

# Multivariable statistical models to predict red cell transfusion in elective surgery

Kevin M. Trentino<sup>1,2</sup>, Frank M. Sanfilippo<sup>3</sup>, Michael F. Leahy<sup>3,4</sup>, Shannon L. Farmer<sup>5,6</sup>, Hamish Mace<sup>7,8</sup>, Adam Lloyd<sup>2</sup>, Kevin Murray<sup>1</sup>



<sup>1</sup>School of Population and Global Health, The University of Western Australia, Perth, Australia;

<sup>2</sup>Data and Digital Innovation, East Metropolitan Health Service, Perth, Australia;

<sup>3</sup>Department of Haematology, PathWest Laboratory Medicine, Royal Perth Hospital, Perth, Australia;

<sup>4</sup>School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia;

<sup>5</sup>Department of Haematology, Royal Perth Hospital, Perth, Australia;

<sup>6</sup>Discipline of Surgery, Medical School, The University of Western Australia, Perth, Australia;

<sup>7</sup>Department of Anaesthesia, Pain and Perioperative Medicine, Fiona Stanley Hospital, Murdoch, Australia;

<sup>8</sup>Division of Emergency Medicine, The University of Western Australia, Perth, Australia

**Background** - Predicting red cell transfusion may assist in identifying those most likely to benefit from patient blood management strategies. Our objective was to identify a simple statistical model to predict transfusion in elective surgery from routinely available data.

**Materials and methods** - Our final multicentre cohort consisted of 42,546 patients and contained the following potential predictors of red cell transfusion known prior to admission: patient age, sex, pre-admission hemoglobin, surgical procedure, and comorbidities. Missing data were handled by multiple imputation methods. The outcome measure of interest was administration of a red cell transfusion. We used multivariable logistic regression models to predict transfusion, and evaluated the performance by applying a 10-fold cross-validation. Model accuracy was assessed by comparing the area under the receiver operating characteristics curve. After applying an optimal probability cut-off we measured model accuracy, sensitivity, specificity, positive predictive value, and negative predictive value.

**Results** - 7.0% (n=2,993) of the study population received a red cell transfusion. Our most simple model predicted red cell transfusion based on admission hemoglobin and surgical procedure with a multiply imputed estimated area under the curve of 0.862 (0.856, 0.864). The estimated accuracy, sensitivity, specificity, positive predictive, and negative predictive values at the probability cut-off of 0.4 were 0.934, 0.257, 0.986, 0.573, and 0.946 respectively.

**Discussion** - A small number of variables available prior to admission can predict red cell transfusion with very good accuracy. Our model can be used to flag high-risk patients most likely to benefit from pre-operative patient blood management measures.

**Keywords:** anemia, erythrocyte transfusion, preoperative care.

## INTRODUCTION

Scores of randomised controlled trials have (RCTs) investigated differing hemoglobin thresholds for red cell transfusions. For example, a recent overview of systematic reviews identified 19 reviews pooling data from 68 unique randomised controlled trials comparing thresholds for red cell transfusion<sup>1</sup>. Many of these trials conducted in the surgical setting

involve elective patients, and while they are important, they nonetheless leave important questions for clinical practice unanswered. For example, are red cell transfusions predictable, what are the risk factors, and are these risk factors modifiable?

The implications for clinical practice and health care systems are considerable. If red cell transfusions can be accurately predicted prior to elective surgery this may mean that a considerable number of transfusions defined as appropriate, through clinical trial data, may be avoided<sup>2</sup>. This has the potential to improve patient safety and reduce health care costs<sup>3</sup>.

Several publications report applying statistical or machine learning techniques to predict red cell transfusion with good accuracy. However, the majority of these studies tend to be in specific patient groups<sup>4-7</sup>, utilise variables that are not routinely available pre-admission, or apply complex machine-learning techniques that make model interpretation and clinical application difficult<sup>8</sup>. We did not find any studies attempting to identify the simplest statistical model to predict red cell transfusion in the elective surgical setting.

