

**Development and Validation of Transfusion Risk
Understanding Scoring Tool (TRUST) to Stratify
Cardiac Surgery Patients According to Their
Blood Transfusion Needs**

By

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for the degree of Master of Science
Graduate Department of Health Policy Management and Evaluation
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ABSTRACT

Allogeneic blood transfusion is associated with transfusion reactions, infection transmission, postoperative morbidity and mortality. Despite these known risks, reports have indicated that more than one-third of patients undergoing elective coronary artery bypass grafting surgery still receive allogeneic blood, and nearly 20% of blood transfusions are associated with cardiac surgery.

The objective of this study was to develop and validate a clinical index to stratify cardiac surgery patients according to their blood transfusion needs. Based on the standards of measurement in clinical research, a valid clinical tool was developed for predicting the need for blood transfusion in patients undergoing cardiac surgery. This clinical tool consists of eight preoperative variables: preoperative hemoglobin, weight, female sex, age, non-elective procedure, preoperative creatinine, previous cardiac surgical procedure, and non-isolated procedure. The clinical tool was internally and externally validated, and the results suggest that it should perform well at other institutions.

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
ANH	Acute Normovolemic Hemodilution
AUC	Area Under Receiver Operating Characteristic Curve
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CD	Canadian Dollar
CPB	Cardio-Pulmonary Bypass
CPBT	Cardio-Pulmonary Bypass Time
CI	Confidence Interval
CVG	Contrast Ventriculography
ECHO	Echocardiography
EACA	Epsilon Aminocaproic Acid
EPO	Erythropoietin
EPV	Event Per Variable
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
LVEF	Left Ventricular Ejection Fraction
LTRS	Litmathe Transfusion Risk Score
MTRS	Magovern Transfusion Risk Score
NIH	National Institute of Health
OR	Odds Ratio
PRBC	Packed Red Blood Cell
PABD	Preoperative Autologous Blood Donation
PHL	P-Value for Hosmer-Lemeshow Goodness of Fit statistics
PTDM	Pharmacologically Treated Diabetes Mellitus
RNVG	Radio Nucleotide Ventriculography
RCT	Randomized Clinical Trial
RBCs	Red Blood Cells
ROC	Receiver Operating Characteristic Curve
RR	Relative Risk
SE	Standard Error
TXA	Tranexamic Acid
TRUST	Transfusion Risk Understanding Scoring Tool
USD	American Dollar

Dedication

*To My Wife: Norah and Son: Abdurrahman
For Their Love and Support
Without Their Help This Thesis Could Not Have Been Possible*

INTRODUCTION AND OVERVIEW

Allogeneic blood transfusion is associated with transfusion reactions, infection transmission, postoperative morbidity and mortality. Despite these known risks, reports have indicated that more than one-third of patients undergoing elective coronary artery bypass grafting surgery still receive allogeneic blood, and nearly 20% of blood transfusions are associated with cardiac surgery.

Several studies have identified preoperative variables that are associated with the perioperative allogeneic blood transfusion; however, only a few studies have used these variables to develop models for prediction of the exposure to transfusion in patients undergoing cardiac surgery, and only two studies used the predictive models to construct transfusion risk scoring systems for coronary artery bypass surgery patients. These scoring systems are the only scoring systems available, but there are limitations that make them less applicable to current practice.

The objective of this study was to develop and validate a clear and simple clinical tool to stratify cardiac surgery patients according to their blood transfusion needs. This tool may be used to guide the targeted application of blood conservation strategies, and aid in designing randomized controlled trials (e.g. stratified randomization using a prognostic factor) to test the effect of certain interventions on blood transfusion.

Primary data sources for the development of this index were: the cardiac surgery clinical database and the cardiac anesthesia database at Toronto General Hospital, Toronto, Ontario, Canada. The cardiac surgery clinical database at Sunnybrook and Women's College Health Science Centre, Toronto, Canada was used for cross-validation of the index. Multivariable logistic regression modeling techniques were used

to appropriately select and weight the predictor variables for inclusion in the predictive index and to assess the impact of the preoperative variables on the risk of exposure to allogeneic blood transfusion.

This thesis is organized into five chapters and an appendix. Background information about blood transfusion and blood conservation strategies in cardiac surgery are discussed in chapter A. Chapter B discusses a systematic review of the literature, and critical appraisal of currently available clinical indices that predict allogeneic blood transfusion after cardiac surgery. Chapter C includes details of the methods used to develop, validate and cross-validate the index. The results are detailed in chapter D. Finally, chapter E states the conclusions of the study together with a discussion about the implications and limitations as well as future research direction. The thesis ends with the appendix which includes extra exhibits of data that may assist in understanding certain aspects, but are not essential in the body of the thesis.

CHAPTER A

Blood Transfusion and Blood Conservation Strategies in Cardiac Surgery: Current State of Knowledge

A.1. BACKGROUND

A.1.1. Historical Overview

In 1825, *Syng Physick* performed the first known human blood transfusion ¹. In 1828, It was reported that *Blundell* performed the first successful human blood transfusion to a patient with postpartum hemorrhage ². The discovery of ABO blood groups (A, B, and O by *Karl Landsteiner* in 1900 and AB by *Von Decastello* and *Sturli* in 1902) and the advances in the techniques of cross-matching, anticoagulation, storage of blood and the establishment of blood banks made routine blood transfusion possible ³. It was reported that the first blood bank was established in 1937 in the United States ³.

A.1.2. Rates of Transfusion: Epidemiology

Approximately 60% to 70% of all blood products given to patients are transfused at or near the time of operation ³⁻⁷. *Goodnough et al* reported that approximately 10 million units of packed red blood cells (RBCs) were transfused in the United States in 1980 ⁸. The number peaked at 12.2 million, and 11.4 million in 1986 and 1997 respectively ^{8,9}.

A.1.3. Rates of Transfusion: Cardiac Surgery

Reports have indicated that more than one-third of patients undergoing elective coronary artery bypass grafting surgery (CABG) still require allogeneic blood ¹⁰. It has been estimated that 11% of red cell resources were used for transfusion support of

patients undergoing CABG in the United States ¹¹, and nearly 20% of blood transfusions are associated with cardiac surgery ^{10,11}. Previous studies showed that the rates of blood transfusion during or after cardiac surgery ranged from 10% to 70% ¹¹⁻¹⁹.

A.1.4. Cost of Blood Transfusion

The estimated cost for the patient of one unit of packed red blood cells (PRBCs) is US \$250 to \$550 ²⁰⁻²³. In 1996, *Tretiak et al* studied the cost of one unit transfusion of PRBC in eight different institutions across Canada ²⁴. The mean cost of an allogeneic transfusion was CD \$210 per one unit of red blood cells. In a subsequent study by *Dranitsaris et al* in 2000, the cost per one unit red blood cell transfusion was CD \$261 ²⁵. In a meta-analysis conducted by *Amin et al*, the cost of one unit PRBC transfusion in Canada had increased 24% from 1996 to 2000 ²⁶. Table A.1 summarizes the results of various studies.

Table A.1: Cost of PRBCs transfusion in various studies

Study	Year	Country	Cost per Unit	Cost in \$CD*
Hadjianastassiou et al ²⁷	2002	United Kingdom	£090.06	\$201.32
Kavanagh et al ²²	2001	United States of America	\$316.00	\$374.85
Cremieux et al ²¹	2000	United States of America	\$469.00	\$567.11
Dranitsaris et al ²⁵	2000	Canada	\$261.30	\$261.30
Cantor et al ²⁰	1998	United States of America	\$548.00	\$706.17
Duffy & Tolley ²⁸	1997	United Kingdom	£033.73	\$075.40
Kemper et al ²⁹	1997	United States of America	\$428.95	\$518.68
Tretiak et al ²⁴	1996	Canada	\$210.00	\$210.00
Forbes et al ³⁰	1991	United States of America	\$374.00	\$452.24

CD: Canadian Dollar, *: December 2004 conversion rate

A.1.5. Complications of Blood Transfusion

Complications of blood transfusion can be classified as immunogenic, infectious, and complications related to massive blood transfusion ³¹. These complications are summarized in Table A.2.

Several strategies have been developed to decrease transfusion rates and therefore reduce the risks and cost of allogeneic blood transfusion. These strategies are summarized in Table A.3 and the text below discusses each strategy in detail.

Table A.2: Blood transfusion-related complications

Risk	Risk of Event *
Immunogenic	
Febrile non- hemolytic transfusion reactions	1 in 300
Acute hemolytic transfusion reactions	1 in 40,000
Delayed hemolytic transfusion reactions	1 in 7,000
Transfusion-related acute lung injury	1 in 5,000
Urticarial transfusion reactions	1 in 100
Anaphylactic transfusion reactions	1 in 40,000
Viral Transmission	
Hepatitis B virus	1 in 82,000
Hepatitis C virus	1 in 3,100,000
Human Immunodeficiency virus	1 in 4,700,000
Human T-Lymphocyte viruses I and II	1 in 3,000,000
Massive-Transfusion-Related Complications	
Coagulopathy	
Citrate toxicity	
Hypothermia	
Acid-base disturbances	
Electrolyte disturbances	

* From the Bloody Easy Guide for Blood Transfusion Medicine³²

Table A.3: Blood conservation strategies in cardiac surgery

1. Preoperative autologous blood donation
2. Use of erythropoietin with and without preoperative autologous blood donation
3. Intraoperative use of antifibrinolytic agents
4. Cell salvage (intraoperative & postoperative recovery of blood)
5. Acute normovolemic hemodilution

A.2. BLOOD CONSERVATION STRATEGIES IN CARDIAC SURGERY

A.2.1. Preoperative Autologous Blood Donation (PABD)

Autologous blood donation entails that the patient donates his or her own blood for an elective operation 1-2 weeks prior to surgery. In fact, the participation in PABD was less than 5% in patients undergoing elective operations³³. However, when it was recognized that HIV could be transmitted by blood transfusion, 50% to 75% of the patients undergoing elective surgery participated in PABD, and as a result, 1 of every 12 blood units collected in the United States was the result of PABD³⁴.

Goodnough et al reported several advantages of PABD: 1) it reduces the risk of infection transmission particularly viral transmission, 2) avoids red cells alloimmunization, 3) supplements blood resource, and 4) provides a compatible blood for patients with alloantibodies⁸. However, PABD is not free of disadvantages.

Goodnough et al reported that PABD does not eliminate the risk of bacterial contamination, does not eliminate the risk of administrative errors resulting in ABO incompatibility and results in discarding of the blood that is not transfused⁸.

The effect of PABD on the risk of exposure to perioperative allogeneic blood transfusion has been studied in many randomized controlled clinical trials (RCTs)³⁵⁻⁴². In a meta-analysis by *Henry et al*, the overall effect of PABD led to a significant reduction in the risk of exposure to allogeneic blood transfusion : Relative Risk (RR) =0.37, 95% Confidence Interval (CI) : 0.26,0.54; p-value < 0.0001⁴³. Because of the poor methodological quality of the included trials, *Henry et al* concluded that, a large high quality RCTs are required to examine whether or not the benefits of PABD outweigh the risks⁴³.

Cost-effectiveness of PABD has been evaluated in patients undergoing CABG surgery⁴⁴. The preoperative donation of two units was estimated to have a cost of US \$500,000 per quality-adjusted life-year. In comparison, most commonly accepted medical and surgical interventions have a cost of less than US \$50,000 per quality-adjusted life-year^{8,45}. Reduced cost-effectiveness of PABD and reduced risk of transmission of viral infection by allogeneic blood have lead to re-evaluation the practice of PABD⁴⁶⁻⁴⁸.

A.2.2. Use of Erythropoietin with and without PABD

Erythropoietin (EPO) is a glycoprotein hormone that stimulates erythropoiesis and is the primary regulator of red blood cells production⁴⁹⁻⁵¹. It is available in the recombinant form which has been shown to be identical to the endogenous form⁵¹. EPO increases hematocrit when given without autologous blood donation⁵². Therefore there is a potential risk of thromboembolic complications. *Messmer et al* reported that

autologous donation is recommended to be undertaken if the hematocrit rises over 50% during EPO therapy so as to reduce the risk of thrombotic complications⁵³.

In a meta-analysis by *Laupacis et al* the odds ratio (OR) for the proportion of patients transfused with allogeneic blood in studies of EPO to augment autologous donation was (OR=0.42, 95% CI: 0.28, 0.62; P < 0.0001) for orthopedic surgery and (OR=0.25, 95% CI: 0.08, 0.82; P = 0.02) for cardiac surgery⁵⁴.

The cost-effectiveness of the use of EPO in cardiac surgery has been addressed in two studies based on decision analysis models^{55,56}. Both studies concluded that the use of EPO to reduce the risk of exposure to allogeneic blood transfusion was not cost-effective. Therefore, although EPO administration before cardiac surgery is associated with a significant reduction in the risk of exposure to allogeneic blood transfusion, further cost effectiveness studies are warranted to justify its use.

A.2.3. Intraoperative use of Antifibrinolytic Agents

A.2.3.a. Aprotinin

Aprotinin is a serine protease inhibitor that possesses anti-fibrinolytic properties^{57,58}. Beside its anti-fibrinolytic properties, *Mohr et al* documented that aprotinin exerts an indirect preservative effect on platelet function during extracorporeal circulation⁵⁹.

The effect of aprotinin in reducing the need for allogeneic blood has been studied in a large number of randomized clinical trials. To date there are four large systematic reviews of these trials. These systematic reviews included up to 62 randomized controlled clinical trials⁶⁰⁻⁶³ and demonstrated a significant effect of aprotinin in

reducing the need for allogeneic blood transfusion after cardiac surgery. Results of these systematic reviews and meta-analyses are summarized in Table A.4.

Table A.4: Summary of the effect size of aprotinin in various meta-analyses

Outcome	Number of Studies	Number of Patients	Summary Estimate	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P-Value
A (<i>Henry et al</i> ⁶⁰)	55	6569	RR 0.69	0.64	0.76	<0.001
H (<i>Henry et al</i> ⁶⁰)	62	7027	RR 0.70	0.64	0.76	<0.001
I (<i>Henry et al</i> ⁶⁰)	25	2764	RR -1.08	-1.47	-0.69	<0.001
H (<i>Laupacis et al</i> ⁶¹)	45	5808	OR 0.31	0.25	0.39	<0.001
A (<i>Levi et al</i> ⁶²)	40	4821	OR 0.37	0.32	0.42	<0.001
A (<i>Munoz et al</i> ⁶³)	46	3781	OR 0.28	0.22	0.37	<0.001

RR: Relative Risk, OR: Odds Ratio

A: Number of patients exposed to allogeneic blood (cardiac surgery)

H: Number of patients exposed to allogeneic blood (all surgeries)

I: Number of units of blood transfused

A.2.3.b Epsilon Aminocaproic Acid and Tranexamic Acid

Epsilon Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) are synthetic lysine analogs that inhibit fibrinolysis⁶⁴. TXA is however, a more potent drug than EACA^{64,65}. In cardiac surgery, the effect of EACA on blood loss has been studied in several randomized clinical controlled trials⁶⁶⁻⁷⁴. *Munoz et al* reviewed these trials and concluded that EACA has a significant effect in reducing blood loss after cardiac surgery⁶³.

The effect of EACA in the exposure to allogeneic blood has been addressed in several randomized trials^{66,68,70,71}. *Henry et al* pooled these trials which included a total of 208 participants, of whom 106 were randomized to EACA and 102 were randomized to a control group. *Henry et al* reported that there was no statistically significant effect of EACA in reducing the need for allogeneic blood transfusion (RR=0.48, 95%CI: 0.19, 1.19)⁶⁰. *Laupacis et al* found similar results where EACA did not have a statistically significant effect on the proportion of patients transfused (OR=0.20, 95% CI: 0.04,1.12; P = 0.07)⁶¹.

Many trials have compared TXA with control in cardiac surgery^{68,70,71,75-87}. *Henry et al* conducted a meta-analysis that included 15 randomized controlled clinical trials⁶⁰. These trials included a total of 1151 patients, of whom 661 were randomized to TXA and 490 were randomized to a control group. *Henry et al* concluded that the use of TXA significantly reduced the need for allogeneic blood transfusion (RR=0.71, 95%CI: 0.57, 0.88)⁶⁰.

A.2.4 Cell Salvage (Intraoperative and Postoperative Recovery of Blood)

Carless et al defined cell salvage as a term that covers a range of techniques that scavenge blood from operative fields or wound sites, and re-infuse the blood back into the patient⁸⁸.

In cardiac surgery, many clinical trials have evaluated the effectiveness of cell saving techniques in reducing the exposure to blood transfusion⁸⁹⁻¹⁰⁵. These trials have been recently systematically reviewed by *Carless et al*⁸⁸. The pooling of 21 clinical trials involving CABG patients showed significant effect of cell saving techniques in reducing

the exposure to blood transfusion (RR= 0.76, 95% CI: 0.68, 0.88; P=0.0001). Although cell salvage has been shown to be effective in reducing the risk of exposure to allogeneic blood transfusion; it has disadvantages which include: dilutional coagulopathy, air embolism and bacterial contamination ³².

A.2.5 Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) was described by *Goodnough et al* to be the approach that entails the removal of whole blood from the patient immediately before surgery and simultaneous replacement with an acellular fluid, such as crystalloid and colloid, to maintain normovolemia ⁸. Blood is collected in standard blood bags containing anticoagulant, and re-infused when indicated ⁸. In a report of the American Society of Anesthesiologists Task Force on Blood Component Therapy, ANH has been suggested as an inexpensive and effective mean of reducing allogeneic blood exposure ¹⁰⁶.

Goodnough et al stated the following advantages of ANH over PABD: first, the units procured by hemodilution do not require testing, so the costs are substantially lower than those of PABD, second, since the units of blood are not moved from the operating room, the possibility of an administrative error that could lead to ABO-incompatible blood transfusion is theoretically eliminated, as is the risk of bacterial contamination, third, blood obtained by ANH does not require additional investment of time by the patient since it is done at the time of surgery, nor does it prolong the duration of surgery or anesthesia ⁸.

The effectiveness of ANH in reducing the risk of exposure to allogeneic blood transfusion has been addressed in several randomized clinical trials^{94,107-111}. In a meta-analysis by *Bryson et al*, the overall effect of ANH significantly reduced the risk of exposure to allogeneic blood transfusion (OR=0.51, 95% CI: 0.26, 0.99)¹¹². However, the results of this meta-analysis should be carefully interpreted as majority of the included studies had methodological concerns (e.g. blinding).

A.3. TRANSFUSION THRESHOLDS FOR GUIDING ALLOGENEIC BLOOD TRANSFUSION

In a recent systematic review on the transfusion thresholds and other strategies for guiding allogeneic blood transfusion, *Hill et al* stated that several published guidelines have advised against a single threshold for red cell transfusion, recommending that a range of hemoglobin values between 60 and 100 g/L can be used, depending on the presence of serious comorbidity¹¹³.

In cardiac surgery, *Bracey et al* conducted a large RCT where 428 patients undergoing elective CABG were randomized to patients receiving transfusion at hemoglobin level less than 80 g/L (intervention group) and patients receiving transfusion on instruction of their individual physicians (control group). The intervention group had significantly less blood transfusion ($p = 0.005$)¹¹⁴. Additionally, there was no significant difference in morbidity and mortality rates between the two groups. Therefore, *Bracey et al* concluded that a lower hemoglobin threshold of 80 g/L does not adversely affect patient's outcome¹¹⁴.

In critically ill patients, on the other hand, *Hebert et al* conducted a large randomized controlled clinical trial, where 838 patients were randomized to a restrictive strategy (transfusion at hemoglobin less than 70 g/L) and a liberal strategy (transfusion at hemoglobin less than 100 g/L) ¹¹⁵. They reported that the overall, 30-day mortality was not significantly different between the two groups (18.7% versus 23.3%, P=0.11). The mortality rates during hospitalization were lower in the restrictive strategy group (22.2% versus 28.1%, P=0.05). They also reported that, other mortality rates including the mortality rate during the entire stay in the intensive care unit (13.9 % versus 16.2 %, P=0.29) and the 60-day mortality rate (22.7 % versus 26.5 %, P=0.23) were also lower in the restrictive strategy group. *Hebert et al* concluded that a restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina ¹¹⁵.

A.4. GUIDELINES FOR BLOOD TRANSFUSION

There have been several guidelines for blood transfusion including that for cardiac surgery ^{106,116-123}. *Goodnough et al* stated that these guidelines recommend blood not to be transfused prophylactically, and suggest that in patients who are not critically ill, the threshold for transfusion should be hemoglobin of 70 to 80 g/L and a hemoglobin level of 80 g/L seems an appropriate threshold for transfusion in surgical patient with no risk factors of ischemia, whereas a threshold of 100 g/L can be justified for patients who are considered at risk ^{9,115}.

A.5. MAGNITUDE OF THE PROBLEM

Blood transfusion needs significantly increase with older age, female sex, urgent operations, and comorbid diseases ^{11,15-19}. A report from the Society of Thoracic Surgeons national adult cardiac database committee and the Duke Clinical Research Institute in 2002, examined the trends in risk profile of 1,154,486 patients who underwent isolated CABG at 522 participant sites in the United States and Canada during the decade 1990 to 1999 ¹²⁴. It showed that the number of annual CABG procedures performed increased progressively from 1990 to 1997, with 22,945 and 190,552 CABG procedures performed respectively. Although these numbers decreased to 178,763 and 136,330 CABG procedures in 1998 and 1999 respectively, the numbers of CABG procedures performed on patients older than 65 years of age progressively increased from 11,770 in 1990 to 104,369 in 1997, and 99,657 in 1998 ¹²⁴. The report also showed that, over time, patients were more likely to be older, of female sex, and have more comorbidity ($p < 0.05$) ¹²⁴.

