data, we could not assess the predictive value of potentially important variables such as preoperative drugs [except for heparin, coumadin (through measurement of INR), and ASA] and use of synthetic colloids.³⁷ Future studies are required to delineate the effects of these factors on MBT.

Owing to institutional variations in transfusion practice,⁶ our prediction rule may not be valid at other institutions. The prediction rule, however, did perform well in the validation set, even though patients in the validation set differed from those in the training set on several important variables such as date of surgery and case-mix. Moreover, the variables included in the prediction rule are not site-specific; the same variables have been found to be associated with blood loss in other studies. Although these factors suggest that the prediction rule should be externally generalizable, it needs to be assessed at other institutions.

Future studies are also needed to assess the clinical utility of the prediction rule. Moreover, owing to the low predictive accuracy of the prediction rule in the moderate-risk group, there is a need to investigate strategies that may improve its predictive ability in this group, such as point-of-care coagulation testing prior to termination of CPB.³⁸ Finally, it is important to determine why some patients with no clinical risk factors for MBT nevertheless bleed excessively after cardiac surgery. A potentially important area of investigation in these patients is the role of genotype in bleeding.³⁹

In summary, we developed and internally validated a prediction rule (and a simple risk score) that can accu-

rately predict the risk of MBT in the majority of cardiac surgical patients. Future studies are required to refine the predictive ability of the prediction rule and to assess its external generalizability and clinical utility.

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