The aim of our study was to create simple clinical prediction models (prognostic) to estimate the probability of a patient being transfused red cells during their elective surgical admission. In this manuscript, we describe both the development and the validation of our models.

## MATERIALS AND METHODS

We designed a retrospective observational study sourcing data from the Western Australia Patient Blood Management data system<sup>9</sup>. The Royal Perth Hospital Human Research Ethics Committee waived the requirement for written informed consent and granted ethical approval. We reported our results according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement<sup>10</sup>.

Data were sourced from four public hospitals in Western Australia, with adults admitted for elective surgical procedures included for analysis. The prediction outcome of interest was exposure to a red cell transfusion that occurred intraoperatively or post-operatively. Our dataset consisted of a number of variables, six of which were available prior to admission: patient age, sex,

surgical specialty, surgical procedure, comorbidities, and pre-admission hemoglobin level.

Our initial dataset consisted of all overnight elective surgical admissions admitted to the four study hospitals between July 2014 and June 2020 (Figure 1). We planned to include in our analysis all elective surgical patients. However, as there were a large number of surgical procedure categories we made a post-hoc decision to exclude procedures with less than 10 people transfused over the study period leaving a final cohort of 42,546 admissions.

Our univariable analysis compared predictors known prior to admission between those receiving red cell transfusions and those not transfused. Categorical variables were analysed using the  $\chi$ -squared test, and continuous variables were analysed using the independent  $t$ -test for mean differences. We performed univariable analyses on complete cases in our original dataset.

Missing pre-admission data were handled through multiple imputation. We applied multivariate imputation by chained equations (MICE), and created 20 copies of our dataset with missing values replaced by imputed values. A sensitivity analysis was performed on complete cases from the original dataset.

Rather than apply variable selection techniques for variable inclusion we included variables available at pre-admission that are thought to be clinically relevant based on medical expertise and previous publications<sup>11,12</sup>. Based

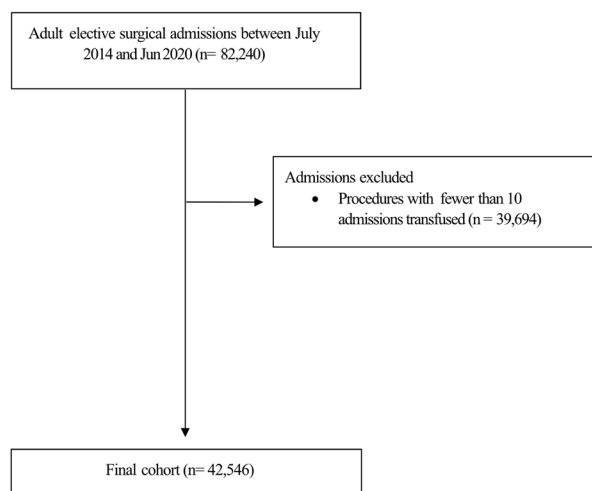


Figure 1 - Flowchart of patient identification for the study cohort

on this, Model 1 included pre-admission hemoglobin, type of surgical procedure, patient age, sex, and comorbidities (Charlson comorbidity index). As our aim was to create the simplest statistical model possible, Model 2 only included pre-admission hemoglobin and surgical procedure. In addition, a previous study indicated that red cell transfusion in elective surgery could be accurately predicted by pre-operative anaemia and perioperative blood loss<sup>11</sup>. Although perioperative blood loss is not known prior to admission we included a model (Model 3) that used pre-operative hemoglobin and hemoglobin decrease, as a surrogate for blood loss, for the purpose of comparing it to the results of our first two models.

We evaluated the performance of our prediction models by applying 10-fold cross-validation. We applied this technique to measure the accuracy of our predictions when applied to test data (data not used to develop the statistical model)<sup>13</sup>. Prediction models were assessed by comparing the area under the receiver operating characteristics curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. We combined model estimates after multiple imputation using Rubin's rules, and applied robust summary measures (medians and ranges) to combine model accuracy scores.