In a Canadian study by *Abramov et al*, trends in CABG surgery were examined over 9 years (from 1990 to 1998) in a total of 4,839 patients who underwent isolated CABG surgery ¹²⁵. The annual number of patients undergoing CABG surgery increased progressively from 320 in 1990 to 932 in 1998. *Abramov et al* concluded that the later time cohort showed significant increase in age, female gender, diabetes mellitus, renal failure, peripheral vascular disease and urgent procedures ($p < 0.05$) ¹²⁵.

A.6. PREDICTING THE EXPOSURE TO ALLOGENEIC BLOOD TRANSFUSION IN CARDIAC SURGERY

Predicting blood transfusion in cardiac surgery is important for many reasons: it provides patients with important information about their transfusion–related risks, helps the medical team to anticipate patients' transfusion needs and guides the clinician in ordering additional tests; both hematological and non-hematological. Furthermore, it guides consultation of the appropriate medical services (e.g. hematology) and provides better blood resource allocation. Because blood preparation takes time; predicting blood transfusion needs will help clinicians to order blood in advance and avoid unwanted delays. Several strategies have been developed to reduce the rates of the exposure to allogeneic blood transfusion in cardiac surgery. They include preoperative autologous blood donation, intraoperative use of antifibrinolytic agents, cell salvage, and acute normovolemic hemodilution. As several of these strategies are expensive, targeting their use to the identified high risk groups (of being exposed to allogeneic blood transfusion) would be more cost-effective^{8,9}. Therefore, a predictive scoring system that will guide the application of such strategies in the target risk groups, and that would potentially reduce total cost of care is needed. For example, indiscriminate use of PABD in patients undergoing CABG surgery is not cost-effective. The estimated cost of PABD is US \$508,000 to US \$909,000 per quality-adjusted life-year⁴⁴. In comparison, most commonly accepted medical and surgical interventions have a cost of less than US \$50,000 per quality-adjusted life-year as reported by *Birkmeyer et al*⁴⁴. By stratifying patients according to the risk of transfusion and using PABD only for those at high risk for transfusion, it will be possible for PABD to be more cost-effective. Furthermore,

some blood tests (e.g. cross-matching) can be potentially eliminated for patients in the identified low-risk group, which can reduce cost and improve blood bank efficiency as suggested by *Karkouti et al*¹⁴. In addition, such a scoring system may be useful in designing randomized clinical trials to test the effect of certain interventions on blood transfusion. Both the decision concerning which patient to randomize and the design of randomization process (for example, stratified randomization using prognostic factors) are aided by the availability of accurate prognostic estimates before randomization¹²⁶.

CHAPTER B

Currently Available Clinical Indices for the Estimation of the Risk of Exposure to Allogeneic Blood Transfusion in Cardiac Surgery: Review and Critical Appraisal

B.1. LITERATURE SEARCH

All studies, in which a predictive scoring system was constructed, were included in this review. A predictive scoring system is defined as a decision-making tool for clinicians that includes relevant variables obtained from history, physical examination, or diagnostic tests and that provides a probability of an outcome¹²⁷. The outcome of interest was the probability of exposure to allogeneic blood transfusion during or after cardiac surgery (binary outcome: YES/NO).

Studies were identified by searching MEDLINE, EMBASE and the Cochrane Controlled Trial Register (CCTR) on the Cochrane Library from the earliest achievable date of each database to November 2004, supplemented by manual search of reference lists of retrieved studies. No language restrictions were applied. The following terms and keywords were used: erythrocyte transfusion OR blood transfusion OR blood component transfusion OR [blood AND transfusion] AND [score OR scoring system OR rule OR index OR tool OR measurement OR instrument] AND [predict OR predicting OR prediction].

B.2. RESULTS

Several studies have identified preoperative variables that are associated with perioperative blood transfusion; however, only ten studies have used these variables to develop models for prediction of blood transfusion after cardiac surgery^{11-19,128}. These studies are summarized in Table B.1. Of these studies, only two used the predictive model to construct a risk scoring system: *Magovern et al*¹⁶ Transfusion Risk Scoring System (MTRS) and *Litmathe et al*¹⁵ Transfusion Risk Scoring System (LTRS). (Table B.2 and Table B.3).

Table B.1.: Studies that developed models for predicting the need for blood transfusion during or after cardiac surgery

Study	Population	Data collection	Statistics	Outcome	Transfusion rates	Variables in final model	Accuracy of final model
Cosgrove ¹³ 1985	441 consecutive first-time CABG cases by 1 surgeon (1981)	Clinical database	Logistic regression, not validated	Blood transfusion during total perioperative period	10%	RBC volume, age	Not reported
Bilfinger ¹² 1989	467 consecutive first-time CABG cases at 1 hospital (1985-88)	Clinical database	Logistic regression, cross validation	Blood transfusion during total perioperative period	44.1%	Preoperative Hct, age, sex, weight	90% sensitivity
Ferraris ¹²⁸ 1989	159 consecutive CABG cases at 1 hospital performed by one surgeon	Clinical database	Logistic regression	Blood transfusion of more than 5 units of PRBC		Bleeding time, and RBC volume	
Magovern ¹⁶ 1996	2455 consecutive CABG cases at 1 hospital (1992-94)	Clinical database	multivariate regression, Prospective validation (422 patients)	Blood transfusion during total perioperative period	60%	Sex, age, body mass index, PVD, diabetes, RBC mass, LVF, reoperation, albumin level, renal dysfunction, Cardinogenic shock, emergency operation, urgent operation, catheterization problem	0.78 area under ROC curve
Surgeonor ¹¹ 1998	3252 consecutive CABG, 5 hospitals	Discharge record	Logistic regression. Prospective validation 741 patients	Blood transfusion during total perioperative period	68%	Admission Hct, age, sex, reoperation, smoking, coagulation defects, diabetes with renal dysfunction, recent MI, disasters, hospital	87% sensitivity, 45% specificity

Table B.1. Continued: Studies that developed models for predicting the need for blood transfusion during or after cardiac surgery

Study	Population	Data collection	Statistics	Outcome	Transfusion rates	Variables in final model	Accuracy of final model
Karkouti ¹⁴ 2001	1007 consecutive elective first-time CABG at one hospital	Clinical database	Logistic regression, Prospective validation	Blood transfusion on the day of surgery or one day after	29.4%	Preoperative Hemoglobin, age, sex, weight	0.86 area under ROC curve
Parr ¹⁹ 2003	600 consecutive congenital and acquired cardiac surgery patients	Prospective collection	Logistic regression	More than 2 units transfusion all blood products		Age, Creatinine, low surface area, lower bypass temperature	Not reported
Litmathe ¹⁵ 2003	400 consecutive CABG at 1 hospital (1999)	Clinical database	Logistic regression	Blood transfusion during total perioperative period	33%	Emergency operation, Cardinogenic shock, urgent operation, LVEF<.35, anemia, age>70, female sex, Creatinine>1.6mg/dl, redo operation, IDDM.	Not validated
Ouattara ¹⁸ 2003	335 consecutive CABG at 1 hospital	Clinical database	Logistic regression	Blood transfusion during total perioperative period	42%	Preoperative Hemoglobin, Emergency operation, Reoperation, COPD, and Complex surgery	Not validated
Moskowitz ¹⁷ 2004	307 consecutive CABG and valve patients at 1 hospital	Clinical database	Logistic regression	Blood transfusion during total perioperative period	11%	RBC mass, Type of operation, Urgency, Number of diseased vessels, Preoperative Prothrombin time, and Creatinine	

CABG: Coronary Artery Bypass Grafting, Hct: Hematocrit, MI: Myocardial Infarction, PVD: Peripheral Vascular Disease, RBC: Red Blood Cell, LVF: Left Ventricular Function, LVEF: Left Ventricular Ejection Fraction, IDDM: Insulin-Dependent Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, RBC: Red Blood Cell

Table B.2: Magovern Transfusion Risk Score (MTRS)*

Predictor	Score
Emergency operation	4
Cardiogenic shock	3
Urgent operation	3
Catheterization –induced coronary occlusion	3
Low body mass index	2
Left ventricular ejection fraction <0.30	2
Age>74 y	2
Female sex	2
Low red cell mass	2
Peripheral vascular disease	1
Insulin-dependent diabetes	1
Serum creatinine >1.8 mg/dL (159 µmol/L)	1
Serum albumin < 4.0 g/dL (40g/L)	1
Redo operation	1

* *Magovern et al*¹⁶ (1996)

Table B.3: Litmathe Transfusion Risk Score (LTRS)*

Predictor	Score
Emergency operation	4
Cardiogenic shock	3
Urgent operation	2
Left ventricular ejection fraction <0.35	3
Anemia	3
Age>70 y	1
Female sex	1
Serum creatinine >1.6 mg/dL (141 µmol/L)	1
Redo operation	2
Insulin-dependent diabetes mellitus	1

* *Litmathe et al*¹⁵ (2003)

B.3. CLINIMETRIC PROPERTIES AND METHODOLOGICAL QUALITY ASSESSMENT

Clinimetric properties of the prediction indices were evaluated using the standards recommended by *Kirshner et al*¹²⁹ and *Feinstein*¹³⁰. They include item generation, item reduction, administration, coding, scoring, sensibility, reliability and validity. Furthermore, methodological quality was assessed according to the criteria recommended by *Wasson et al*¹³¹ and recently modified by *Laupacis et al*¹²⁷. The main changes made by *Laupacis* and colleagues were: increased emphasis on prospective validation, reliability of predictive variables, sensibility of derived rules, and guidance through the course of action rather than presenting a probability (Table B.4).

Table B.4: Methodological standards for clinical prediction indices*

<p>Outcome Definition Clinically important** Blind assessment when appropriate</p> <p>Predictive variable Identification and definition Blind assessment</p> <p>Important patient characteristics described</p> <p>Study site described</p> <p>Mathematical technique described</p> <p>Results of the rule described</p> <p>Reproducibility Of predictive variable** Of the rule**</p> <p>Sensibility Clinically sensible** Easy to use** Probability of disease described** Course of action described**</p> <p>Prospective validation</p> <p>Effect of clinical use prospectively measured</p>

* *Laupacis et al*¹²⁷, (1997)

** Included in the original methodological standards for prediction rules developed by *Wasson et al*¹³¹, (1985)

B.3.1. Item generation and reduction

Item generation refers to the approach used to bringing together a set of relevant variables (items) that might plausibly be included in the index (e.g. literature search), and item reduction refers to deletion of those items from the first version of an index that do not contribute to, or detract from, the usefulness on the index (e.g. statistically insignificant variable).

In the MTRS the items were generated using variables previously described as having association with blood transfusion (e.g. anemia, female sex, older age and small body-size)^{12,13,128}, and the clinical judgment of surgeons. Variables initially were reduced to variables that were known prior to operation (preoperative variables). The remaining variables were then further reduced by using forward stepwise multivariable logistic regression. The developers did not mention specifically what statistical approach they adopted to keep variables in or remove them from the model. However, according to the published manuscript, all included variables in the final model were statistically significant (P-value < 0.05), indicating that the developers kept only the statistically significant variables that independently predicted transfusion. In the LTRS, on the other hand, variable generation was not described, and variables were reduced using a forward stepwise multivariable logistic regression. Only statistically significant (P-value < 0.05) were kept in the model.

B.3.2. Administration, Coding and scoring

Administration refers to the approach used to administer an index to the consumer (e.g. physician). Coding and scoring refer to the approach used to code and assign weights (scores) to individual items in an index.

The final model included fourteen variables in the MTRS and ten variables in the LTRS. Regression coefficient and odds ratios were given for each variable. Independent predictive preoperative variables from the regression analysis were then used to generate a transfusion risk scoring system. Each variable in both scoring systems was given a specific weight based on its associated regression coefficient, odds ratio, and clinical relevance as judged by the surgeons. The MTRS and LTRS are additive algorithms to give single overall score ranging from 0 to 28 in the MTRS and from 0 to 21 in the LTRS. Clinicians use the measures by adding up the scores associated with variables in a given patient to get overall score. The overall score is then used to stratify patients from low to high risk as follows: low risk (0-1), intermediate risk (2-6), and high risk (7 or more) in the MTRS, and low risk (0-2), intermediate risk (3-7), and high risk (more than 7) in the LTRS. From the manuscripts, it is not clear how the developers of either scoring system assigned scores to variables and although it was mentioned that scores were based on beta coefficients, odds ratio, and clinical relevance, it was expected that either regression coefficients or odds ratios would be rounded to the next integer and used as a score¹³². Furthermore, authors did not describe how the risk cut-points were assigned.

B.3.3. SENSIBILITY

Sensibility of a clinical index refers to whether or not the index makes a clinical sense (a mixture of common sense, knowledge of pathophysiology, and clinical reality)¹³³. Components of sensibility are: purpose of the clinical index, face validity, content validity and feasibility. A systematic approach was used to evaluate the sensibility of the MTRS and LTRS based on the recommendations of *Feinstein*¹³³ and *Laupacis et al*¹²⁷.

B.3.3.a. Purpose

The purpose of the MTRS and LTRS was prediction and that was clearly addressed by the developers; the attribute was “risk of exposure to blood transfusion during or after CABG surgery”. Predictive variables were given clear definitions and the study site was a teaching, tertiary care hospital in both scoring systems. Patients included were patients undergoing isolated CABG surgery. No restrictions were applied to patients' demographic characteristics or urgency of the operation.

B.3.3.b. Face validity

Face validity is concerned with the judgmental appraisal of the *surface* of the instrument without profound attention to its component parts¹³³. The MTRS and LTRS were designed to be used by the medical team caring for CABG patients. Variables are logical and make biological sense in their association with the risk of exposure to allogeneic blood transfusion. The first four variables in the MTRS seem to be addressing the same clinical phenomenon namely urgency of the operation, for example, emergency operation (first variable) and catheterization-induced coronary

occlusion (fourth variable). Both of these variables are emergency conditions. Therefore, the fourth variable seems to be collinear with the first and might have been more practical to be presented as a combined variable.

B.3.3.c. Content validity

Content validity, as opposed to face validity, is the assessment of *underlying* components of an index¹³³. The MTRS and LTRS were developed retrospectively from clinical databases that were not designed specifically for these scoring systems. The developers did not give details on the missing data within the database and their extent. Furthermore, database validation and verification of data accuracy were not addressed. Ideally, developers should have used and reported ways to assess database accuracy such as re-abstracting a random sample of a given percentage of the medical records of CABG patients and comparing all outlying values to patients' records to identify and correct errors. The developers specified relevant variables statistically by using multivariable logistic regression. The developers kept only the statistically significant variables in the final predictive models. This approach may render models to be clinically less relevant. Clinical judgment is an important component and needs to be incorporated in the decision to keep variables or remove them from the model.

The developers did not give enough details in the published manuscripts about the modeling process, issues of collinearity, interaction and over-fitting of the models. Nevertheless the developers of the MTRS indicated that the model's calibration was assessed by the Hosmer-Lemeshow goodness-of-fit statistic with an associated P-value of 0.885. This indicates adequate fit as the Hosmer-Lemeshow goodness-of-fit statistics

compares the predicted probability with actual probability within population subgroups (i.e. the larger the p-value, the better the fit) ¹³⁴. The developer of the LTRS did not address the model calibration or fit. Table 5 summarizes the statistical details of the contents of both scoring systems.

Table B.5: Statistical details of *Magovern et al*, and *Litmathe et al* studies

Variable	Adjusted β -Coefficient		Adjusted Odds Ratio		P-Value
	Magovern ¹⁶	Litmathe ¹⁵	Magovern ¹⁶	Litmathe ¹⁵	
Emergency operation	2.083	1.98	7.6	6.9	<0.01
Cardiogenic shock	1.547	1.46	4.6	4.5	<0.04
Urgent operation	1.46	1.22	4.3	4.2	<0.01
Left ventricular ejection fraction <0.35	1.357	1.45	3.9	3.7	<0.01
Anemia	1.144	1.12	2.0	2.1	<0.01
Age*	0.912	1.01	1.9	1.8	<0.01
Female sex	0.675	0.55	1.9	1.6	<0.01
Serum creatinine	0.624	0.48	1.6	1.4	<0.01
Redo operation	0.614	0.48	1.8	1.4	<0.02
Insulin-dependent diabetes mellitus	0.579	0.46	1.7	1.2	<0.02
Catheterization-induced coronary occlusion	2.098	Not included	3.6	Not included	<0.01
Body Mass Index	0.983	Not included	1.9	Not included	<0.01
Peripheral vascular disease	0.655	Not included	1.9	Not included	<0.01
Serum albumin	0.492	Not included	1.5	Not included	<0.01

* Age >74 y in MTRS and Age>70 y in LTRS

B.3.3.d. Feasibility

The included variables and their aggregate scores are easy to understand and apply. Calculations do not require special tests or skills. The time spent to use the MTRS and LTRS does not seem to be an issue due to the simplicity of the calculations. An actual percentage of the risk of receiving blood transfusion would be more informative; however, the clinical application of logistic regression model would require a calculator. The developers chose selected cutoff values in the MTRS and LTRS and the variables were simplified (by categorization) to allow development of a simple rule for use in the routine clinical practice.

B.3.4. RELIABILITY

Reliability refers to the consistency across repeated measurements. The MTRS and LTRS are clinimetric indices that include unrelated clinical variables; therefore it is important to discuss the reliability of these variables individually.

B.3.4.a. Emergency operation, Urgent operation, Cardiogenic shock, Peripheral vascular disease

In the MTRS and LTRS, each one of the above clinical conditions (variables) was given a specific definition. However, these definitions were, for the most part, subjective and institution-dependent which may limit their generalizability. Additionally, definition variation may affect reliability of the data. Sources of variations include: first, the within clinician variation, as the same clinician may have two different clinical judgments about the same clinical problem at two different times. Second, the between-clinician variations, as two different clinicians may have two different opinions about the same

clinical problem. The third source of variation is the between-institution variations. For example, in the MTRS, emergency operation was defined as a procedure performed on a patient in unstable condition and refractory to all forms of therapy. At our institution (Toronto General Hospital), an emergency operation is defined as an operation that needs to be done within 12 hours of hospitalization. The fourth source of variation is the complexity of such clinical conditions, as there are often multidisciplinary teams involved in the clinical decision process. All of the above mentioned sources of variation emphasize the difficulty in reproducing the definitions of these clinical conditions. Therefore, reliability is adversely affected.

B.3.4.b. Left Ventricular Ejection Fraction (LVEF)

There are three methods of estimating LVEF: first, contrast ventriculography (CVG), which is considered to be the gold standard method. *Rogers et al*¹³⁵ showed that the correlation coefficient between repeated measurements by two different observers was 0.99 (inter-rater reliability). The correlation coefficient is an indicator of the overall fit of the least square line fitted through the plotted points between first and repeated measurements. Such high correlation was confirmed by other studies^{135,136}. The second method of measuring LVEF is radio-nucleotide ventriculography (RNVG), which has gained wide-spread use because of its reliability (correlation coefficient > 0.95), accuracy, and non-invasive nature¹³⁷⁻¹³⁹. The third method is echocardiography (ECHO), which is the least invasive; however, it is operator dependent. In the literature CVG and RNVG are considered as reference methods against which echocardiography is compared. In a recent systematic review conducted by *McGowan et al*¹⁴⁰, twenty-five studies comparing ECHO to reference methods, were identified. The reported

correlation coefficient between ECHO and the other reference methods ranged from 0.6 to 0.98. The consistency across repeated assessments in different studies with different measurement methods indicates reliability.

B.3.4.c. Hemoglobin, creatinine, and albumin levels

Hemoglobin assessments are used widely to screen individuals for anemia. The conventional method of measuring hemoglobin is reliable. It has been shown that the correlation coefficient between repeated measurements is greater than 0.95¹⁴¹.

Serum creatinine is the most widely used laboratory test to assess kidney function and repeated measurements are reliable in stable kidney function with correlation coefficient of more than 0.90¹⁴². Sources of variations include unstable renal function, muscle mass and age.

Albumin is a protein synthesized by the liver. Albumin is reliable in stable clinical conditions with correlation coefficients of more than 0.80^{143,144}. There are various sources of variations that could alter the albumin level. Most of these sources are within patient variability. They include nutritional status, hepatic impairment and renal impairment^{143,144}.

B.3.4.d. Gender, Redo Operation, Presence of Diabetes, Age and Low Body Mass Index

Gender, redo operation and presence of insulin- dependent diabetes mellitus are binary variables (YES/NO), and they are fixed over time. Therefore, their reliability is expected to be high. Recording error is a potential source of variability. Age and low body mass index are potentially less reliable than the former variables. Variations could result from date of birth associated errors (for age), and protocols used for weighing,

weighing scales, and errors in calculation or unit conversion (e.g. pound to kilogram for body mass index).

B.3.5. VALIDITY

Validity is defined as the extent to which an instrument measures what it is intended to measure. There are many ways of testing validity, the choice of which depends on the purpose of measurement. Since the purpose of the MTRS and LTRS is prediction of certain clinical outcome (exposure to allogeneic blood transfusion during or after CABG), validity was assessed through face validity, content validity, and criterion validity. Face validity and content validity were discussed under sensibility (see above).

B.3.5.a. Criterion validity

Criterion validity evaluates the relationship of the scale with other measures of the phenomenon under study; ideally, a “gold standard”. Criterion validity is of two types: concurrent validity and predictive validity¹⁴⁵. With concurrent validity the correlation is made at the same time, on the other hand, with predictive validity, the criterion will be available in the future¹⁴⁵ which is the case in the MTRS and LTRS.

For the prediction of the criterion to be valid, the sample size has to be appropriate to the data and number of predictive variables used in the model. General guidelines have been suggested for the minimum number of events per variable (EPV) required in the multivariable analysis. It is generally suggested that a minimum of ten events per variable analyzed are required to maintain the validity of the model¹⁴⁶⁻¹⁴⁸. In the MTRS and LTRS, the rates of transfusion were 60% and 33% respectively, and the number of events (blood transfusions) was more than 1000 and 132 respectively. If we

apply the EPV rule (number of events / number of variables) to the MTRS and LTRS, which included fourteen and ten independent predictive variables respectively, we get an EPV much larger than 10 indicating adequate sample size.

There are generally three methods of validating predictive models: data-splitting, cross-validation, and bootstrapping¹⁴⁹. The LTRS was not validated. The developers of the MTRS used a data-splitting technique, where a portion (80%) of the sample (n = 2,033) was used to develop the prediction index (training set), and the remaining portion (20%) of the sample (n = 422) was used to validate the index (validation set). Such splitting of the original sample to two parts carries two potential problems. First, it reduces the sample size for developing the predictive model. Second, the validation is in the same original dataset (i.e. same population) and that adversely affects the generalizability of the resultant clinical index. The most stringent method of validation is to externally validate the model in a different population. This validation method will test whether the instrument was properly translated in another population and whether cultural, geographical, or institutional variations make earlier findings non applicable. The literature search did not reveal any external cross-validation studies for the MTRS, and that leaves generalizability to be questioned.

The gold standard used for outcome is the exposure to allogeneic blood transfusion. Since the gold standard is binary, it is important to choose a score cutoff point in order to interpret the overall score in terms of the outcome categories. Receiver operating characteristic (ROC) curves provide a method whereby the investigator can select a cutoff point that optimizes the predictive ability of an index to those who receive blood transfusion (i.e. sensitivity) and those who do not (i.e. specificity). Predictive

accuracy then can be quantified by calculating the area under ROC curve. An area of 0.5 indicates no predictive discrimination and an area of 1.0 indicates perfect separation of patients with different outcomes ¹⁵⁰. The MTRS had an area under ROC in the validation group of 0.77 which indicates fair predictive accuracy.

B.4. DISCUSSION

B.4.1. Theoretical framework and definition of the concept

The risk of exposure to allogeneic blood transfusion during or after cardiac surgery (attribute) can be measured through the following categories (domains): 1) demographic factors and factors associated with low preoperative red cell volume, 2) emergency and unstable preoperative status, 3) comorbid conditions, and 4) others.

Demographic factors and factors associated with low preoperative red cell volume include: advanced age, female sex, low body mass index and low preoperative hemoglobin^{12,13,128}. Reduced red cell volume before the operation is exacerbated intra-operatively due to blood loss associated with the surgery and hemodilution caused by the extra crystalloid volume from the cardiopulmonary bypass circuit priming solution. These factors lead to an increase in the likelihood of exposure to allogeneic blood transfusion.

Emergency and unstable preoperative conditions before operation (e.g. arrest in the catheterization laboratory) are related to the risk of transfusion as many of these patients are anticoagulated or on antiplatelet medications at the time of operation. Survival is the overwhelming issue and low hemoglobin is not desirable. Furthermore, in such situations, there is little time for preoperative preparation and optimization of the physiological status; thus, many of the blood-conservation strategies cannot be applied¹⁴.

Comorbid conditions (e.g. diabetes mellitus and renal disease) are associated with the risk of transfusion because they lead to increases in the postoperative morbidity

and hospital length of stay which in turn, are associated with an increased need of transfusion^{80,151}.

Other variables that cannot be classified in the previous domains include type of operation, cardiopulmonary bypass time and redo operations. Redo operations are obviously associated with risk of transfusion because redo operations are technically more difficult and blood loss is more likely than first-time operations¹⁵². This framework is summarized in Table B.6.

Table B.6: Preoperative variables that have been shown to be associated with the risk of getting blood transfusion during or after cardiac surgery: Theoretical framework.

Domain	Variable (item)	Studies
Demographics and factors associated with low preoperative red cell volume	Age	11-16,19
	Preoperative hemoglobin	11-19
	Female sex	11,12,14-16
	Body mass index	16
Emergency and unstable preoperative status	Emergency operation	15,16,18,19
	Urgent operation	15-17,19
	Cardiogenic shock	11,15,16
	Catheterization-induced coronary occlusion	11,16
Comorbid conditions	Left ventricular ejection fraction	15,16
	Insulin-dependent diabetes mellitus	11,15,16
	Renal dysfunction	11,15-17,19
Others	Type of operation	153
	Cardiopulmonary bypass time	14
	Redo operation	11,15,16,18

B.4.2. Limitations of MTRS and LTRS

There are several factors that make the MTRS and LTRS less applicable to current practice. First, because they were developed and validated (validation is only applicable to the MTRS) at single institutions, it may not be possible to generalize their use to other institutions. Furthermore, for the clinical index to be appropriately used, the included variables have to be reproduced in the population to which it will be applied¹²⁷; that is, the reliability of the index. Several variables in the MTRS and LTRS are not reproducible in other institutions. An example is the definition of emergency operation where it was defined, in the MTRS, as a procedure performed on patient in unstable condition and refractory to all forms of therapy. At Toronto General Hospital (TGH), on the other hand, emergency operation is defined as an operation that needs to be done within 12 hours of hospitalization. This in turn precludes validating the MRTS and LTRS at TGH.

Second, these scoring systems were limited to CABG patients. Such limitation renders them to be inapplicable to other cardiac surgical procedures (e.g. valve, combined procedures, and others).

The third limitation is related to the definition of follow-up period. Entire hospitalization was used as the follow-up period in the MTRS and LTRS. Defining the follow-up period to include the entire hospitalization is a major problem as follow-up time is not equivalent for all patients which may lead to blood transfusions that are not related to surgery. *Magovern et al* found that the occurrence of postoperative complications after CABG surgery (e.g. sternal wound infection, systemic sepsis and gastro-intestinal bleeding) was significantly associated with postoperative blood

transfusion¹⁶. *Lithmathe et al* reported similar findings¹⁵. *Karkouti et al* critiqued using transfusion at any time during the entire hospitalization as the outcome and suggested limiting the follow-up period to one or two days after surgery¹⁴.

The fourth limitation is related to the statistical approach used. The MTRS and LTRS were developed based on the *forward stepwise* multiple logistic regression technique which kept only the statistically significant variables. This selection technique has been criticized as it negates clinical judgment¹⁴⁹. Clinical judgment and statistical findings need to be combined in decision-making. That becomes even more important when two or more variables are collinear (that is, both variables are measuring the same phenomenon). Clinical judgment is applied to keep the variable that is more important, feasible or easier to measure. The first four variables in the MTRS, for example, measure the same clinical phenomenon (i.e. emergency condition). Therefore, the risk of collinearity is increased. Some of these variables could be eliminated. Thereby; avoiding collinearity and making the index more practical. Furthermore, scores assigned to each variable in the MTRS and LTRS were based on odds ratios, clinical judgment and regression coefficients. *Harrell* critiqued using odds ratios to generate scores and suggested using regression coefficients¹⁵⁴. *Moons et al* critiqued a scoring system that was based on odds ratios from a logistic regression model and stated that: “because the clinical index was developed with logistic regression model which takes the form: $Logit(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_n X_n$, the formula shows that the predictive variables X_1, X_2, \dots, X_n are linearly and on an *additive* scale related to the outcome $Logit(Y)$, with relative weights $\beta_1, \beta_2, \dots, \beta_n$, that is, the regression coefficients. For logistic regression models, *Moons et al* stated that: for a particular subject with certain

profile X_1, X_2, \dots, X_n , the regression coefficients multiplied by the patients X values simply may be added to obtain the $Logit(Y)$, and with exponential transformation to get probability of Y . The exponential form of the model is: $Y = e^{\beta_0} \times e^{\beta_1 X_1} \times e^{\beta_2 X_2} \times \dots \times e^{\beta_n X_n}$, where e^{β} the odds ratio is (OR) for predictor X . The second formula shows that the odds ratios are not supposed to be added but multiplied. Another major problem with using odds ratios to assign scores to a predictor arises when predictors have an OR of one, reflecting regression coefficient of zero, that is, no association with the outcome”

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B.5. SUMMARY

Several studies have identified preoperative variables that are associated with the perioperative blood transfusion. However, few studies have used these variables to develop models for prediction of transfusion in patients undergoing cardiac surgery, and two studies used these models to construct predictive scoring systems. Though the MTRS and LTRS were the only scoring systems available, there are factors that make them inapplicable to current practice. Therefore, further studies are required to develop a transfusion risk score on the basis of methodological standards of measurement in clinical research.

CHAPTER C

Development and Validation of Transfusion Risk Understanding Scoring Tool (TRUST) to Stratify Cardiac Surgery Patients According to Their Blood Transfusion Needs

MATERIALS AND METHODS

C.1. OBJECTIVES

- 1- To measure the perioperative probability (in the operative and first postoperative days) of allogeneic blood exposure according to predefined preoperative variables (e.g. age, sex and hemoglobin level) in adult (age \geq 18 y) patients undergoing cardiac surgery at Toronto General Hospital after taking into consideration other factors (e.g. type of operation).
- 2- To construct a Transfusion Risk Understanding Scoring Tool (TRUST) to predict the perioperative probability (in the operative and first postoperative days) of allogeneic blood exposure.
- 3- To internally validate TRUST in a subset of the data.
- 4- To externally validate (cross-validate) TRUST at a different institution (Sunnybrook and Women's College Health Science Centre).

C.2. STUDY DESIGN

A retrospective cohort study design was adopted. We acknowledge that a prospective cohort study is theoretically a better study design as it gives the investigator the opportunity to measure the exposure variables of interest and provides a clear chronological sequence of events. However, for our objectives, a retrospective study

design becomes more efficient as it provides similar information (as those with a prospective design) with less cost and time.

C.3. TARGET POPULATION

The target population includes all consecutive adult patients (age \geq 18 y) undergoing cardiac surgery at TGH between May 3, 1999 and June 29, 2004.

Excluded patients are: 1) Jehovah's Witness patients, 2) those who participated PABD, as they may be transfused at higher hemoglobin concentrations than the general population¹⁵⁵, 3) those who received preoperative erythropoietin as it may reduce the need for allogeneic blood transfusion⁵⁴, 4) off-pump cardiac surgery patients as this surgical procedure is systematically different from on-pump procedures, and 5) heart transplantation and mechanical assist device patients as most (if not all) of them receive blood transfusion.

C.4. DEFINITION OF THE PRIMARY OUTCOME

Primary outcome was defined as the exposure to allogeneic blood transfusion (i.e. PRBC transfusion) during the follow-up time (operative and first postoperative days). This is a binary outcome that can take only YES or NO values. This outcome has been used previously in many clinical studies that addressed predictors of blood transfusion in cardiac surgery¹¹⁻¹⁸. Selection of such an outcome provides a prediction of those who will likely be exposed to blood transfusion. This in turn is important in providing a primary prevention measures that may help avoiding blood transfusion and consequently avoiding blood transfusion-related risks and cost.

C.5. PRIMARY EXPOSURE (INDEPENDENT VARIABLES)

C.5.1. Strategies to improve validity and reliability of exposure variables

Because our objective is to develop a valid, clear and simple index that can be used at other institutions, several steps were adopted (see below for details): first, focus was placed on the variables that are not site-specific (e.g. age, sex, body mass index and preoperative hemoglobin). These variables have been shown to be predictive at other institutions¹¹⁻¹⁹. Second, continuous variables were dichotomized for practical reasons, and cutoff values were determined according to clinical and statistical considerations (see below). Third, the resultant Transfusion Risk Understanding Scoring Tool (TRUST) was validated in a subset of the data. Additionally, TRUST was cross-validated at a second institution (Sunnybrook and Women's College Health Science Centre).

C.5.2. Definition of Primary Exposure and Clinimetric Properties (Validity and Reliability) of the Independent Variables

Primary exposure was defined as variables that are known prior to the time of surgery (preoperative) and may independently predict the primary outcome. These variables constitute the *theoretical framework* (see above: B.4.1).

C.5.2.a. Age

Age was defined as the age of the patient at the time of operation measured in years. This continuous variable was dichotomized to: 0= age less than the cutoff value and 1= age equals to or more than the cutoff value. Age is a hard clinical variable that is expected to be valid and reliable. Variations could result from date of birth associated errors; however, this seems to be unlikely as date of birth is considered to be one of the

identifying information of patients in the databases. Furthermore, all patients at TGH receive a hospital card with their date of birth printed, and the age of the patients is calculated by computer, thus, eliminating human errors. Several studies have shown that age is an independent predictor of blood transfusion after cardiac surgery ^{11-16,19}.

C.5.2.b. Gender

This hard clinical variable is defined as the sex of the patient at the time of operation coded as follows: 0= male sex and 1= female sex. Several studies have shown that gender is an independent predictor of blood transfusion after cardiac surgery ^{11,12,14-16}.

C.5.2.c. Body Mass Index

Body mass index (BMI) is calculated as weight in kilograms divided by height in meter squared. Weight and BMI have been shown to be predictors of blood transfusion after cardiac surgery ^{12,14,16}. BMI (as opposed to weight) adjusts weight for height; thus is a theoretically less biased measure. Furthermore, weight and height are collinear and indexing them to BMI avoids collinearity. BMI is measured at the time of operation using a standard hospital procedure for all patients, and then calculated by computer to avoid human errors. It is then dichotomized to: 0= BMI equal to or more than the cutoff value and 1= BMI less than the cutoff value.

C.5.2.d. Preoperative Hemoglobin Level

Hemoglobin assessments are used widely to screen individuals for anemia. The conventional method of measuring hemoglobin is reliable. It has been shown that the correlation coefficient between repeated measurements is greater than 0.95 ¹⁴¹. Several

studies have shown that preoperative hemoglobin is an independent predictor of blood transfusion after cardiac surgery^{14,15,18}. Hemoglobin level is a continuous variable measured in grams per liter (g/L). It is dichotomized to: 0=hemoglobin equals to or more than the cutoff value and 1= hemoglobin less than the cutoff value.

C.5.2.e. Preoperative Creatinine Level

Serum creatinine is the most widely used laboratory test to assess kidney function. Repeated measurements are reliable in stable kidney function with correlation coefficient greater than 0.90¹⁴². Sources of variations include unstable renal function, muscle mass and age. Estimated creatinine clearance (using the Cockcroft-Gault equation^{156,157}), as opposed to serum creatinine, is adjusted for patient's weight, age and sex, and therefore theoretically is less biased than serum creatinine. However in a recent study by *Wijeysundera et al*¹⁵⁸, both serum creatinine and creatinine clearance were correlated to clinical outcomes after cardiac surgery. Estimated creatinine clearance (as opposed to serum creatinine) has the disadvantage of being less practical because a mathematical formula has to be used for its calculation^{156,157}. Serum creatinine level has been shown to predict the need for blood transfusion after cardiac surgery in previous studies^{11,15-17,19}. It is a continuous variable measured in micromole per liter ($\mu\text{mol/L}$), and is dichotomized to: 0= creatinine level less than the cutoff value and 1=creatinine level equals to or more than the cutoff value.

C.5.2.f. Left Ventricular Ejection Fraction

There are three methods of estimating left ventricular ejection fraction (LVEF): first, contrast ventriculography (CVG), which is considered to be the gold standard method. *Rogers et al*¹³⁵ showed that the correlation coefficient between repeated

measurements by two different observers was 0.99. The correlation coefficient is an indicator of the overall fit of the least square line fitted through the plotted points between first and repeated measurements. Such high correlation was confirmed by other studies ^{135,136}. The second method of measuring LVEF is radio-nucleotide ventriculography (RNVG), which has gained wide-spread use because of its reliability (correlation coefficient > 0.95), accuracy, and non-invasive nature ¹³⁷⁻¹³⁹. The third method is echocardiography (ECHO), which is the least invasive. It is however, operator dependent. In the literature CVG and RNVG are considered as reference methods against which echocardiography is compared. In a recent systematic review conducted by *McGowan et al* ¹⁴⁰, 25 studies comparing ECHO to reference methods, were identified. The reported correlation coefficient between ECHO and the other reference methods ranged from 0.60 to 0.98. This continuous variable was dichotomized to: 0= LVEF less than 0.40 and 1= LVEF equals or more than 0.40. This cutoff point has been used in previous studies ^{15,16}. LVEF has been shown to be associated with the risk of exposure to blood transfusion during or after cardiac surgery ^{15,16}. At TGH, all previously mentioned methods for the estimation of LVEF were used.

C.5.2.g. Previous Cardiac Surgery (redo procedure)

Redo procedure is defined as a cardiac surgical procedure that is performed on the patient following a previous one. This hard binary clinical variable is coded as: 0=not a redo procedure and 1= redo procedure. Redo procedures have been shown to be independent predictors of the need for blood transfusion in cardiac surgery ^{15,16,18}.

C.5.2.h. Diabetes Mellitus

As the definitions of diabetes may vary, pharmacologically-treated diabetes mellitus (PTDM) was chosen as it is more reliable and valid definition that can be used at other institutions. Furthermore, it makes the use of this variable easy and practical (as opposed to blood sugar level or other biochemical markers). PTDM was defined as a patient who is using insulin or oral hypoglycemic medications for treatment of diabetes prior to surgery. This binary variable was coded as: 0= No PTDM and 1= PTDM. Diabetes mellitus prior to cardiac surgery has been shown to be associated with the risk of exposure to blood transfusion ^{11,15,16}.

C.5.2.i. Timing of the procedure

Timing of the procedure can be elective, semi-elective, semi-urgent, urgent and emergent. These definitions vary in different institutions. An example of that is the definition of urgent and emergent procedures. In one study, they were defined as: operations done within 48 hours of an acute ischemic event requiring an intraaortic balloon pump and inotropic agents or intravenous nitroglycerin, and procedures performed on a patient in unstable conditions and refractory to all forms of therapy respectively ¹⁶. At TGH, on the other hand, urgent and emergent operations are defined as: procedures done within 72 hours and 12 hours of the initial event respectively. Because our objective is to have an index with reproducible variables, timing of the operation was dichotomized to: 0=elective procedure and 1= non-elective procedure. We assume that this dichotomization will reduce the variability as the definition of an elective procedure is more reliable and valid, and avoids possible collinearity (e.g. urgent, semi-emergent, emergent).

C.5.2.j. Type of the procedure

Based on the work done by *Hardy et al*¹⁵³ to stratify cardiac surgical procedure according to blood transfusion needs, this variable was dichotomized to: 0= isolated procedures (e.g. isolated CABG, and isolated valve surgery), and 1= non-isolated procedures (e.g. CABG and valve surgery). Definitions of the primary exposure variables are summarized in Table C.1.

Table C.1.: Definition of Exposure variables

Domain	Variable definition	Type	Unit
Factors associated with low preoperative red cell volume	Age at time of operation	Continuous	year
	Preoperative hemoglobin	Continuous	g/dL
	Female sex	Binary	0/1
	Height	Continuous	cm
	Weight	Continuous	kg
	Body mass index	Continuous	kg/m ²
Emergency and unstable preoperative status	0=Elective or 1=Non-elective	Binary	0/1
Comorbid conditions	Left ventricular ejection fraction, obtained by echocardiography or angiography dichotomized as follows: 0 \geq 40%, 1: <40%	Binary	0/1
	Pharmacologically-treated diabetes mellitus	Binary	Yes/No
	Serum creatinine level	Continuous	μ mol/L
	Estimated creatinine clearance	Continuous	ml/min
Others	Type of operation classified as follows: 0=isolated procedure, and 1= non-isolated procedure	Categorical	0/1
	Previous cardiac surgery (redo operation)	Binary	0/1

C.6. CONFOUNDING VARIABLES AND EFFECT MODIFIERS

It has been shown that some intraoperative variables may increase the likelihood of exposure to allogeneic blood transfusion. Intraoperative variables that are associated with blood transfusion include type of operation^{19,153} and cardiopulmonary bypass time (CPBT)^{14,16,19}. Since the type of operation is known before the time of operation, it was considered a preoperative variable and included in the model. CPBT was not included in the predictive model as it was not known prior to the time of operation. Additionally, it was assumed that the effect of CPBT will be minimized because we included surgery types.

Administration of antifibrinolytic agents may reduce the risk of exposure to blood transfusion. At TGH, all patients receive Tranexamic acid (TXA) or aprotinin. Almost all patients receive TXA (>95%), and a minority (< 5%) receive aprotinin. Antifibrinolytic agents were not included as all patients are exposed to them and they are not known prior to the time of operation.

C.7. SAMPLE SIZE

General guidelines have been suggested for the minimum number of events per variable (EPV) required in the multivariable analysis. It is generally suggested that a minimum of ten events per variable analyzed are required to maintain the validity of the model¹⁴⁶⁻¹⁴⁸.

More than 2700 open-heart surgical procedures are performed every year at TGH¹⁴. A recent study by *Karkouti et al*¹⁴ showed that the rate of transfusion was 29.4% in patients undergoing elective first-time CABG at TGH. Our sample includes all consecutive patients admitted to TGH for cardiac surgery from May 1999 to June 2004

which encompasses more than 11,000 patients and therefore yields expected events of 3300. Our framework included 10 preoperative variables that are potentially predictive of the exposure of blood transfusion. Such a large number of events per variable ensures adequate sample size for model validity.