Traditionally prediction models use a probability cut-off of 50% for binary classification<sup>14</sup>. This selection assumes that false negative and false positive errors are of equal importance, however frequently in the medical context false negatives result in greater consequences than a false positive result. Therefore, we aimed to choose an appropriate probability cut-off value for our prediction that applied a cost ratio of false negative to false positive classifications to create a weighted error rate<sup>15</sup>. Our cost ratio was derived from an economic evaluation, which compared the hospital costs of transfused and non-transfused patients. After adjusting for relevant confounders transfused patients had 1.83 times higher costs than non-transfused patients<sup>3</sup>. Therefore, we applied the following formula:  $Number\ needed\ to\ misdiagnose = (1/(1.83 \times false\ negatives) + false\ positives)^{-1}$ .

## RESULTS

Between July 2014 and June 2020 there were 82,240 overnight elective surgical admissions at the four study hospitals. After removing procedures with less than

10 people transfused over the study period we were left with a final cohort of 42,546 admissions (Figure 1).

The characteristics of hospital admissions are presented in Table I. The 42,546 admissions had a mean (SD) age of 60.3 (17.4) and 21,803 (51.3%) were female. Overall, 2,993 (7.0%) admissions received a red cell transfusion. The most common elective surgical specialty was orthopaedics

**Table I - Characteristics of study patients stratified by sex**

Characteristics	Female (n=21,803)	Male (n=20,743)	Total (n=42,546)
Age, years (SD)	56.6 (18.9)	64.3 (14.7)	60.34 (17.40)
<b>Hospital (%)</b>			
Hospital 1	7,511 (34.4)	5,250 (25.3)	12,761 (30.0)
Hospital 2	3,505 (16.1)	2,745 (13.2)	6,250 (14.7)
Hospital 3	4,107 (18.8)	4,965 (23.9)	9,072 (21.3)
Hospital 4	6,680 (30.6)	7,783 (37.5)	14,463 (34.0)
<b>Pre-operative hemoglobin g/L, (SD)</b>	129.45 (14.54)	138.93 (19.21)	133.89 (17.54)
<b>Nadir hemoglobin, g/L (SD)</b>	105.93 (19.90)	110.71 (24.22)	108.26 (22.24)
<b>Received red cell transfusion (%)</b>	1433 (6.6)	1,560 (7.5)	2,993 (7.0)
<b>Surgical specialty (%)</b>			
Breast Surgery	2,640 (12.1)	112 (0.5)	2,752 (6.5)
Cardiothoracic	1,353 (6.2)	2,827 (13.6)	4,180 (9.8)
Ear Nose Throat/Maxillofacial	110 (0.5)	171 (0.8)	281 (0.7)
Gastrointestinal surgery	3,614 (16.6)	4,132 (19.9)	7,746 (18.2)
Gynaecology	431 (2.0)	1 (0.0)	432 (1.0)
Miscellaneous Surgery	837 (3.8)	1,287 (6.2)	2,124 (5.0)
Neurosurgery	1,141 (5.2)	1,139 (5.5)	2,280 (5.4)
Obstetrics	4,007 (18.4)	0 (0.0)	4,007 (9.4)
Orthopaedics	4,664 (21.4)	4,482 (21.6)	9,146 (21.5)
Plastic Surgery	408 (1.9)	607 (2.9)	1,015 (2.4)
Urology	1,041 (4.8)	2,600 (12.5)	3,641 (8.6)
Vascular Surgery	1,557 (7.1)	3,385 (16.3)	4,942 (11.6)
<b>Charlson comorbidity score (%)</b>			
0	15,365 (70.5)	11,771 (56.8)	27,136 (63.8)
1	2,104 (9.7)	2,989 (14.4)	5,093 (12.0)
2	1,855 (8.5)	2,978 (14.4)	4,833 (11.4)
3+	2,474 (11.3)	3,003 (14.5)	5,477 (12.9)