C.8. DATA ANALYSIS

C.8.1. Exploratory Analysis

The statistical software package SAS (version 8.2, SAS institute, Cary, NC) was used for all statistical analyses. Categorical variables were summarized as frequencies and percentages, and continuous variables as means and standard deviations.

The sample population was randomly divided into two groups: 2/3 of the total sample which was allocated to develop the predictive index (training set), and the remaining 1/3 was allocated to validate the index (validation set). Important exposure variables were tabulated for comparison of development and validation cohorts. Categorical variables were compared using the Pearson Chi-square test for independent proportions, and student t-test was used to compare continuous variables.

C.8.2. Dichotomization of continuous variables

For practical reasons, continuous variables under evaluation (age, weight, BMI, hemoglobin level, platelet count, International Normalized Ratio (INR), serum creatinine level and creatinine clearance) were dichotomized to get a practical index for clinical use. Best cutoff values were determined nonparametrically by ROC statistics, and the maximum area under ROC curve (AUC) was chosen as the cutoff value.

Receiver operating characteristic curves provide a method whereby the investigator can select a cutoff point that optimizes the predictive ability of the model to those who receive blood transfusion (i.e. sensitivity) and those who do not (i.e. specificity). An ROC curve is constructed by plotting the sensitivity (true positive fraction) on the vertical axis against the false positive fraction (1- specificity) on the horizontal axis for each decision threshold^{159,160}. Predictive accuracy can be then quantified by calculating the area under ROC curve^{159,161,162}. An area of 0.5 indicates no predictive discrimination (equivalent to chance alone) and an area of 1.0 indicates perfect separation of patients with different outcomes¹⁵⁰.

C.8.3. Model Development

As the outcome of interest is binary (exposure to allogeneic blood transfusion: YES/NO), multivariable logistic regression modeling techniques were used to determine the relationship between each independent variable and the exposure to allogeneic blood transfusion. Chi-square analyses and unadjusted logistic regression (to determine regression coefficient and odds ratios) were used for categorical variables and t-test for continuous variables. The odds ratio (OR) is a measure of the odds of an outcome occurring in one group relative to the odds of an outcome occurring in a reference group. An OR greater than one indicates a risk greater than that for the reference group, whereas an OR less than one indicates a risk less than that for the reference group. The reference group was selected to be protective compared to other categories for each variable under consideration, therefore producing OR estimates above one. Logistic regression was used to appropriately select and weight the predictor variables

for inclusion in the predictive index, assess the impact of the preoperative variables on the risk of exposure to allogeneic blood transfusion and facilitate the creation of a simple additive scoring system^{134,149}. Unadjusted (univariable) data-analyses were carried out initially to estimate the effect of each potentially predictive variable individually, followed by the adjusted (multivariable analysis).

Efforts were made to maximize predictive performance using variables that can be easily and reliably determined in clinical practice. All-variables regression was adopted for model building (i.e. no selection methods were applied: stepwise selection for example), and insignificant variables (p -value associated with regression coefficient > 0.05) were removed from the initial (all variables) model. Interaction terms were only kept in the model if they had biological plausibility.

C.8.4. Model Assessment

Here, ROC curves were used again to provide a method whereby the investigator can select a cutoff point that optimizes the predictive ability of the model to those who receive blood transfusion (i.e. sensitivity) and those who do not (i.e. specificity). An ROC curve was constructed by plotting the sensitivity (true positive fraction) on the vertical axis against the false positive fraction (1- specificity) on the horizontal axis for each decision threshold^{159,160}. Predictive accuracy was then quantified by calculating the area under ROC curve (AUC)^{159,161,162}. An area of 0.5 indicates no predictive discrimination (equivalent to chance alone) and an area of 1.0 indicates perfect separation of patients with different outcomes¹⁵⁰. Statistical properties of the AUC were determined based on Mann-Whitney statistics^{159,163}. This method is

recommended to estimate the standard error nonparametrically for AUC, as it is comparable to the sampling variability obtained from parametric approach ¹⁶⁴. Model calibration and fit were assessed using Hosmer-Lemeshow goodness-of-fit statistics which compares the predicted probability with actual probability within population subgroups; i.e. the larger the p-value, the better the fit ¹³⁴.

C.8.5. Item Reduction

As the objective was to construct a scoring system to predict the probability of exposure to blood transfusion, efforts were made to identify the best model for prediction that is accurate, sensible, valid, reliable, and easy to use with the least possible number of items. Efforts were made to replace variables that would require a calculator for their estimation (e.g. creatinine clearance and body mass index) by more readily available variables that do not require calculator (e.g. creatinine and weight). Furthermore, the full model was reduced by one item at a time and the best model for prediction was selected. This process was repeated until the model had only one item. A decision to select the best model was based on: first, validity, reliability, and sensibility of the model. Second, ROC statistics as quantified by the AUC (i.e. the larger the area the better the model) see above. Third, Hosmer-Lemeshow Goodness of fit statistics (i.e. the larger the p-value the better the model) see above. Fourth, the Maximum Likelihood Score method which aids in finding a specified number of best models containing one or more variables up to the single model containing all of the explanatory variables ¹⁶⁵. The criterion used to determine "best" is based on the global score chi-squared statistic ¹⁶⁵. For two models A and B, each having the same number of explanatory variables, model A is considered to be better than model B if the global score chi-squared statistic for A

exceeds that for B ¹⁶⁵. Fifth, the model fit statistics: *Akaike* Information Criterion (AIC) and the Schwarz Criterion (SC). AIC and SC can be used to compare models with different number of variables, and the ones with smaller values are preferred ¹⁶⁶.

C.8.6. Score Assignment

Score assignment for each predictor can be determined using the following methods: first, scores are assigned by rounding the OR estimate for each independent variable in the final model to the nearest integer, assigning a score of zero to the reference group. This method has been used previously to develop the length of ICU stay following cardiac surgery ^{167,168}. Similarly, the Charlson Comorbidity Index was created from simple addition of hazard ratios ¹⁶⁹. Second, the scoring system can be developed based on assigning values by increasing integer, starting with zero for the reference category ¹⁷⁰. Third, the model is evaluated using a scoring system based on logistic regression coefficient estimates. Here, logistic regression coefficient estimates are multiplied (e.g. by ten) then rounded to the nearest integer to develop an additive scoring system, a method suggested by *Harrell* ¹⁵⁴ who critiqued previous methods that were not based on regression coefficients (see section B.4.2).

Score assignment for each predictor variable in our index was based on the method suggested by *Harrell* as it is the most methodologically and mathematically sound method ¹³². Specifically, the regression coefficient of each predictive variable was multiplied by 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. Resultant numbers were rounded to next integer, therefore, getting 10 different additive scoring systems from the same model.

ROC statistics were used to determine the best scoring system (i.e. the one with the highest discriminatory performance as quantified by AUC).

C.8.7. Index Validation

The final TRUST was validated in a randomly selected subset of the data (1/3 of the dataset), and ROC analysis was conducted to assess the discriminatory performance of the index in the validation cohort. The predicted probabilities at each total score were compared to the observed proportions of patients exposed to blood transfusion.

C.8.8. Index Cross-Validation and Sensitivity Analysis

The most stringent method of validating an index is to apply it to a different population (different from the development population) to evaluate its performance. Cross-validation of TRUST (i.e. validation of the model in an external dataset) was performed at Sunnybrook and Women's College Health Science Centre. Area under the curve derived from ROC analysis was used to assess the discriminatory performance of the developed scoring system. Furthermore, the observed proportions of patients exposed to blood transfusion at each total score were compared to the predicted probabilities by TRUST.

Additionally, as transfusion practice may change over time, a sensitivity analysis to assess the robustness of TRUST was carried out. Data were stratified by year of operation (from 1999 to 2004), thereby applying TRUST to six different datasets. Again, ROC statistics were used, and observed proportions were compared to predicted probabilities.

C.9. DATA SOURCES AND MANAGEMENT

The primary data sources for the model development and internal validation were: the cardiac surgery clinical database and the cardiac anesthesia clinical database at TGH. The validity of the cardiac surgery clinical database is maintained by a database manager who checks the data completed by physician against medical records. The validity of the cardiac anesthesia database is maintained by re-abstracting a random sample of 10 percent of the records. In addition all outlying values are compared to patients' records to identify and correct errors in the database.

The primary data source for the model cross-validation (external validation) was the cardiac surgery clinical database at Sunnybrook and Women's College Health Science Centre. Here again, a database manager checks the data completed by physicians against medical records. All electronic datasheets were kept in a secure locked cabinet to ensure data security.

C.10. ETHICS

Research Ethics Board (REB) approval from the University Health Network Research Ethics Board was obtained (Appendix C.1). REB approval from the Sunnybrook and Women's College Health Science Centre was obtained (Appendix C.2). REB approval from the University of Toronto was obtained (Appendix C.3, and Appendix C.4).

CHAPTER D

RESULTS

D.1. DESCRIPTIVE STATISTICS

The final dataset included information on 11,113 adult patients, who underwent cardiac surgery at TGH between May 3, 1999 and June 29, 2004. Random allocation created a model development cohort with 7,446 patients (2/3 of the total sample size), and a validation group of 3,667 patients (1/3 of the total sample size). The missing data were 2.4%, and 2% in the development and validation cohorts respectively. Statistical details of these groups are tabulated in Table D.1. Development and validation groups were similar in all respects evaluated ($P > 0.05$).

Exposure to blood transfusion was defined as the exposure to blood in the operative and first postoperative days. 51.5% and 52.4% of the patients were exposed to blood transfusion in the development and validation cohorts respectively (Figure D.1).

D.2. DICHOTOMIZATION OF CONTINUOUS VARIABLES

The cutoff values were: 65 year for age, 135 g/L for hemoglobin, $255 \times 1000/\text{mm}^3$ for platelets, 1.1 for INR, 120 $\mu\text{mol/L}$ for serum creatinine, 75 ml/minute for estimated creatinine clearance, 77 Kg for weight and 27 Kg/m^2 for BMI. Table D.2 summarizes these cutoff values. More details of different cutoff values are presented in Appendix D.1.

D.3. MODEL DEVELOPMENT

D.3.1. Univariable (unadjusted) data analysis

Univariable data analyses that include unadjusted regression coefficients, and odds ratio estimates were carried out for all variables under evaluation. Continuous variables (age, hemoglobin level, platelets count, serum creatinine, estimated creatinine clearance, INR, and body mass index) were analyzed initially in the continuous form, and as binary variables. All variables were significantly associated with the risk of exposure to blood transfusion ($P < 0.05$) with the exception of platelet count as a binary variable ($P = 0.09$). Table D.3 summarizes the statistical details of the unadjusted analysis.

D.3.2. Multivariable (adjusted) data analysis and Model Assessment

All candidate variables were examined using logistic regression. Analyses of all variables with no dichotomization of continuous variables revealed that platelet count, and INR were not significantly associated with the risk of blood transfusion ($P > 0.05$). Dichotomization of continuous variables showed similar results. Therefore, insignificant variables (platelets count and INR) were excluded. The full model (Model A) included ten binary variables. The area under the ROC curve for model A was 0.80 (Standard Error (SE) = 0.0052) and the probability associated with Hosmer-Lemeshow goodness of fit statistic (PHL) was 0.90. Table D.4 summarizes the statistical details of model A.

D.3.3. Improving feasibility of Model A

The above full model (Model A) contains ten statistically significant variables. Because two of these variables, creatinine clearance and BMI, require an arithmetic calculation, efforts were made to replace them by simpler variables that do not require calculation. Estimated creatinine clearance was replaced by serum creatinine level, and BMI was replaced by body weight. The AUC of the resultant model (Model B) was 0.80 (SE = 0.0051), and PHL=0.41. Table D.5 summarizes the statistical details of Model B.

D.3.4. Item reduction of Model B

Further attempts were made to simplify model B by reducing its items while maintaining the highest possible discriminatory performance of the model. Model B contains ten statistically significant variables that independently predict the exposure to blood transfusion. Model B was reduced by one item at a time and the best model for prediction was selected based on clinical, practical and statistical criteria described in section C.8.5. Of all best subsets, the eight item model (Model C) was selected as the final model with an AUC = 0.80 (SE= 0.0051), and PHL = 0.97. Table D.6 summarizes the statistical properties of model B, and all subsets of the reduced model. Table D.7 summarizes the statistical details of the final model used to construct the index (Model C).

D.4. SCORE ASSIGNMENT

Scores assigned to each variable in the final model (Model C) were based on the regression coefficients derived from the adjusted logistic regression. To get a practical additive scoring algorithm, regression coefficients were multiplied by one, two, three, four, five, six, seven, eight, nine, and ten. The resultant numbers were rounded to the next integer. This approach has yielded ten different additive scoring systems with a total scores ranging from 8 to 59. Discriminatory performance of each scoring system was evaluated nonparametrically using ROC statistics. Of these ten candidate scoring systems, the second scoring system with each of the eight regression coefficients multiplied by 2 and rounded to the next integer was the simplest scoring system with the maximum discriminatory performance (AUC = 0.80, SE = 0.0052, PHL= 0.99). The first scoring system (regression coefficient multiplied by 1 and rounded to the next integer) was the simplest scoring system (where the total score was simply the sum of number of the variables) with similar discriminatory performance to the second one (AUC=0.79, SE=0.0052, PHL=0.70). The simplest scoring system had a better performance in the different cohorts of patients. Table D.8 summarizes the method used to derive scores, and Table D.9 summarizes the discriminatory performance of the candidate scoring systems. Based on the discriminatory performance, fit statistics and on ease of use, the first scoring system (regression coefficient multiplied by 1 and then rounded to the next integer) was selected for derivation of the final transfusion risk understanding scoring tool (TRUST).

D.5. TRANSFUSION RISK UNDERSTANDING SCORING TOOL (TRUST)

TRUST includes eight variables. Independent predictive preoperative variables from the regression analysis were then used to generate a transfusion risk scoring system. Each variable was given a specific weight based on its associated regression coefficient (regression coefficient multiplied by 1 and then rounded to the next integer). The TRUST is an additive algorithm to give a single overall score ranging from 0 to 8 (i.e. number of variables is the total score). Based on the predicted probabilities, the overall score is then used to stratify patients from baseline to very high risk as follows: baseline risk (0), low risk (1), intermediate risk (2), high risk (3) and very high risk (4 or more). The probabilities of exposure to blood transfusion are arbitrarily divided into five quintiles: (0.0- <0.2), (0.2- <0.4), (0.4- <0.6), (0.6- <0.8), and (0.80 and more) in the baseline, low, intermediate, high, and very high groups respectively. Table D.10 and Figure D.2.

D.6. SCORING SYSTEM ASSESSMENT

D.6.1. Internal Validation

The observed proportions of patients exposed to blood transfusion at each different total score value in the development and validation cohorts were compared to the predicted probabilities by TRUST. Almost all of the observed proportions fall within the 95% confidence limits of the predicted probabilities. All observed proportions fall within the predicted probability quintiles of TRUST: (AUC= 0.79, SE=0.0052) and (AUC=0.78, SE=0.0076) for the development and internal validation cohorts respectively. Table D.11 gives details of all observed proportions and the statistical

details in different cohorts of patients. Figure D.3, and D.4 depict the scoring system assessment graphically.

D.6.2. External validation (cross-validation)

Between June 1999 and May 2004, information on 5,316 consecutive adult cardiac surgery patients was obtained from the Sunnybrook cardiac surgery clinical database. 3.2% of the data were missing. The area under ROC curve was 0.81 (SE=0.006). All observed proportions of patients exposed to blood transfusion fell within the predicted limits of TRUST. Table D.11, and Figure D.4.

D.6.3. Sensitivity analysis

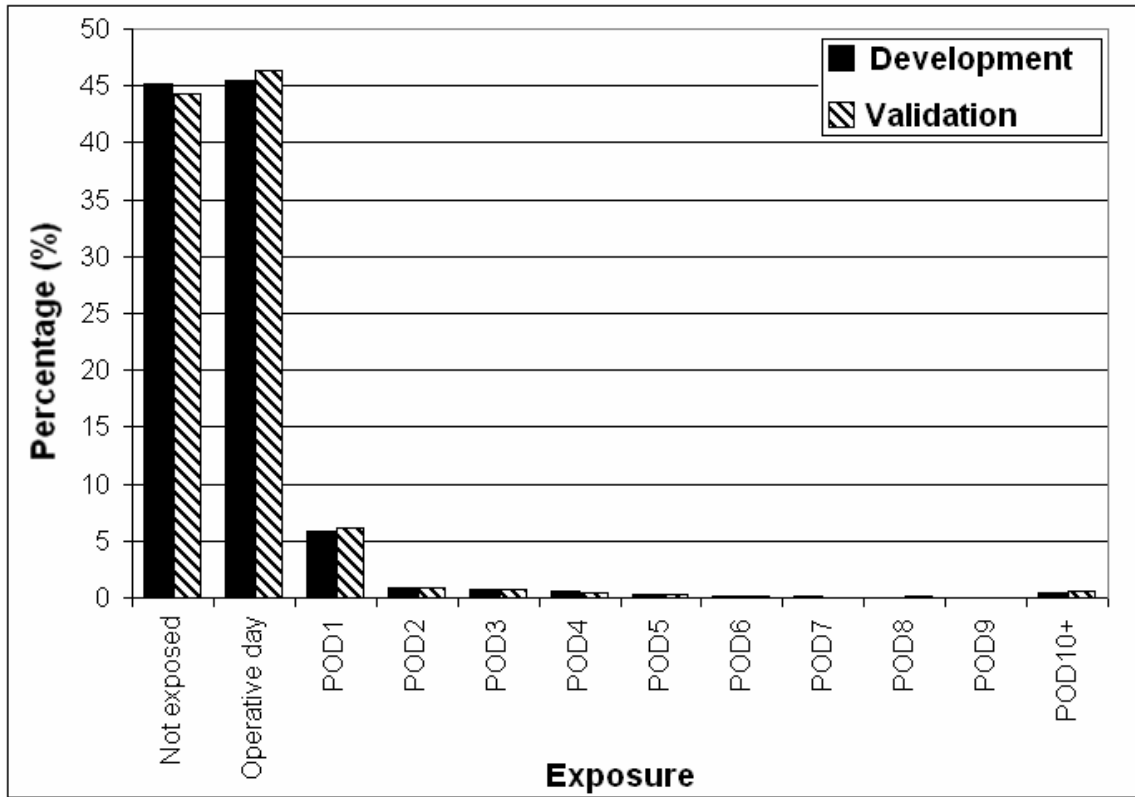
The development dataset was divided into six subsets based on the year of operation (1999- 2004). Such data allocations was carried out to test the robustness of the TRUST scoring system in different data subsets and to examine if the it is sensitive to year of operation as blood transfusion practice may change over time. Approximately all observed proportions of patients exposed to blood transfusions fell into the risk groups of TRUST. For the years 1999 to 2004 the AUC estimates for TRUST were 0.79, 0.80, 0.80, 0.79, 0.75, and 0.82 respectively. Table D.12, and Figure D.5

Table D.1: Statistical details of development and validation cohort

Variable	Development Cohort (N=7446)			Validation Cohort (N=3667)			P-Value
	n	mean	(SD)	n	mean	(SD)	
Age (years)	7427	62.5	12.1	3662	62.1	12.6	0.11
Hemoglobin (g/L)	7311	134.0	15.5	3617	133.8	15.2	0.71
Platelet (x1000/mm ³)	7276	231.8	69.7	3602	231.0	70.3	0.54
INR	7300	1.0	0.2	3612	1.0	0.1	0.59
Serum creatinine (µmol/L)	7409	97.4	62.2	3649	97.3	63.0	0.91
Estimated creatinine clearance (ml/min)	7406	83.0	32.1	3646	84.8	32.8	0.27
Height (cm)	7421	168.5	10.2	3656	168.5	10.6	0.83
Weight (Kg)	7424	79.0	16.1	3659	79.0	15.7	0.87
BMI (kg/m ²)	7420	27.7	5.6	3656	27.9	6.4	0.39
CPBT (min)	7421	100.6	37.6	3661	101.0	40.3	0.62
	n		%	n		%	P-Value
Female sex	2009		27.0	969		26.4	0.51
Aprotinin	384		5.2	213		5.8	0.16
EACA	6927		94.7	3404		94.1	0.16
Non-elective surgery	3054		41.2	1525		41.6	0.63
Redo surgery	632		8.5	325		8.8	0.51
LVEF < 40%	1513		20.4	779		20.2	0.28
Diabetes	1955		26.3	921		25.1	0.18
IDDM	402		5.4	201		5.5	0.86
CABG	5700		76.7	2780		75.9	0.33
Aortic valve	1368		18.4	708		19.3	0.24
Mitral valve	983		13.2	492		13.4	0.77
Tricuspid valve	192		2.5	104		2.8	0.43
Pulmonary valve	114		1.5	57		1.5	0.93
Other procedures	994		13.4	513		14.0	0.36

INR: International normalized ratio, BMI: Body mass index, CPBT: Cardio-pulmonary bypass time, EACA: Epsilon aminocaproic acid, LV: Left ventricle ejection fraction, IDDM: Insulin-dependent diabetes mellitus, CABG: Coronary artery bypass grafting

Figure D.1: Exposure to blood transfusion over time



POD: Post-Operative Day

Table D.2: Dichotomization of continuous variables

Variable	Unit	Cut-off value
Age	year	65
Hemoglobin	g/L	135
Platelet	(x1000/mm ³)	255
International Normalized Ratio (INR)	No unit	1.1
Serum creatinine	μmol/L	120
Estimated creatinine clearance	ml/minute	75
Weight	kg	77
Body Mass Index	kg/m ²	27

Table D.3. Unadjusted odds ratio estimates for independent variables (univariable analysis)

Variable	β SE	OR	LCL	UCL	AUC SE
Age ¹	0.042 0.002	1.044	1.039	1.048	0.655 0.006
Age ²	0.957 0.048	2.60	2.37	2.859	0.617 0.006
Hemoglobin ¹	-0.071 0.002	0.931	0.927	0.935	0.759 0.006
Hemoglobin ²	1.650 0.051	5.211	4.714	5.760	0.694 0.006
Platelets ¹	0.001 0.0003	1.001	1.001	1.002	0.519 0.007
Platelets ²	-0.078 0.047	0.925	0.844	1.014	0.510 0.007
INR ¹	0.595 0.127	1.814	1.414	2.326	0.538 0.007
INR ²	0.267 0.050	1.305	1.184	1.439	0.530 0.007
Creatinine ¹	0.004 0.001	1.004	1.002	1.005	0.514 0.007
Creatinine ²	0.813 0.076	2.255	1.945	2.616	0.542 0.007
Creatinine Clearance ¹	-0.025 0.001	0.975	0.973	0.977	0.713 0.006
Creatinine Clearance ²	1.300 0.050	3.671	3.331	4.045	0.654 0.006
Body Mass Index ¹	-0.068 0.005	0.934	0.925	0.943	0.613 0.006
Body Mass Index ²	0.689 0.047	1.992	1.816	2.185	0.585 0.007
Weight ¹	-0.047 0.002	0.954	0.951	0.957	0.699 0.006
Weight ²	1.220 0.050	3.384	3.075	3.724	0.647 0.006
Female sex	1.352 0.0581	3.865	3.449	4.331	0.624 0.006
Non-Elective Surgery	0.717 0.048	2.048	1.864	2.251	0.586 0.007
Redo Surgery	0.433 0.085	1.541	1.304	1.822	0.517 0.007
LV Grade >2	0.395 0.058	1.485	1.324	1.665	0.532 0.007
Diabetes	0.237 0.053	1.267	1.142	1.406	0.523 0.007
Combined Surgery	0.506 0.058	1.659	1.482	1.858	0.542 0.007

β = Regression Coefficient, SE= Standard Error, OR=Odds Ratio, LCL= 95% lower Confidence Limit, UCL= 95% Upper Confidence Limit. AUC= Area under Receiver Operating Characteristics Curve, 1= Continuous, 2= Binary, LV Grade= Left Ventricular Grade, -2Log= -2Log Likelihood,

Table D.4: Statistical details of the full model (Model A)

Parameter	DF	Regression Coefficient	Standard Error	Odds Ratio	95% LCL	95% UCL	P-Value
Hemoglobin	1	1.106	0.058	3.02	2.70	3.39	<0.0001
Female Sex	1	1.078	0.069	2.94	2.57	3.37	<0.0001
Redo surgery	1	0.654	0.107	1.92	1.56	2.37	<0.0001
Creatinine Clearance	1	0.637	0.064	1.89	1.67	2.14	<0.0001
Non-Elective Surgery	1	0.584	0.058	1.79	1.60	2.01	<0.0001
Age	1	0.554	0.062	1.74	1.54	1.96	<0.0001
Body Mass Index	1	0.522	0.058	1.69	1.51	1.89	<0.0001
Non-Isolated Surgery	1	0.508	0.071	1.66	1.45	1.91	<0.0001
LV Grade > 2	1	0.384	0.070	1.47	1.28	1.69	<0.0001
Diabetes	1	0.214	0.064	1.24	1.09	1.40	<0.0001

DF= Degrees of Freedom, LCL= Lower Confidence Limit, UCL= Upper Confidence Limit

Table D.5: Statistical details of the full model (Model B)

Parameter	DF	Regression Coefficient	Standard Error	Odds Ratio	95% LCL	95% UCL	P-Value
Hemoglobin	1	1.119	0.059	3.06	2.73	3.43	<0.0001
Female Sex	1	0.883	0.071	2.42	2.10	2.78	<0.0001
Redo surgery	1	0.645	0.107	1.91	1.54	2.35	<0.0001
Creatinine Level	1	0.599	0.090	1.82	1.53	2.17	<0.0001
Non-Elective Surgery	1	0.602	0.059	1.83	1.63	2.05	<0.0001
Age	1	0.754	0.056	2.13	1.90	2.37	<0.0001
Body Weight	1	0.947	0.058	2.58	2.30	2.89	<0.0001
Non-Isolated Surgery	1	0.517	0.071	1.68	1.46	1.93	<0.0001
LV Grade > 2	1	0.394	0.070	1.48	1.29	1.70	<0.0001
Diabetes	1	0.180	0.064	1.20	1.06	1.36	<0.0001

DF= Degrees of Freedom, LCL= Lower Confidence Limit, UCL= Upper Confidence Limit

Table D.6: Statistical properties of model B and subset models

	10		8***							
Items	Full Model Model B	9	Reduced Model Model C	7	6	5	4	3	2	1
1	HGB	HGB	HGB	HGB	HGB	HGB	HGB	HGB	HGB	NHGB
2	AGE	AGE	AGE	AGE	AGE	AGE	AGE	AGE	AGE	
3	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT	WEIGHT		
4	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE			
5	NONELECT	NONELECT	NONELECT	NONELECT	NONELECT	NONELECT				
6	COMBINED	COMBINED	COMBINED	COMBINED	COMBINED					
7	CREAT	CREAT	CREAT	CREAT						
8	REDO	REDO	REDO							
9	POORLV	POORLV								
10	DIABETES									
AUC	0.804	0.803	0.801	0.798	0.795	0.789	0.782	0.773	0.735	0.694
HLP	0.408	0.638	0.971	0.622	0.635	0.6189	0.509	0.244	0.996	0
SCORE	1967.602	1962.041	1939.439	1913.164	1872.797	1816.583	1738.606	1650.609	1495.610	1097.213
AIC	7838.558	7844.495	7888.711	7923.005	7986.404	8059.811	8185.636	8301.986	8734.134	8985.518
SC	7914.333	7913.381	7950.723	7978.127	8034.651	8101.165	8220.108	8329.563	8754.818	8999.312
-2LogL	7816.558	7824.495	7870.711	7907.005	7972.404	8047.811	8175.636	8293.986	8728.134	8981.518

AUC: Area Under ROC Curve, HLP: Probability associated with Hosmer-Lemeshow Goodness of Fit, SCORE: Likelihood score, AIC: Akaike Information Criterion, SC: Schwarz Criterion, -2LogL: minus two multiplied by the logarithm of the Likelihood, HGB: Hemoglobin Level, CREAT: Creatinine Level, NONELECT: non-elective surgery, COMBINED: non-isolated surgery, and ***: Model C

Table 7: Statistical details of the final model (Model C)

Parameter	DF	Regression Coefficient	Standard Error	Odds Ratio	95% LCL	95% UCL	P-Value
Hemoglobin	1	1.15	0.06	3.15	2.81	3.53	<0.0001
Female Sex	1	0.84	0.07	2.42	2.02	2.66	<0.0001
Redo surgery	1	0.64	0.11	2.32	1.53	2.33	<0.0001
Creatinine Level	1	0.63	0.09	1.88	1.58	2.24	<0.0001
Non-Elective Surgery	1	0.64	0.06	1.90	1.70	2.13	<0.0001
Age	1	0.76	0.06	2.14	1.91	2.38	<0.0001
Body Weight	1	0.93	0.06	2.53	2.26	2.83	<0.0001
Non-Isolated Surgery	1	0.52	0.07	1.67	1.46	1.92	<0.0001

DF= Degrees of Freedom, LCL= Lower Confidence Limit, UCL= Upper Confidence Limit

Table D.8: Score assignment

Variable	BETA	BETAx1* (TRUST)	BETAx2*	BETAx3*	BETAx4*	BETAx5*	BETAx6*	BETAx7*	BETAx8*	BETAx9*	BETAx10*
COMBINED	0.515	1	1	2	2	3	3	4	4	5	5
REDO	0.637	1	1	2	3	3	4	4	5	6	6
CREAT	0.632	1	1	2	3	3	4	4	5	6	6
NONELECT	0.642	1	1	2	3	3	4	4	5	6	6
AGE	0.759	1	2	2	3	4	5	5	6	7	8
FEMALE	0.840	1	2	3	3	4	5	6	7	8	8
WEIGHT	0.928	1	2	3	4	5	6	6	7	8	9
HGB	1.147	1	2	3	5	6	7	8	9	10	11
MIN	0	0	0	0	0	0	0	0	0	0	0
MAX	6.0994	8	12	19	26	31	38	41	48	56	59
AUC	0.80	0.79	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
SE	0.0051	0.0052	0.0052	0.0052	0.0051	0.0051	0.0051	0.0051	0.0051	0.0051	0.0051
HLP	0.97	0.70	0.99	0.40	0.25	0.96	0.99	0.91	0.91	0.93	0.98

AUC: Area Under ROC Curve, HLGf: Probability associated with Hosmer-Lemeshow Goodness of Fit, HGB: Hemoglobin Level, CREAT: Creatinine Level, NONELECT: non-elective surgery, COMBINED: non-isolated surgery, MIN: Minimum score, MAX: Maximum score, BETA: regression coefficient, and *: Rounded to next integer

Table D.9: Comparison between the candidate scoring systems

	Simplest (TRUST) $\beta * 1$	Simple $\beta * 2$
Minimum score	0	0
Total score	8	12
Development cohort		
AUC	0.79	0.80
HLP	0.70	0.99
Validation cohort		
AUC	0.78	0.78
HLP	0.68	0.65
Cross-validation cohort		
AUC	0.81	0.81
HLP	0.22	0.01
1999 cohort		
AUC	0.79	0.79
HLP	0.07	0.07
2000 cohort		
AUC	0.80	0.81
HLP	0.73	0.96
2001 cohort		
AUC	0.80	0.80
HLP	0.50	0.09
2002 cohort		
AUC	0.79	0.79
HLP	0.98	0.97
2003 cohort		
AUC	0.75	0.76
HLP	0.20	0.44
2004 cohort		
AUC	0.82	0.83
HLP	0.01	0.04

AUC: Area under receiver operating characteristic curve

HLP: Probability associated with Hosmer-Lemeshow goodness of fit

β : Regression coefficient

Table D.10: Transfusion Risk Understanding Scoring Tool (TRUST)

Variable	Score
Hemoglobin level < 135 g/L*	1
Weight < 77 kg	1
Female sex	1
Age > 65 year	1
Non-elective surgery	1
Serum creatinine level > 120 µmol/L**	1
Previous cardiac surgery	1
Non-isolated surgery	1
Interpretation of the total score	
(0) Baseline risk	→ Probability of exposure to transfusion (0.00-0.19)
(1) Low risk	→ Probability of exposure to transfusion (0.20-0.39)
(2) Intermediate risk	→ Probability of exposure to transfusion (0.40-0.59)
(3) High risk	→ Probability of exposure to transfusion (0.60-0.79)
(4-8) Very high risk	→ Probability of exposure to transfusion (0.80-1.00)
* 135 g/L of hemoglobin = 13.5 g/dL	
** 120 µmol/L of serum creatinine = 1.36 mg/dL	
Exact Probabilities can be calculated using this formula: $P = \frac{e^{-1.9503+(0.8377 \times TotalScore)}}{1+e^{-1.9503+(0.8377 \times TotalScore)}}$	

Table D.11: TRUST: Observed and predicted probabilities in different patients' cohorts

TRUST overall score	Lower limit of predicted probability by TRUST	Upper limit of predicted probability by TRUST	Predicted probability	95% lower confidence limit of the predicted probability	95% upper confidence limit of the predicted probability	Observed proportions in development cohort who were exposed to transfusion	Observed proportions in validation cohort who were exposed to transfusion	Observed proportions in cross-validation cohort who were exposed to transfusion
0	0	19	12.5	11.3	13.8	12.4	15.4	06.9
1	20	39	24.7	23.3	26.3	24.4	25.9	20.4
2	40	59	43.2	41.8	44.5	42.9	43.7	36.8
3	60	79	63.7	62.3	65.1	63.9	62.9	58.9
4	80	100	80.2	78.8	81.6	81.5	80.6	80.9
5	80	100	90.4	89.2	91.4	90.3	88.8	91.4
6	80	100	95.6	94.8	96.2	93.6	91.2	100
7	80	100	98.0	97.6	98.4	85.7	93.3	100
8	80	100	99.1	98.9	99.3	100	100	.
AUC						0.79	0.78	0.81
HLP						0.70	0.68	0.22

AUC: Area under the curve, HLP: Probability associated with Hosmer-Lemeshow goodness of fit

Table D.12: TRUST: Observed and predicted probabilities in different patients' cohorts: Sensitivity analysis

TRUST overall score	Lower limit of predicted probability by TRUST	Upper limit of predicted probability by TRUST	Predicted probability	95% lower confidence limit of the predicted probability	95% upper confidence limit of the predicted probability	Observed proportions of patients in 1999 cohort who were exposed to transfusion	Observed proportions of patients in 2000 cohort who were exposed to transfusion	Observed proportions of patients in 2001 cohort who were exposed to transfusion	Observed proportions of patients in 2002 cohort who were exposed to transfusion	Observed proportions of patients in 2003 cohort who were exposed to transfusion	Observed proportions of patients in 2004 cohort who were exposed to transfusion
0	0	19	12.5	11.3	13.8	13.4	7.9	15.5	15.4	15.7	14.5
1	20	39	24.7	23.3	26.3	16.1	20.7	28.8	31.2	25.7	26.5
2	40	59	43.2	41.8	44.5	35.2	36.1	45.8	49.8	43.3	54.3
3	60	79	63.7	62.3	65.1	48.7	60.2	68.4	71.1	58.7	78.4
4	80	100	80.2	78.8	81.6	73.8	76.1	86.8	84.4	77.8	92.6
5	80	100	90.4	89.2	91.4	89.8	90.3	91.6	95.8	81.4	89.1
6	80	100	95.6	94.8	96.2	88.9	96.4	96.8	91.3	86.4	100
7	80	100	98.0	97.6	98.4	100	80.0	100	75.0	81.8	100
8	80	100	99.1	98.9	99.3	.	.	.	100	.	.
AUC						0.79	0.80	0.80	0.79	0.75	0.82
HLP						0.07	0.73	0.46	0.98	0.20	0.01

AUC: Area under the curve, HLP: Probability associated with Hosmer-Lemeshow goodness of fit