Values are number (proportion) or mean (SD)

**Table II - Admission hemoglobin, hemoglobin decrease, and nadir hemoglobin in top 10 elective surgical procedures, sorted by highest number of patients receiving a red cell transfusion**

Elective Procedure	N.	Admission hemoglobin	Hemoglobin decrease	Nadir hemoglobin	% RBC transfused
Coronary artery bypass graft	1,545	141 [131, 151]	56 [46, 65]	82 [72, 94]	26%
Heart valve replacement	1,297	134 [123, 145]	48 [28, 62]	85 [72, 99]	24%
Hip arthroplasty	2,764	139 [130, 149]	31 [23, 39]	107 [95, 118]	6%
Revision hip arthroplasty	468	135 [122, 144]	36 [25, 49]	93 [81, 109]	28%
Colectomy	1,060	129 [116, 142]	24 [17, 32]	102 [88, 116]	11%
Anterior resection of rectum	920	137 [126, 148]	27 [20, 39]	107 [91, 120]	11%
Knee arthroplasty	3,349	139 [130, 149]	28 [22, 37]	110 [100, 121]	3%
Other repair proc on vascular sites	794	140 [128, 151]	27 [18, 38]	111 [92, 126]	12%
Pancreatectomy	527	135 [125, 144]	38 [27, 49]	94 [80, 107]	16%
Cystectomy	175	133 [120, 145]	45 [34, 57]	83 [74, 96]	37%

Hemoglobin (g/L) values are medians [25<sup>th</sup>, 75<sup>th</sup> percentiles].

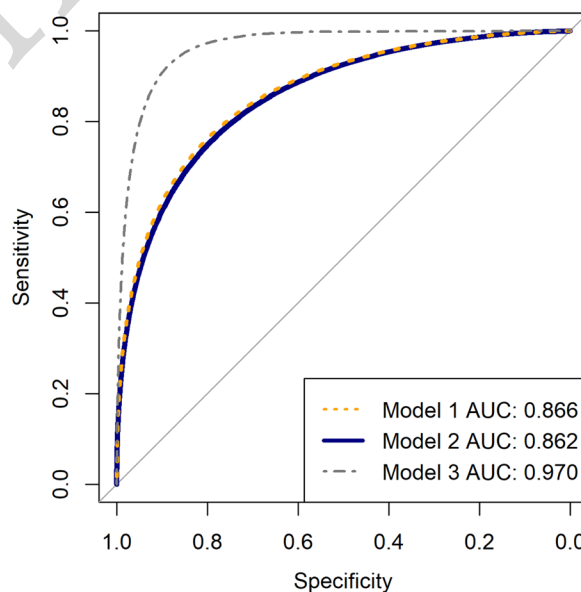
(9,146, 21.5%) followed by gastrointestinal surgery (7,746, 18.2%) and vascular surgery (4,942, 11.6%).

Table II lists the admission hemoglobin, hemoglobin decrease, and nadir hemoglobin values for the top 10 elective surgical procedures sorted by number of patients transfused. The elective surgical procedure with the greatest incidence of red cell transfusions was coronary artery bypass graft surgery (n=402) followed by heart valve replacements (n=311) and hip arthroplasty (n=167).

In our unadjusted analysis, patient exposed to red cell transfusion were older (mean difference=6.88 years, 95% CI, 6.24 to 7.53), had lower pre-admission hemoglobin levels (mean difference=14.17 g/L, 95% CI 13.49 to 14.86), and were more likely to be male (odds ratio=1.16, 95% CI, 1.07 to 1.25). Admissions with a Charlson comorbidity score of 3 or higher had 3.20 (95% CI 2.91 to 3.51) times higher odds of transfusion than admissions with a score of 0.