Figure D.2: Predicted probabilities by TRUST

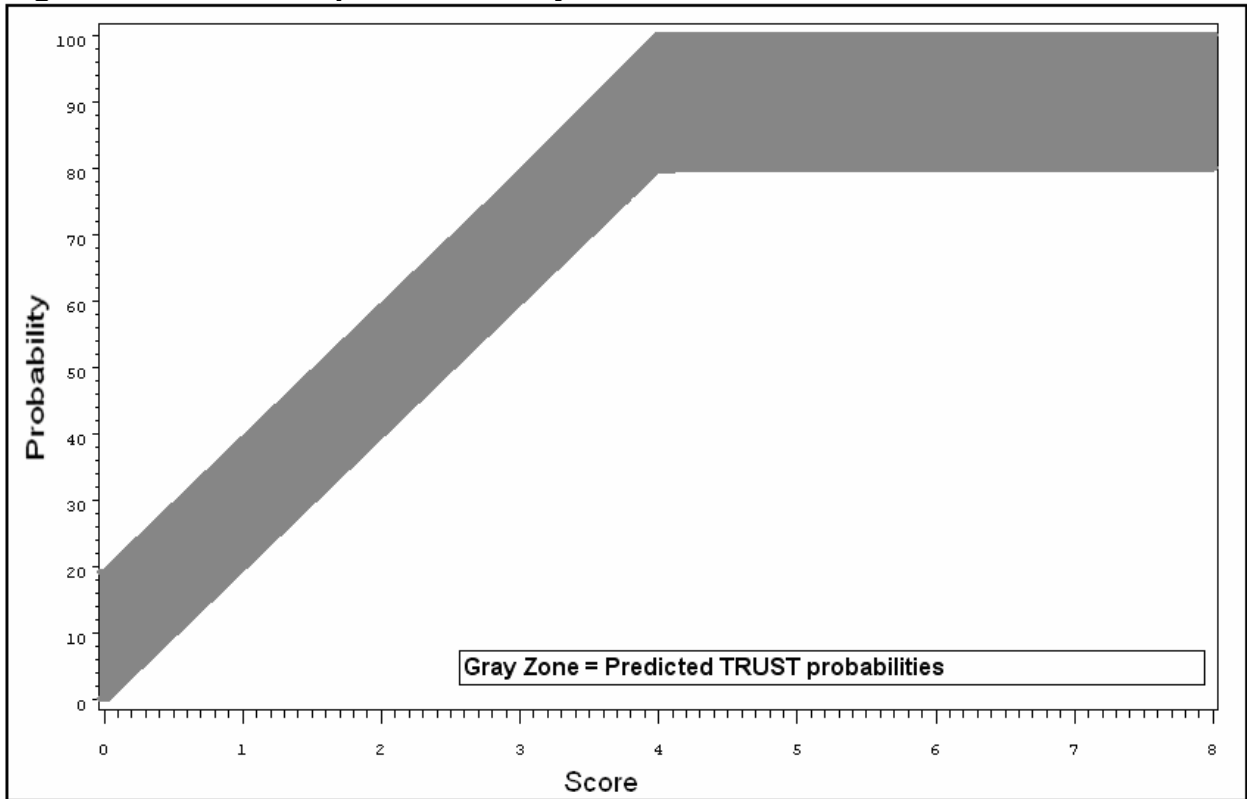


Figure D.3: Predicted probabilities with their 95% confidence limits

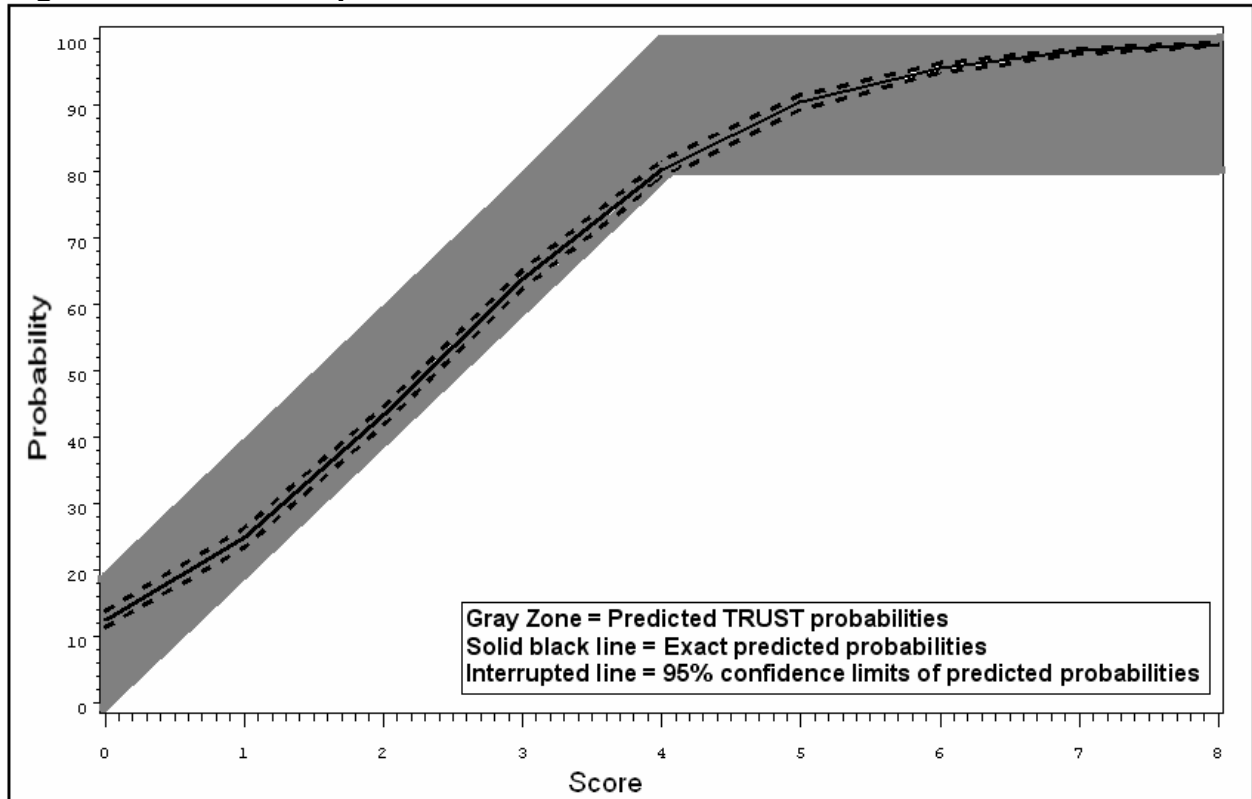


Figure D.4: Assessment of TRUST

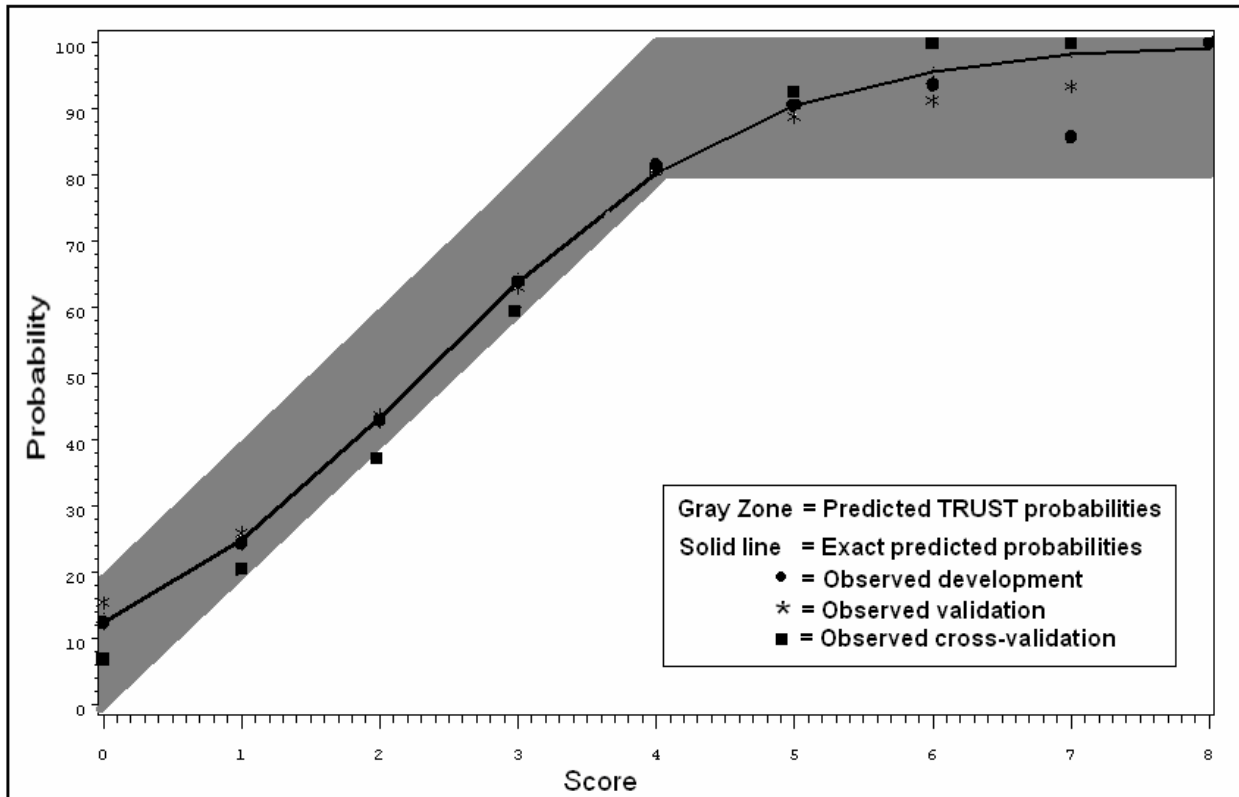
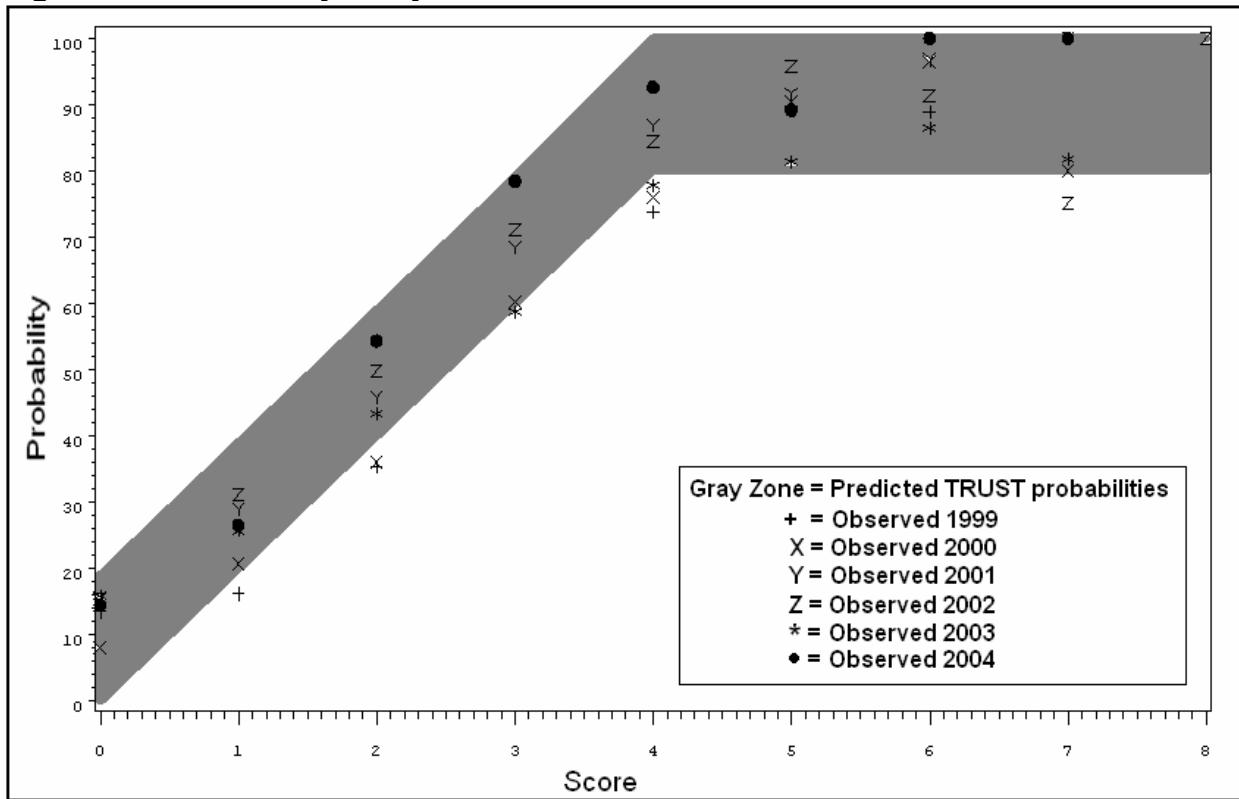


Figure D.5: Sensitivity analysis



CHAPTER E

DISCUSSION AND CONCLUSION

Cardiac surgery continues to place a large demand on the available blood supply. It has been estimated that 11% of red cell resources were used for transfusion support of patients undergoing CABG¹¹, and nearly 20% of blood transfusions are associated with cardiac surgery¹⁷¹. Despite major advances in perioperative blood conservation, transfusion rates in cardiac surgery remain high with large variations among individual centers¹¹. Reported average transfusion rates for CABG procedures vary between 10% and 70%^{10,151}. To improve transfusion practice in cardiac surgery, several guidelines for blood conservation and transfusion have been developed^{119-121,172,173}.

Karkouti et al stated that: “the guidelines for blood administration which has been in use at TGH since 1996 state that under normal conditions, blood should be administered to patients only when their hematocrit is less than or equal to 0.18 while they are on cardiopulmonary bypass, less than or equal to 0.20 after bypass during surgery, and less than or equal to 0.24 on two consecutive measurements during the postoperative period”¹⁴. Additionally, *Karkouti et al* stated that: “blood conservation methods used before elective surgery at TGH included discontinuation of anti-platelets and anti-coagulant medications 1 week before surgery and screening for and correction of coagulation disorders. Blood conservation methods used during surgery included the routine administration of an antifibrinolytic agent (50-100 mg/kg of tranexamic acid)”¹⁴.

Karkouti et al reported a transfusion rate of 29.4% in patients undergoing elective first-time CABG at TGH¹⁴. In our study, the rate of exposure to blood transfusion was 51%. Unlike previous studies that included CABG procedures only, our study included all cardiac surgical procedures that required cardiopulmonary bypass (except heart transplant and ventricular assist devices) with different urgency levels. *Hardy et al* reported that the risk of exposure to blood transfusion was higher in patients undergoing combined cardiac procedures or valvular procedures more than CABG procedures¹⁵³. Furthermore, urgency of the cardiac procedures was a strong independent predictor of the exposure to blood transfusion^{15,16}. Thus, our finding of a higher rate of transfusion in a broader cardiac surgery population than CABG procedures with different urgency levels is not surprising.

To date, there have been 10 studies that developed models for the prediction of the risk of exposure to blood transfusion in cardiac surgery. Of these studies, only two used the predictive model to construct a risk scoring system: MRTS and LTRS transfusion risk scoring systems^{15,16}. Reliability of the predictive variables, definition of the follow-up time, lack of external validation, and limitation to CABG patients are major factors that make MTRS and LTRS less applicable to current practice.

In our study, all eligible consecutive patients (n=11,113) undergoing a cardiac surgical procedure (CABG and non-CABG) over a 6-year period were analyzed. Consequently, this series is a representative sample of the situation commonly found in clinical practice. The focus was on including variables that are valid, reliable and readily available in routine clinical practice.

For practical reasons, all included continuous variables (hemoglobin level, age, weight and serum creatinine level) were dichotomized and the best cutoff values were determined based on ROC statistics. Because of the concern that such dichotomization might result in a major loss of data and therefore precision; additional analyses of these variables was carried out in the continuous form. These analyses did not show a major loss of precision and dichotomization had a superior model's fit (Appendix E.1).

Based on the standards of measurement in clinical research, and by the adherence to the appropriate model-building standards, this study identified 8 preoperative clinical variables that independently predicted the exposure to blood transfusion: preoperative hemoglobin, weight, female sex, age, non-elective procedure, preoperative creatinine, previous cardiac surgical procedure, and non-isolated procedure. They constitute the clinical predictive index, TRUST. In a subset of the data (n=3,667), TRUST was internally validated (AUC=0.78, SE=0.007).

TRUST was cross-validated at SWCHSC (n=5,316) where it performed well (AUC=0.82, SE=0.006). Additionally, as transfusion practices may change over time, a sensitivity analyses to assess the robustness of TRUST were carried out. Data used to develop TRUST were stratified by the year of operation (from 1999 to 2004); thereby applying TRUST to six different datasets. Here, again TRUST performed well.

The TRUST is an additive algorithm to give single overall score ranging from 0 to 8 (i.e. number of variables is the total score). Clinicians use it by adding up the number of variables in a given patient to get an overall score. Based on the predicted probabilities, the overall score is then used to stratify patients from baseline to very high risk as follows: baseline risk (0), low risk (1), intermediate risk (2), high risk (3), and very

high risk (4 or more). The probabilities of exposure to blood transfusion are divided into five quintiles as follows: (0.0- <0.2), (0.2- <0.4), (0.4- <0.6), (0.6- <0.8), and (0.80 and more) in the baseline, low, intermediate, high, and very high groups respectively.

TRUST is a simple and easy to use instrument that does not require any special skills to apply.

As TRUST predicts the probability of exposure to blood transfusion in the operative and first postoperative days, patients can be stratified according to their risk of exposure to blood transfusion before their surgery. Beside presentation of the probabilities, attempts were made to use TRUST as a screening tool to identify those who will be exposed to blood transfusion (sensitivity) from those who will not (specificity) by determining a score cutoff value that can then be used for screening. Sensitivity, specificity, total error, and AUC were identified for each score cutoff value.

Sensitivity and specificity are measures of criterion validity, with opposing forces. That is, in attempts to maximize one component, the complement is sacrificed (i.e. setting a higher sensitivity would compromise the specificity of the instrument, selecting more individuals unnecessarily).

For TRUST, the cutoff value that was associated with the minimal total error (i.e. maximum AUC, and subsequently maximum discriminatory performance) was 3 in development, validation, and cross-validation cohorts (i.e. using a total score of 3 or more was associated with the least total error). For the cutoff value of 3 or more, sensitivities were: 70%, 69%, and 68% in the development, validation and cross-validation cohorts respectively, and specificities were: 76%, 74%, and 80% in the development, validation, and cross-validation cohorts respectively (Appendix E.2-4).

Cost-effectiveness studies are required to justify the use of TRUST as a screening tool as many patients will be included unnecessarily. However, targeting a high-risk population is important for achieving cost-effective interventions. TRUST provides a valid prediction of such high-risk patients in whom expensive interventions can be applied (e.g. blood conservation strategies). On the other hand, some blood tests (e.g. cross-matching) potentially can be eliminated for patients in the identified low-risk group, thus, reducing cost and improving blood bank efficiency ¹⁴.

Unlike MTRS or LTRS, which required more complex calculation and lacked reliability of some variables, TRUST is a simple additive scoring tool where the overall score is simply the sum of clinical variables. All variables included in TRUST are reliable and known major risk factors for the exposure to blood transfusion in patients undergoing cardiac surgery. They have been shown to be predictive of the exposure to blood transfusion at other institutions^{12-16,19,128}. Therefore, it is expected that TRUST will perform well at other institutions.

TRUST enables clinicians to stratify their patients according to their risk of exposure to blood transfusion and provide them with important information about their transfusion-related risks, helps the medical team to anticipate patients' transfusion needs and guides the clinician in ordering additional tests; both hematological and non-hematological. Furthermore, it guides consultation of the appropriate medical services (e.g. hematology) and provides better blood resource allocation. Because blood preparation takes time predicting blood transfusion needs will help clinicians to order blood in advance and avoid unwanted delays.

A retrospective cohort study design was adopted for the development of TRUST. A prospective design is theoretically a better study design as it gives the investigator the opportunity to measure the exposure variables of interest and provides a clear chronological sequence of events. However, for our objectives, a retrospective study design became more efficient as it provided similar information (as those with a prospective design) with less cost and time.

TRUST was developed from databases that were not collected for the purpose of this study. However, the definitions, and methods of measurements of the variables included in TRUST are unlikely to be different if the databases were collected for the purpose of this study. Additionally, databases used, were validated and had a small rate of missing values (less than 3%).

As with other studies that are based on existing databases, researchers are restricted to variables existing in the database. Therefore, there may be a concern that other important variables were not included in the predictive index. All major variables that are known to be associated with the risk of exposure to blood transfusion were included in the databases used in this study. In the MRTS, albumin level was included as an independent predictor of blood transfusion. Only one study has shown albumin to be a significant predictor of the exposure to blood transfusion; however, it was the weakest predictor in the model ¹⁶. In another study albumin level was not significantly associated with exposure to blood products after cardiac surgery ¹⁹. The lack of consistency reduces its likelihood of being an important predictor variable.

Because off-pump cardiac surgical procedures were excluded in this study, TRUST may not be applicable for patients undergoing this surgical procedure. Off-pump

procedures were excluded as they are systematically different procedures, and several clinical trials have shown that the blood transfusion rates are significantly less than with on-pump procedures ¹⁷⁴.

As in other studies, the outcome used in this study identifies patients who were exposed to allogeneic blood transfusion, and not necessarily the appropriate exposure to blood transfusion. Additionally, TRUST is not to be an absolute indication for blood transfusion; clinical judgment is always important. Moreover, selecting the eight-item TRUST does not mean that other items are not important in predicting the risk of blood transfusion. However, in practice, the eight-item TRUST was the most practical while maintaining the maximum discriminatory performance.

Cross-validation of TRUST was performed in the city of Toronto (as with the development and validation). TRUST needs to be cross-validated at institutions outside Toronto to test its performance in different geographical areas at different times. TRUST provides a valuable tool in designing randomized clinical trials to test the effect of certain interventions on blood transfusion. Both the decision concerning which patient to randomize and the design of randomization process (for example, stratified randomization using prognostic factors) are aided by the availability of accurate prognostic estimates before randomization ¹²⁶.

CONCLUSION

Based on the standards of measurement in clinical research, a valid clinical tool was developed to stratify cardiac surgery patients according to their blood transfusion needs. This clinical tool consists of eight preoperative variables: preoperative hemoglobin, weight, female sex, age, non-elective procedure, preoperative creatinine, previous cardiac surgical procedure, and non-isolated procedure. The clinical tool was internally and externally validated, and the results suggest that it should perform well at other institutions.

References

1. Schmidt PJ. Transfusion in America in the eighteenth and nineteenth centuries. *New England Journal of Medicine* 1968; 279:1319-1320.
2. Blundell J. Successful Case of Transfusion. *Lancet* 1828; 1:431.
3. Fakhry SM, Rutherford EJ, Sheldon GF. Blood Transfusion. In Sabiston *Textbook of Surgery*. W. B. Saunders Company; 2001:69.
4. Cook SS, Epps J. Transfusion practice in central Virginia. *Transfusion* 1991; 31:355-360.
5. Lenfant C. Transfusion practice should be audited for both undertransfusion and overtransfusion. *Transfusion* 1992; 32:873-874.
6. Surgenor DM, Wallace EL, Hao SH, Chapman RH. Collection and transfusion of blood in the United States, 1982-1988. *New England Journal of Medicine* 1990; 322:1646-1651.
7. Wallace EL, Surgenor DM, Hao HS, An J, Chapman RH, Churchill WH. Collection and transfusion of blood and blood components in the United States, 1989. *Transfusion* 1993; 33:139-144.
8. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. Second of two parts-blood conservation. *New England Journal of Medicine* 1999; 340:525-533.
9. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts-blood transfusion. *New England Journal of Medicine* 1999; 340:438-447.
10. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, D'Ambra MN, Mangano DT, Spiess BD. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. *Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology* 1998; 88:327-333.
11. Surgenor DM, Churchill WH, Wallace EL, Rizzo RJ, McGurk S, Goodnough LT, Kao KJ, Koerner TA, Olson JD, Woodson RD. The specific hospital significantly affects red cell and component transfusion practice in coronary artery bypass graft surgery: a study of five hospitals. *Transfusion* 1998; 38:122-134.
12. Bilfinger TV, Conti VR. Blood conservation in coronary artery bypass surgery: prediction with assistance of a computer model. *Thoracic & Cardiovascular Surgeon* 1989; 37:365-368.

13. Cosgrove DM, Loop FD, Lytle BW, Gill CC, Golding LR, Taylor PC, Forsythe SB. Determinants of blood utilization during myocardial revascularization. *Annals of Thoracic Surgery* 1985; 40:380-384.
14. Karkouti K, Cohen MM, McCluskey SA, Sher GD. A multivariable model for predicting the need for blood transfusion in patients undergoing first-time elective coronary bypass graft surgery. *Transfusion* 2001; 41:1193-1203.
15. Litmathe J, Boeken U, Feindt P, Gams E. Predictors of homologous blood transfusion for patients undergoing open heart surgery. *Thoracic & Cardiovascular Surgeon* 2003; 51:17-21.
16. Magovern JA, Sakert T, Benckart DH, Burkholder JA, Liebler GA, Magovern GJ, Sr., Magovern GJ, Jr. A model for predicting transfusion after coronary artery bypass grafting. *Annals of Thoracic Surgery* 1996; 61:27-32.
17. Moskowitz DM, Klein JJ, Shander A, Cousineau KM, Goldweit RS, Bodian C, Perelman SI, Kang H, Fink DA, Rothman HC, Ergin MA. Predictors of transfusion requirements for cardiac surgical procedures at a blood conservation center. *Annals of Thoracic Surgery* 2004; 77:626-634.
18. Ouattara A, Niculescu M, Boccara G, Landi M, Vaissier E, Leger P, Riou B, Gandjbakch I, Coriat P. Identification of risk factors for allogenic transfusion in cardiac surgery from an observational study. *Annales Francaises d Anesthesie et de Reanimation* 2003; 22:278-283.
19. Parr KG, Patel MA, Dekker R, Levin R, Glynn R, Avorn J, Morse DS. Multivariate predictors of blood product use in cardiac surgery. *Journal of Cardiothoracic & Vascular Anesthesia* 2003; 17:176-181.
20. Cantor SB, Hudson DV, Jr., Lichtiger B, Rubenstein EB. Costs of blood transfusion: a process-flow analysis. *Journal of Clinical Oncology* 1998; 16:2364-2370.
21. Cremieux PY, Barrett B, Anderson K, Slavin MB. Cost of outpatient blood transfusion in cancer patients. *Journal of Clinical Oncology* 2000; 18:2755-2761.
22. Kavanagh BD, Fischer BA, Segreti EM, Wheelock JB, Boardman C, Roseff SD, Cardinale RM, Benedict SH, Goram AL. Cost analysis of erythropoietin versus blood transfusions for cervical cancer patients receiving chemoradiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2001; 51:435-441.
23. Kirklin/Barratt-Boyes. Postoperative care. In *Cardiac Surgery*. Philadelphia: 2003:227.
24. Tretiak R, Laupacis A, Riviere M, McKerracher K, Souetre E. Cost of allogeneic and autologous blood transfusion in Canada. Canadian Cost of Transfusion Study Group. *Canadian Medical Association Journal* 1996; 154:1501-1508.

25. Dranitsaris G. The cost of blood transfusion in cancer patients: A reanalysis of a Canadian economic evaluation. *Journal of Oncology and Pharmaceutical Practice* 2000; 6:37-42.
26. Amin M, Fergusson D, Wilson K, Coyle D, Hebert P. The Cost of allogeneic red blood cells: A Systematic Review. *Transfusion Medicine* 2003; 13 :275-285.
27. Hadjianastassiou VG, Virich G, Lennox IA. Use of the blood transfusion service in total knee replacement arthroplasty. The cost implications. *Knee* 2002; 9:145-148.
28. Duffy G, Tolley K. Cost analysis of autologous blood transfusion, using cell salvage, compared with allogeneic blood transfusion. *Transfusion Medicine* 1997; 7:189-196.
29. Kemper RR, Menitove JE, Hanto DW. Cost analysis of intraoperative blood salvage during orthotopic liver transplantation. *Liver Transplantation & Surgery* 1997; 3:513-517.
30. Forbes JM, Anderson MD, Anderson GF, Bleecker GC, Rossi EC, Moss GS. Blood transfusion costs: a multicenter study. *Transfusion* 1991; 31:318-323.
31. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Isselbacher KJ. *Harrison's Principles of Internal Medicine*. McGraw-Hill; 2004.
32. Callum JL, Pinkerton PH. *Bloody Easy: Blood Transfusions, Blood Alternatives and Transfusion Reactions: A Guide to Transfusion Medicine*. Toronto, Ontario, Canada: Sunnybrook & Women's College Health Science Center; 2003.
33. Toy PT, Strauss RG, Stehling LC, Sears R, Price TH, Rossi EC, Collins ML, Crowley JP, Eisenstaedt RS, Goodnough LT. Predeposited autologous blood for elective surgery. A national multicenter study. *New England Journal of Medicine* 1987; 316:517-520.
34. Goodnough LT, Monk TG, Brecher ME. Autologous blood procurement in the surgical setting: lessons learned in the last 10 years. *Vox Sanguinis* 1996; 71:133-141.
35. Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *New England Journal of Medicine* 1993; 328:1372-1376.
36. Elawad AA, Jonsson S, Laurell M, Fredin H. Predonation autologous blood in hip arthroplasty. *Acta Orthopaedica Scandinavica* 1991; 62:218-222.
37. Hedstrom M, Flordal PA, Ahl T, Svensson J, Dalen N. Autologous blood transfusion in hip replacement. No effect on blood loss but less increase of

plasminogen activator inhibitor in a randomized series of 80 patients. *Acta Orthopaedica Scandinavica* 1996; 67:317-320.

38. Heiss MM, Mempel W, Jauch KW, Delanoff C, Mayer G, Mempel M, Eissner HJ, Schildberg FW. Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. *Lancet* 1993; 342:1328-1333.
39. Heiss MM, Fasol-Merten K, Allgayer H, Strohleim MA, Tarabichi A, Wallner S, Eissner HI, Jauch KW, Schildberg FW. Influence of autologous blood transfusion on natural killer and lymphokine-activated killer cell activities in cancer surgery. *Vox Sanguinis* 1997; 73:237-245.
40. Hoyneck van Papendrecht MA, Hop W, Langenhorst BL, Kothe FC, Marquet RL, Jeekel J. Feasibility of a predeposit autologous blood donation program in colorectal cancer patients: results from a randomized clinical study. *Vox Sanguinis* 1992; 62:102-107.
41. Kajikawa M, Nonami T, Kurokawa T, Hashimoto S, Harada A, Nakao A, Takagi H. Autologous blood transfusion for hepatectomy in patients with cirrhosis and hepatocellular carcinoma: use of recombinant human erythropoietin. *Surgery* 1994; 115:727-734.
42. Lorentz A, Osswald PM, Schilling M, Jani L. A comparison of autologous transfusion procedures in hip surgery. *Anaesthesist* 1991; 40:205-213.
43. Henry DA, Carless PA, Moxey AJ, O'Connell D, Forgie MA, Wells PS, Fergusson D. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2002;CD003602.
44. Birkmeyer JD, AuBuchon JP, Littenberg B, O'Connor GT, Nease RF, Jr., Nugent WC, Goodnough LT. Cost-effectiveness of preoperative autologous donation in coronary artery bypass grafting. *Annals of Thoracic Surgery* 1994; 57:161-168.
45. Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordsij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. *Transfusion* 1993; 33:544-551.
46. Cohen JA, Brecher ME. Preoperative autologous blood donation: benefit or detriment? A mathematical analysis. *Transfusion* 1995; 35:640-644.
47. Linden JV, Kruskall MS. Autologous blood: always safer? *Transfusion* 1997; 37:455-456.
48. Piliavin JA. Why do they give the gift of life? A review of research on blood donors since 1977. *Transfusion* 1990; 30:444-459.
49. Henry DH, Spivak JL. Clinical use of erythropoietin. *Current Opinion in Hematology* 1995; 2:118-124.

50. Erslev AJ. Erythropoietin. *New England Journal of Medicine* 1991; 324:1339-1344.
51. Crosby E. Perioperative use of erythropoietin. *American Journal of Therapeutics* 2002; 9:371-376.
52. Anonymous. Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. Canadian Orthopedic Perioperative Erythropoietin Study Group. *Lancet* 1993; 341:1227-1232.
53. Messmer K. Consensus statement: using epoetin alfa to decrease the risk of allogeneic blood transfusion in the surgical setting. Roundtable of Experts in Surgery Blood Management. *Seminars in Hematology* 1996; 33:Suppl-80.
54. Laupacis A, Fergusson D. Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Transfusion Medicine* 1998; 8:309-317.
55. Coyle D, Lee KM, Fergusson DA, Laupacis A. Cost effectiveness of epoetin-alpha to augment preoperative autologous blood donation in elective cardiac surgery. *Pharmacoeconomics* 2000; 18:161-171.
56. Marchetti M, Barosi G. Cost-effectiveness of epoetin and autologous blood donation in reducing allogeneic blood transfusions in coronary artery bypass graft surgery. *Transfusion* 2000; 40:673-681.
57. Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs. *Arzneimittel-Forschung* 1983; 33:479-494.
58. Royston D. Aprotinin versus lysine analogues: the debate continues. *Annals of Thoracic Surgery* 1998; 65:Suppl-19.
59. Mohr R, Goor DA, Lusky A, Lavee J. Aprotinin prevents cardiopulmonary bypass-induced platelet dysfunction. A scanning electron microscope study. *Circulation* 1992; 86:Suppl-9.
60. Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, Sly K, Laupacis A, Fergusson D. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2001;CD001886.
61. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Anesthesia & Analgesia* 1997; 85:1258-1267.

62. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briet E, Buller HR. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. *Lancet* 1999; 354:1940-1947.
63. Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT, Dacey LJ. Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. *Circulation* 1999; 99:81-89.
64. Faught C, Wells P, Fergusson D, Laupacis A. Adverse effects of methods for minimizing perioperative allogeneic transfusion: a critical review of the literature. *Transfusion Medicine Reviews* 1998; 12:206-225.
65. Mannucci PM. Hemostatic drugs. *New England Journal of Medicine* 1998; 339:245-253.
66. Daily PO, Lamphere JA, Dembitsky WP, Adamson RM, Dans NF. Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting. A randomized, prospective, double-blind study. *Journal of Thoracic & Cardiovascular Surgery* 1994; 108:99-106.
67. DelRossi AJ, Cernaianu AC, Botros S, Lemole GM, Moore R. Prophylactic treatment of postperfusion bleeding using EACA. *Chest* 1989; 96:27-30.
68. Hardy JF, Belisle S, Dupont C, Harel F, Robitaille D, Roy M, Gagnon L. Prophylactic tranexamic acid and epsilon-aminocaproic acid for primary myocardial revascularization. *Annals of Thoracic Surgery* 1998; 65:371-376.
69. Landymore RW, Murphy JT, Lummis H, Carter C. The use of low-dose aprotinin, epsilon-aminocaproic acid or tranexamic acid for prevention of mediastinal bleeding in patients receiving aspirin before coronary artery bypass operations. *European Journal of Cardio-Thoracic Surgery* 1997; 11:798-800.
70. Menichetti A, Tritapepe L, Ruvolo G, Speziale G, Cogliati A, Di Giovanni C, Pacilli M, Criniti A. Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: aprotinin vs tranexamic acid vs epsilon aminocaproic acid. *Journal of Cardiovascular Surgery* 1996; 37:401-407.
71. Penta dP, Pierri MD, Scafuri A, De Paulis R, Colantuono G, Caprara E, Tomai F, Chiariello L. Intraoperative antifibrinolysis and blood-saving techniques in cardiac surgery. Prospective trial of 3 antifibrinolytic drugs. *Texas Heart Institute Journal* 1995; 22:231-236.
72. Slaughter TF, Faghih F, Greenberg CS, Leslie JB, Sladen RN. The effects of epsilon-aminocaproic acid on fibrinolysis and thrombin generation during cardiac surgery. *Anesthesia & Analgesia* 1997; 85:1221-1226.

73. Vander Salm TJ, Ansell JE, Okike ON, Marsicano TH, Lew R, Stephenson WP, Rooney K. The role of epsilon-aminocaproic acid in reducing bleeding after cardiac operation: a double-blind randomized study. *Journal of Thoracic & Cardiovascular Surgery* 1988; 95:538-540.
74. Vander Salm TJ, Kaur S, Lancey RA, Okike ON, Pezzella AT, Stahl RF, Leone L, Li JM, Valeri CR, Michelson AD. Reduction of bleeding after heart operations through the prophylactic use of epsilon-aminocaproic acid. *Journal of Thoracic & Cardiovascular Surgery* 1996; 112:1098-1107.
75. Benoni G, Fredin H. Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty: a prospective, randomised, double-blind study of 86 patients. *Journal of Bone & Joint Surgery - British Volume* 1996; 78:434-440.
76. Blauhut B, Harringer W, Bettelheim P, Doran JE, Spath P, Lundsgaard-Hansen P. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. *Journal of Thoracic & Cardiovascular Surgery* 1994; 108:1083-1091.
77. Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: a double-blind, randomized, placebo-controlled trial. *Anesthesia & Analgesia* 1997; 85:963-970.
78. Coffey A, Pittmam J, Halbrook H, Fehrenbacher J, Beckman D, Hormuth D. The use of tranexamic acid to reduce postoperative bleeding following cardiac surgery: a double-blind randomized trial. *American Surgeon* 1995; 61:566-568.
79. Corbeau JJ, Monrigal JP, Jacob JP, Cottineau C, Moreau X, Bukowski JG, Subayi JB, Delhumeau A. Comparison of effects of aprotinin and tranexamic acid on blood loss in heart surgery. *Annales Francaises d Anesthesie et de Reanimation* 1995; 14:154-161.
80. Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J, Niemela H. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. *British Journal of Anaesthesia* 1995; 74:534-537.
81. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemela HM, Mantyla SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. *Anesthesia & Analgesia* 1997; 84:839-844.
82. Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. *Circulation* 1991; 84:2063-2070.

83. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL. The dose-response relationship of tranexamic acid. *Anesthesiology* 1995; 82:383-392.
84. Katoh J, Tsuchiya K, Sato W, Nakajima M, Iida Y. Additional postbypass administration of tranexamic acid reduces blood loss after cardiac operations. *Journal of Thoracic & Cardiovascular Surgery* 1997; 113:802-804.
85. Katsaros D, Petricevic M, Snow NJ, Woodhall DD, Van Bergen R. Tranexamic acid reduces postbypass blood use: a double-blinded, prospective, randomized study of 210 patients. *Annals of Thoracic Surgery* 1996; 61:1131-1135.
86. Pugh SC, Wielogorski AK. A comparison of the effects of tranexamic acid and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing cardiac surgery. *Journal of Cardiothoracic & Vascular Anesthesia* 1995; 9:240-244.
87. Shore-Lesserson L, Reich DL, Vela-Cantos F, Ammar T, Ergin MA. Tranexamic acid reduces transfusions and mediastinal drainage in repeat cardiac surgery. *Anesthesia & Analgesia* 1996; 83:18-26.
88. Carless PA, Henry DA, Moxey AJ, O'Connell DL, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2003;CD001888.
89. Axford TC, Dearani JA, Ragno G, MacGregor H, Patel MA, Valeri CR, Khuri SF. Safety and therapeutic effectiveness of reinfused shed blood after open heart surgery. *Annals of Thoracic Surgery* 1994; 57:615-622.
90. Bouboulis N, Kardara M, Kesteven PJ, Jayakrishnan AG. Autotransfusion after coronary artery bypass surgery: is there any benefit? *Journal of Cardiac Surgery* 1994; 9:314-321.
91. Clagett GP, Valentine RJ, Jackson MR, Mathison C, Kakish HB, Bengtson TD. A randomized trial of intraoperative autotransfusion during aortic surgery. *Journal of Vascular Surgery* 1999; 29:22-30.
92. Dalrymple-Hay MJ, Pack L, Deakin CD, Shephard S, Ohri SK, Haw MP, Livesey SA, Monro JL. Autotransfusion of washed shed mediastinal fluid decreases the requirement for autologous blood transfusion following cardiac surgery: a prospective randomized trial. *European Journal of Cardio-Thoracic Surgery* 1999; 15:830-834.
93. Davies MJ, Cronin KC, Moran P, Mears L, Booth RJ. Autologous blood transfusion for major vascular surgery using the Sorenson Receptal Device. *Anaesthesia & Intensive Care* 1987; 15:282-288.

94. Dietrich W, Barankay A, Diltthey G, Mitto HP, Richter JA. Reduction of blood utilization during myocardial revascularization. *Journal of Thoracic & Cardiovascular Surgery* 1989; 97:213-219.
95. Eng J, Kay PH, Murday AJ, Shreiti I, Harrison DP, Norfolk DR, Barnes I, Hawkey PM, Inglis TJ. Postoperative autologous transfusion in cardiac surgery. A prospective, randomised study. *European Journal of Cardio-Thoracic Surgery* 1990; 4:595-600.
96. Fragnito C, Beghi C, Cavoza C, Sacconi S, Contini SA, Barbosa G. Autotransfusion of the blood drained from mediastinum in the course of myocardial revascularization. *Acta Bio-Medica de I Ateneo Parmense* 1995; 66:195-201.
97. Laub GW, Dharan M, Riebman JB, Chen C, Moore R, Bailey BM, Fernandez J, Adkins MS, Anderson W, McGrath LB. The impact of intraoperative autotransfusion on cardiac surgery. A prospective randomized double-blind study. *Chest* 1993; 104:686-689.
98. Lepore V, Radegran K. Autotransfusion of mediastinal blood in cardiac surgery. *Scandinavian Journal of Thoracic & Cardiovascular Surgery* 1989; 23:47-49.
99. Martin J, Robitaille D, Perrault LP, Pellerin M, Page P, Searle N, Cartier R, Hebert Y, Pelletier LC, Thaler HT, Carrier M. Reinfusion of mediastinal blood after heart surgery. *Journal of Thoracic & Cardiovascular Surgery* 2000; 120:499-504.
100. Parrot D, Lancon JP, Merle JP, Rerolle A, Bernard A, Obadia JF, Caillard B. Blood salvage in cardiac surgery. *Journal of Cardiothoracic & Vascular Anesthesia* 1991; 5:454-456.
101. Schmidt H, Folsgaard S, Mortensen PE, Jensen E. Impact of autotransfusion after coronary artery bypass grafting on oxygen transport. *Acta Anaesthesiologica Scandinavica* 1997; 41:995-1001.
102. Schonberger JP, Bredee J, Speekenbrink RG, Everts PA, Wildevuur CR. Autotransfusion of shed blood contributes additionally to blood saving in patients receiving aprotinin (2 million KIU). *European Journal of Cardio-Thoracic Surgery* 1993; 7:474-477.
103. Tempe DK, Banerjee A, Virmani S, Mehta N, Panwar S, Tomar AS, Ghambeer DK, Nigam M. Comparison of the effects of a cell saver and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing valve surgery. *Journal of Cardiothoracic & Vascular Anesthesia* 2001; 15:326-330.
104. Unsworth-White MJ, Kallis P, Cowan D, Tooze JA, Bevan DH, Treasure T. A prospective randomised controlled trial of postoperative autotransfusion with and

- without a heparin-bonded circuit. *European Journal of Cardio-Thoracic Surgery* 1996; 10:38-47.
105. Zhao K, Xiao M, Deng S. Autotransfusion of shed mediastinal blood after open heart operation. *Chinese Journal of Surgery* 1996; 34:497-499.
 106. Anonymous. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; 84:732-747.
 107. Boldt J, Kling D, Weidler B, Zickmann B, Herold C, Dapper F, Hempelmann G. Acute preoperative hemodilution in cardiac surgery: volume replacement with a hypertonic saline-hydroxyethyl starch solution. *Journal of Cardiothoracic & Vascular Anesthesia* 1991; 5:23-28.
 108. Hallowell P, Bland JH, Buckley MJ, Lowenstein E. Transfusion of fresh autologous blood in open-heart surgery. A method for reducing bank blood requirements. *Journal of Thoracic & Cardiovascular Surgery* 1972; 64:941-948.
 109. Herregods L, Foubert L, Moerman A, Francois K, Rolly G. Comparative study of limited intentional normovolaemic haemodilution in patients with left main coronary artery stenosis. *Anaesthesia* 1995; 50:950-953.
 110. Triulzi DJ, Gilmor GD, Ness PM, Baumgartner WA, Schultheis LW. Efficacy of autologous fresh whole blood or platelet-rich plasma in adult cardiac surgery. *Transfusion* 1995; 35:627-634.
 111. Vedrinne C, Girard C, Jegaden O, Blanc P, Bouvier H, Ffrench P, Mikaeloff P, Estanove S. Reduction in blood loss and blood use after cardiopulmonary bypass with high-dose aprotinin versus autologous fresh whole blood transfusion. *Journal of Cardiothoracic & Vascular Anesthesia* 1992; 6:319-323.
 112. Bryson GL, Laupacis A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogeneic transfusion? A meta-analysis. *The International Study of Perioperative Transfusion. Anesthesia & Analgesia* 1998; 86:9-15.
 113. Hill SR, Carless PA, Henry DA, Carson JL, Hebert PC, McClelland DB, Henderson KM. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database of Systematic Reviews* 2002;CD002042.
 114. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA, Jr., Cooley DA. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion* 1999; 39:1070-1077.
 115. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled

clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. New England Journal of Medicine 1999; 340:409-417.

116. Anonymous. Consensus conference. Perioperative red blood cell transfusion. JAMA 1988; 260:2700-2703.
117. Anonymous. Practice strategies for elective red blood cell transfusion. American College of Physicians. Annals of Internal Medicine 1992; 116:403-406.
118. Anonymous. Guidelines for red blood cell and plasma transfusion for adults and children. Canadian Medical Association Journal 1997; 156:S1-S24.
119. Cooley DA. Conservation of blood during cardiovascular surgery. American Journal of Surgery 1995; 170:Suppl-59S.
120. Goodnough LT, Johnston MF, Ramsey G, Sayers MH, Eisenstadt RS, Anderson KC, Rutman RC, Silberstein LE. Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. Transfusion Practices Committee of the American Association of Blood Banks. Annals of Thoracic Surgery 1990; 50:675-683.
121. Goodnough LT, Despotis GJ, Hogue CW, Jr., Ferguson TB, Jr. On the need for improved transfusion indicators in cardiac surgery. Annals of Thoracic Surgery 1995; 60:473-480.
122. Innes G. Guidelines for red blood cells and plasma transfusion for adults and children: An emergency physician's overview of the 1997 Canadian blood transfusion guidelines. Journal of Emergency Medicine 1998; 16:129-132.
123. Simon TL, Alverson DC, AuBuchon J, Cooper ES, DeChristopher PJ, Glenn GC, Gould SA, Harrison CR, Milam JD, Moise KJ, Jr., Rodwig FR, Jr., Sherman LA, Shulman IA, Stehling L. Practice parameter for the use of red blood cell transfusions: developed by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists. Archives of Pathology & Laboratory Medicine 1998; 122:130-138.
124. Ferguson TB, Jr., Hammill BG, Peterson ED, DeLong ER, Grover FL, STS National Database Committee. A decade of change-Risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990-1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Annals of Thoracic Surgery 2002; 73:480-490.
125. Abramov D, Tamariz MG, Fremes SE, Guru V, Borger MA, Christakis GT, Bhatnagar G, Sever JY, Goldman BS. Trends in coronary artery bypass surgery results: a recent, 9-year study. Annals of Thoracic Surgery 2000; 70:84-90.

126. Spiegelhalter DJ. Probabilistic prediction in patient management and clinical trials. *Statistics in Medicine* 1986; 5:421-433.
127. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. *Journal of American Medical Association* 1997; 277:488-494.
128. Ferraris VA, Gildengorin V. Predictors of excessive blood use after coronary artery bypass grafting. A multivariate analysis. *Journal of Thoracic & Cardiovascular Surgery* 1989; 98:492-497.
129. Kirshner B, Guyatt G. A methodological framework for assessing health indices. *Journal of Chronic Diseases* 1985; 38:27-36.
130. Feinstein AR. *Clinimetrics*. New Haven, Connecticut: Yale University Press; 1987.
131. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. *New England Journal of Medicine* 1985; 313:793-799.
132. Moons KG, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients? *Journal of Clinical Epidemiology* 2002; 55:1054-1055.
133. Feinstein AR. The Theory and Evaluation of Sensibility. In *Clinimetrics*. New Haven: Yale university press; 1987:141-165.
134. Feinstein AR. Multiple logistic regression. In *Multivariable analysis: an introduction*. New Haven: Yale University Press; 1996:297-330.
135. Rogers WJ, Smith LR, Hood WP, Jr., Mantle JA, Rackley CE, Russell RO, Jr. Effect of filming projection and interobserver variability on angiographic biplane left ventricular volume determination. *Circulation* 1979; 59:96-104.
136. Cohn PF, Levine JA, Bergeron GA, Gorlin R. Reproducibility of the angiographic left ventricular ejection fraction in patients with coronary artery disease. *American Heart Journal* 1974; 88:713-720.
137. Upton MT, Rerych SK, Newman GE, Bounous EP, Jr., Jones RH. The reproducibility of radionuclide angiographic measurements of left ventricular function in normal subjects at rest and during exercise. *Circulation* 1980; 62:126-132.
138. van Royen N, Jaffe CC, Krumholz HM, Johnson KM, Lynch PJ, Natale D, Atkinson P, Deman P, Wackers FJ. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *American Journal of Cardiology* 1996; 77:843-850.

139. Wackers FJ, Berger HJ, Johnstone DE, Goldman L, Reduto LA, Langou RA, Gottschalk A, Zaret BL. Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *American Journal of Cardiology* 1979; 43:1159-1166.
140. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *American Heart Journal* 2003; 146:388-397.
141. Morris SS, Ruel MT, Cohen RJ, Dewey KG, de la BB, Hassan MN. Precision, accuracy, and reliability of hemoglobin assessment with use of capillary blood. *American Journal of Clinical Nutrition* 1999; 69:1243-1248.
142. Manjunath G, Sarnak MJ, Levey AS. Estimating the glomerular filtration rate. Dos and don'ts for assessing kidney function. *Postgraduate Medicine* 2001; 110:55-62.
143. Clochesy JM, Davidson LJ, Piper-Caulkins E, Carno MA, Bauldoff GS. Use of serum albumin level in studying clinical outcomes. *Outcomes Management for Nursing Practice* 1999; 3:61-66.
144. Dubois MJ, Vincent JL. Use of albumin in the intensive care unit. *Current Opinion in Critical Care* 2002; 8:299-301.
145. Streiner DL, Norman GR. Validity. In *Health measurement scales: A practical guide to their development and use*. 1995:144-162.
146. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Annals of Internal Medicine* 1993; 118:201-210.
147. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis: Accuracy and precision of regression estimates. *Journal of Clinical Epidemiology* 1995; 48:1503-1510.
148. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* 1996; 49:1373-1379.
149. Harrell FE, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, and Measuring, and Reducing Errors. *Statistics in Medicine* 1996; 15:361-387.
150. Ash AS SM. Evaluating the performance of risk-adjustment methods: dichotomous outcomes. In *Risk adjustment for measuring healthcare outcomes*. Chicago: Health Administration Press; 1997:427-470.

151. Goodnough LT, Johnston MF, Toy PT. The variability of transfusion practice in coronary artery bypass surgery. Transfusion Medicine Academic Award Group. Journal of American Medical Association 1991; 265:86-90.
152. Loop FD, Lytle BW, Gill CC, Golding LA, Cosgrove DM, Taylor PC. Trends in selection and results of coronary artery reoperations. Annals of Thoracic Surgery 1983; 36:380-388.
153. Hardy JF, Perrault J, Tremblay N, Robitaille D, Blain R, Carrier M. The stratification of cardiac surgical procedures according to use of blood products: a retrospective analysis of 1480 cases. Canadian Journal of Anaesthesia 1991; 38:t-7.
154. Harrell FE. Regression Coefficients and Scoring Rules. Journal of Clinical Epidemiology 1996; 49:819.
155. Dupuis JY, Bart B, Bryson G, Robblee J. Transfusion practices among patients who did and did not predonate autologous blood before elective cardiac surgery. Canadian Medical Association Journal 1999; 160:997-1002.
156. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
157. Gault MH, Longrich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. Nephron 1992; 61:249-256.
158. Wijeyesundera DN, Rao V, Beattie WS, Ivanov J, Karkouti K. Evaluating surrogate measures of renal dysfunction after cardiac surgery. Anesthesia & Analgesia 2003; 96:1265-1273.
159. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983; 148:839-843.
160. Metz CE. Basic principles of ROC analysis. Seminars in Nuclear Medicine 1978; 8:283-298.
161. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240:1285-1293.
162. Begg CB, McNeil BJ. Assessment of radiologic tests: control of bias and other design considerations. Radiology 1988; 167:565-569.
163. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44:837-845.

164. Hajian-Tilaki KO, Hanley JA. Comparison of three methods for estimating the standard error of the area under the curve in ROC analysis of quantitative data. *Academic Radiology* 2002; 9:1278-1285.
165. Furnival GM, Wilson RW. *Regression by Leaps and Bounds*. Technometrics 1974; 16:499-511.
166. Sakamoto Y, Ishiguro M, Kitagawa G. *Akaike Information Criterion Statistics*. D. Reidel Publishing Company; 1986.
167. Tu JV, Mazer CD, Levinton C, Armstrong PW, Naylor CD. A predictive index for length of stay in the intensive care unit following cardiac surgery. *Canadian Medical Association Journal* 1994; 151:177-185.
168. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. *Chest* 1992; 102:36-44.
169. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987; 40:373-383.
170. Mclsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *Canadian Medical Association Journal* 1998; 158:75-83.
171. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, Weintraub RM. Comparison of two transfusion strategies after elective operations for myocardial revascularization. *Journal of Thoracic & Cardiovascular Surgery* 1992; 104:307-314.
172. Practice strategies for elective red blood cell transfusion. American College of Physicians. *Annals of Internal Medicine* 1992; 116:403-406.
173. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; 84:732-747.
174. Parolari A, Alamanni F, Cannata A, Naliato M, Bonati L, Rubini P, Veglia F, Tremoli E, Biglioli P. Off-pump versus on-pump coronary artery bypass: meta-analysis of currently available randomized trials. *Annals of Thoracic Surgery* 2003; 76:37-40.

APPENDICES

Appendix C.1: Research Ethics Board Approval at University Health Network



University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital

University Health Network Research Ethics Board
700 University Avenue
8th Floor South Room 8-18
Toronto, Ontario, M5G 1Z5
Phone: 416-946-4438
Fax: 416-595-9164

June 23, 2004

Dr. Stephanie J. Brister
EN 14-214
TGH

Dear Dr. Brister:

**Re: UHN REB #: 04-0317-AE
Developing and Validating a Transfusion Risk Scoring System in Cardiac
Surgery(Chart Review)**

The above named submission for access to health records has received expedited review by the University Health Network Research Ethics Board. The proposal is approved until the expiry date noted below. *Please note that approval for this study will expire on this date unless the UHN REB is otherwise notified.*

We wish to remind you that access to personal health records for research purposes without patient consent is a privilege granted by the REB. Please be sure to adhere at all times to the UHN Policy on Information and Data Security as noted in the Confidentiality Agreement signed as part of this submission.

If, during the course of the research, there are any changes in the approved submission or any new information that must be considered with respect to the study, these should be brought to the immediate attention of the Board.

Yours sincerely,

Ronald Heslegrave, Ph.D.
Chair, University Health Network Research Ethics Board

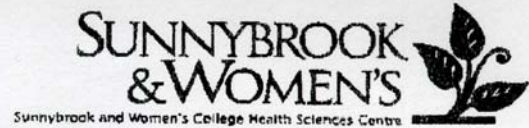
23 June, 2004
Date of REB Approval

23 June, 2005
Expiry Date of REB Approval

The University Health Network REB operates in compliance with the Tri-Council Policy Statement, ICH/GCP Guidelines and REB requirements as defined in Canada's Food and Drug Regulations, Division 5

Appendix C.2: Research Ethics Board Approval at Sunnybrook and Women's College Health Science Center

MEMORANDUM



To: Dr. A. Alghamdi
Cardiac Surgery
Room H406

From: Philip Hébert MD

Date: December 20, 2004

Subject: **Development and Validation of Transfusion Risk Understanding Tool (TRUST) to Stratify Cardiac Surgery Patients According to Their Blood Transfusion Needs**

Research Ethics Board
Sunnybrook Campus

The Research Building
2075 Bayview Avenue,
Room S1 33,
Toronto, ON,
Canada M4N 3M5
Tel 416.480.4276
Fax 416.480.5814

The Research Ethics Board
of Sunnybrook and Women's
College Health Sciences
Centre operates in compliance
with the Tri-Council Policy
Statement, the ICH/GCP
Guidelines and Division 5 of
the Food and Drug Regulations.

Project Identification Number: 463-2004
Approval Date: December 20, 2004

The Research Ethics Board of Sunnybrook & Women's College Health Sciences Centre has conducted an expedited review of the research protocol referenced above on the above captioned date and approved the involvement of human subjects as specified in the protocol.

The quorum for approval did not involve any member associated with this project.

Should your study continue for more than one year you must request a renewal on or before one year from the approval date. Please advise the Board of the progress of your research annually and/or any adverse reactions or deviations which may occur in the future.

The above Project Identification Number has been assigned to your project. Please use this number on all future correspondence.

Philip Hébert, MD PhD FCFPC
Chair, Research Ethics Board
/cap

Sunnybrook and Women's College Health Sciences Centre



Fully affiliated with the University of Toronto

Appendix C.3: Research Ethics Board Approval from the University of Toronto



UNIVERSITY OF TORONTO

Office of the Vice-President, Research and Associate Provost

Ethics Review Office

PROTOCOL REFERENCE #12952

December 6, 2004

Dr. A. Logan
Nephrology
Mt. Sinai Hospital
600 University Ave.
Toronto, ON M5G 1X5

Dr. A. Alghamdi
195 St. Patrick St., Apt. 602B
Toronto, ON M5T 2Y8

Dear Dr. Logan & Dr. Alghamdi:

Re: Protocol entitled, "Development and Validation of Transfusion Risk Understanding Scoring Tool (TRUST) to Stratify Cardiac Surgery Patients According to their Blood Transfusion Needs" by Dr. A. Logan (supervisor), Dr. A. Alghamdi (PhD candidate)

ETHICS APPROVAL

Original Approval Date: December 6, 2004

Expiry Date: December 5, 2005

We are writing to advise you that a member of the Health Sciences II Research Ethics Board has granted approval to the above-named research study, for a period of **one year**, under the Board's expedited review process. Ongoing projects must be renewed prior to the expiry date.

We acknowledge receipt of the UHN REB approval for this chart review study, expiry date June 23, 2005.

During the course of the research, any significant deviations from the approved protocol (**that is, any deviation which would lead to an increase in risk or a decrease in benefit to participants**) and/or any unanticipated developments within the research should be brought to the attention of the Ethics Review Unit. Best wishes for the successful completion of your project.

Yours sincerely,

Marianna Richardson
Ethics Review Coordinator

xc: Dr. A. Moore, Chair Health Sciences II Research Ethics Board
Prof. R. Cockerill, Graduate Coordinator, HPME

Appendix C.4: Research Ethics Board Approval from the University of Toronto



UNIVERSITY OF TORONTO

Office of the Vice-President, Research and Associate Provost

Ethics Review Office

PROTOCOL REFERENCE #13195

January 24, 2005

Dr. A. G. Logan
Nephrology
Mt. Sinai Hospital
600 University Ave.
Toronto, ON M5G 1X5

Mr. A. Alghamdi
195 St. Patrick St., Apt. 602B
Toronto, ON M5T 2Y8

Dear Dr. Logan & Mr. Alghamdi:

Re: Your research protocol entitled, "Development and Validation of Transfusion Risk Understanding Scoring Tool (TRUST) to Stratify Cardiac Patients According to Their Blood Transfusion Needs" by Dr. A. G. Logan (supervisor), Mr. A. Alghamdi (student)

We are writing to advise you that a member of the Health Sciences II Research Ethics Board has granted approval to the amendment to the above-named research study, for a period of **one year**. Ongoing projects must be renewed prior to the expiry date. The amendment involves a specification for the primary data source for cross-validation.

We acknowledge receipt of the Sunnybrook & WCHSC REB approval letter for this study dated Dec. 20, 2004 and the UHN REB approval letter for this study dated June 23, 2004.

During the course of the research, any significant deviations from the approved protocol (**that is, any deviation which would lead to an increase in risk or a decrease in benefit to participants**) and/or any unanticipated developments within the research should be brought to the attention of the Ethics Review Unit.

Best wishes for the successful completion of your project.

Yours sincerely,

A handwritten signature in cursive script that reads "Marianna Richardson".

Marianna Richardson
Ethics Review Coordinator

cc Prof. P. van Lieshout, Acting Chair, Health Sciences II REB
Dr. W. Levinson, Chair, Dept. of Medicine

Appendix D.1: Area under ROC curve of each cutoff point of the continuous variables in the development cohort

AGE	AUC	HGB	AUC	CREA	AUC	CCR	AUC	BMI	AUC
20	0.5	50	0.519	20	0.5	10	0.502	10	0.5
25	0.502	55	0.519	30	0.5	20	0.506	15	0.5
30	0.502	60	0.519	40	0.5	30	0.517	16	0.5
35	0.506	65	0.519	50	0.505	40	0.544	17	0.502
40	0.514	70	0.518	60	0.514	50	0.581	18	0.505
45	0.527	75	0.518	70	0.528	55	0.608	19	0.508
50	0.546	80	0.518	80	0.519	60	0.623	20	0.515
55	0.577	85	0.517	90	0.508	65	0.642	21	0.525
60	0.605	90	0.516	100	0.54	70	0.652	22	0.538
61	0.608	95	0.51	110	0.54	75	0.654	23	0.554
62	0.615	100	0.502	120	0.542	80	0.653	24	0.566
63	0.617	105	0.517	130	0.536	85	0.649	24.5	0.574
64	0.617	110	0.539	140	0.526	90	0.641	25	0.578
65	0.618	115	0.574	150	0.524	100	0.619	25.5	0.583
66	0.616	120	0.608	160	0.522	110	0.586	26	0.583
67	0.619	125	0.641	170	0.519	120	0.557	26.5	0.583
68	0.616	130	0.671	180	0.517	130	0.542	27	0.584
69	0.616	135	0.681	190	0.515	140	0.527	27.5	0.581
70	0.612	140	0.668	200	0.513	150	0.518	28	0.579
71	0.601	145	0.628	210	0.511	160	0.509	29	0.563
72	0.595	150	0.583	220	0.509	170	0.504	30	0.554
73	0.586	155	0.545	230	0.509	180	0.502	31	0.548
74	0.576	160	0.517	240	0.508	190	0.501	32	0.542
75	0.566	165	0.505	250	0.508	200	0.501	33	0.532
80	0.523	170	0.502	260	0.508	210	0.5	34	0.524
85	0.504	175	0.501	270	0.507	220	0.5	35	0.517
90	0.5	180	0.5	280	0.507	230	0.5	36	0.513
		185	0.5	290	0.506	240	0.5	37	0.509
		190	0.5	300	0.505	250	0.5	38	0.507
		195	0.5	350	0.505	260	0.5	39	0.504
		200	0.5	400	0.504	270	0.5	40	0.503
		205	0.5	450	0.504	280	0.5	45	0.5
		210	0.5	500	0.503	290	0.5		
		215	0.5	600	0.502	300	0.5		
				700	0.502				
				800	0.501				
				900	0.501				
				1000	0.5				
Split		Split		Split		Split		Split	
<56	≥65	≥135	<135	<120	≥120	≥75	<75	≥27	<27
51%	49%	52%	48%	87%	13%	56%	44%	52%	48%
μ=53.2	μ=72.3	μ=145.8	μ=121.1	μ=85.6	μ=182.8	μ=104.4	μ=56.0	μ=31.4	μ=24.0
σ=9.5	σ=5.0	σ=8.1	σ=10.8	σ=16.2	σ=146.6	σ=25.6	σ=14.0	σ=5.4	σ=2.2

Appendix D.1: Area under ROC curve of each cutoff point of the continuous variables in the development cohort (continue)

PLT	AUC	INR	AUC	WT	AUC
25	0.5	0.4	0.5	35	0.5
50	0.519	0.5	0.518	40	0.501
75	0.518	0.6	0.518	45	0.505
100	0.514	0.7	0.518	50	0.514
125	0.509	0.8	0.519	55	0.529
150	0.504	0.9	0.518	60	0.557
175	0.507	1	0.526	65	0.598
200	0.509	1.1	0.536	70	0.63
225	0.519	1.2	0.525	71	0.631
230	0.523	1.3	0.516	72	0.631
235	0.528	1.4	0.51	73	0.636
240	0.531	1.5	0.508	74	0.635
245	0.533	1.6	0.505	75	0.638
250	0.536	1.7	0.505	76	0.644
255	0.54	1.8	0.503	77	0.648
260	0.539	1.9	0.501	78	0.647
265	0.539	2	0.501	79	0.649
270	0.538	2.1	0.501	80	0.645
275	0.538	2.2	0.501	81	0.644
280	0.535	2.3	0.501	82	0.641
285	0.535	2.4	0.5	83	0.637
290	0.536	2.5	0.5	84	0.632
295	0.534	2.6	0.5	85	0.628
300	0.532	2.7	0.5	90	0.597
325	0.523	2.8	0.5	95	0.574
350	0.517	2.9	0.5	100	0.553
375	0.512	3	0.5	105	0.535
400	0.508	4	0.5	110	0.524
425	0.505	5	0.5	115	0.514
450	0.503	6	0.5	120	0.509
475	0.502			125	0.505
500	0.502			130	0.502
525	0.501			135	0.501
550	0.501			140	0.5
575	0.501			145	0.5
600	0.5			150	0.5
Split		Split		Split	
≥ 255	<255	≤ 1.1	>1.1	≥ 77	<77
50%	50%	66%	34%	54%	46%
μ=282.6	μ=181.6	μ=1.0	μ=1.2	μ=90.5	μ=65.7
σ=60.6	σ=31.3	σ=0.1	σ=0.3	σ=12.1	σ=7.9

μ: Mean

σ: Standard deviation

Appendix E.1: Statistical properties of the full model and all subset models in the continuous form

Items	10	9	8	7	6	5	4	3	2	1
1	HGB*	HGB*	HGB*	HGB*	HGB*	HGB*	HGB*	HGB*	HGB*	NHGB*
2	AGE*	AGE*	AGE*	AGE*	AGE*	AGE*	AGE*	AGE*	AGE*	
3	WEIGHT*	WEIGHT*	WEIGHT*	WEIGHT*	WEIGHT*	WEIGHT*	WEIGHT*	WEIGHT*		
4	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE			
5	NONELECT	NONELECT	NONELECT	NONELECT	NONELECT	NONELECT				
6	COMBINED	COMBINED	COMBINED	COMBINED	COMBINED					
7	CREAT*	CREAT*	CREAT*	CREAT*						
8	REDO	REDO	REDO							
9	POORLV	POORLV								
10	DIABETES									
AUC	0.827	0.827	0.825	0.822	0.820	0.816	0.813	0.811	0.777	0.759
HLP	0.003	0.002	0.001	0.001	0.003	0.001	0.001	0.001	0.001	0.004
SCORE	2170.773	2165.921	2140.088	2109.091	2099.204	2048.876	2017.707	1973.635	1573.242	1388.470
AIC	7476.801	7480.589	7530.405	7573.770	7610.212	7680.053	7743.199	7791.870	8317.071	8555.906
SC	7552.576	7549.475	7592.418	7628.892	7658.459	7721.407	7777.671	7819.447	8337.755	8569.700
-2LogL	7454.801	7460.589	7512.405	7557.770	7596.212	7668.053	7733.199	7783.870	8311.071	8551.906

AUC: Area Under ROC Curve, HLP: Probability associated with Hosmer-Lemeshow Goodness of Fit, SCORE: Likelihood score, AIC: Akaike Information Criterion, SC: Schwarz Criterion, -2LogL: minus two multiplied by the logarithm of the Likelihood, HGB: Hemoglobin Level, CREAT: Creatinine Level, NONELECT: non-elective surgery, COMBINED: non-isolated surgery, and *: Variable in the continuous form.

Appendix E.2: Sensitivity and Specificity at threshold scores for TRUST in the Development Cohort

Cutoff point	Number of TP	Number of FP	Number of FN	Number of TN	SEN	SPEC	TE	AUC
0	3805	3456	0	0	1.00	0.00	0.48	.
1	3717	2836	88	620	0.98	0.18	0.40	0.58
2	3372	1766	433	1690	0.89	0.49	0.30	0.69
3	2679	846	1126	2610	0.70	0.76	0.27	0.73
4	1687	285	2118	3171	0.44	0.92	0.33	0.68
5	781	79	3024	3377	0.21	0.98	0.43	0.59
6	193	16	3612	3440	0.05	0.99	0.50	0.52
7	31	5	3774	3451	0.01	0.99	0.52	0.50
8	1	0	3804	3456	0.00	1.00	0.52	0.50

TP: True Positive, FP: False Positive, FN: False Negative, TN: True Negative, SEN: Sensitivity, SPEC: Specificity, TE: Total Error, AUC: Area Under the Curve

Appendix E.3: Sensitivity and Specificity at threshold scores for TRUST in the Validation Cohort

Cutoff point	Number of TP	Number of FP	Number of FN	Number of TN	SEN	SPEC	TE	AUC
0	1908	1686	0	0	1.00	0.00	0.47	.
1	1857	1406	51	280	0.97	0.17	0.41	0.57
2	1672	877	236	809	0.88	0.48	0.31	0.68
3	1328	433	580	1253	0.69	0.74	0.28	0.72
4	866	160	1042	1526	0.45	0.91	0.33	0.68
5	393	46	1515	1640	0.21	0.97	0.43	0.59
6	108	10	1800	1676	0.06	0.99	0.50	0.53
7	15	1	1893	1685	0.01	0.99	0.53	0.50
8	1	0	1907	1686	0.00	1.00	0.53	0.50

TP: True Positive, FP: False Positive, FN: False Negative, TN: True Negative, SEN: Sensitivity, SPEC: Specificity, TE: Total Error, AUC: Area Under the Curve

Appendix 4: Sensitivity and Specificity at threshold scores for TRUST in the Cross-Validation Cohort

Cutoff point	Number of TP	Number of FP	Number of FN	Number of TN	SEN	SPEC	TE	AUC
0	2364	2952	0	0	1.00	0.00	0.56	.
1	2322	2388	42	564	0.98	0.19	0.46	0.59
2	2067	1391	297	1561	0.87	0.53	0.32	0.70
3	1604	596	760	2356	0.68	0.80	0.26	0.74
4	1006	178	1358	2774	0.43	0.94	0.29	0.68
5	379	30	1985	2922	0.16	0.99	0.38	0.58
6	59	0	2305	2952	0.03	1.00	0.43	0.51
7	5	0	2359	2952	0.00	1.00	0.44	0.50
8	0	0	2364	2952	0.00	1.00	0.44	.

TP: True Positive, FP: False Positive, FN: False Negative, TN: True Negative, SEN: Sensitivity, SPEC: Specificity, TE: Total Error, AUC: Area Under the Curve