Figure 2 presents the median performance results over 20 imputed datasets of our three predictive models as measured by the AUC. The individual model performance results for each imputed dataset is available in Online Supplementary Content, Table SI. Model 1, which included all available variables known prior to admission, produced similar results (median AUC=0.866, range=0.861, 0.868) to Model 2, our simplified prediction model (median AUC=0.862, range=0.856, 0.864). Model 3, included for comparison purposes, resulted in an AUC of 0.970 (95% CI: 0.968, 0.973). The pooled model outputs for Model 2 are

presented in Table III, with model outputs for Model 1 and Model 3 available in Online Supplementary Content, Table SII and SIII.



**Figure 2 - Receiver operating characteristic curves to predict elective surgical patients receiving a red blood cell transfusion**

Model 1: Red cell transfusion = admission hemoglobin + surgical procedure + age + sex + Charlson score. Model 2: Red cell transfusion = admission hemoglobin + surgical procedure. Model 3 (for comparative purposes): Red cell transfusion = admission hemoglobin + hemoglobin decrease.

**Table III - Multivariable model output to predict red cell transfusion in elective surgery from admission hemoglobin and surgical procedure (Model 2)**

Characteristic	Pooled estimate*	Pooled std. error*	Pooled odds ratio (95% CI)*	Characteristic	Pooled estimate*	Pooled std. error*	Pooled odds ratio (95% CI)*
Admission haemoglobin	-0.06	0.002	0.945 (0.94, 0.949)	<b>Surgical Procedure</b>			
<b>Surgical Procedure</b>				Other excision procedures on abdomen, peritoneum or omentum	1.96	0.35	7.08 (3.56, 14.11)
Amputation of ankle or foot	-1.13	0.29	0.32 (0.18, 0.57)	Other debridement of SSCT	-0.62	0.33	0.54 (0.28, 1.02)
Amputation of pelvis or hip	1.67	0.40	5.32 (2.44, 11.60)	Other excision procedures on knee or leg	0.80	0.34	2.22 (1.15, 4.29)
Anterior resection of rectum	0.51	0.25	1.67 (1.03, 2.73)	Other gastrectomy	-0.21	0.38	0.81 (0.38, 1.72)
Arterial bypass graft using composite, sequential or crossover graft	2.53	0.46	12.57 (5.07, 31.14)	Other procedures on female genital organs	0.96	0.37	2.61 (1.27, 5.34)
Arterial bypass graft using vein	1.27	0.32	3.55 (1.88, 6.70)	Other repair procedures on vascular sites	0.79	0.25	2.21 (1.34, 3.64)
Arterial bypass graft using synthetic material	2.16	0.34	8.67 (4.46, 16.85)	Other repair procedures on shoulder	-1.68	0.37	0.19 (0.09, 0.38)
Arthroplasty of hip	0.13	0.24	1.14 (0.72, 1.81)	Other revision procedures on knee	0.59	0.27	1.81 (1.07, 3.06)
Arthroplasty of knee	-0.70	0.25	0.50 (0.31, 0.81)	Pancreatectomy	0.98	0.25	2.67 (1.62, 4.40)
CABG	1.90	0.23	6.70 (4.25, 10.55)	Partial resection of lung	-0.95	0.38	0.39 (0.18, 0.81)
Caesarean section	-2.25	0.27	0.10 (0.06, 0.18)	Procedures for surgically created arteriovenous fistula	-2.49	0.33	0.08 (0.04, 0.16)
Cardiac valve repair	1.23	0.43	3.42 (1.46, 7.97)	Radical nephrectomy	0.39	0.29	1.48 (0.84, 2.59)
Cardiac valve replacement	1.43	0.23	4.18 (2.65, 6.59)	Reconstruction procedures on breast	-0.06	0.34	0.94 (0.48, 1.83)
Cholecystectomy	-2.01	0.33	0.13 (0.07, 0.25)	Rectosigmoidectomy or proctectomy	1.50	0.27	4.48 (2.63, 7.64)
Closure of stoma of small intestine	-0.92	0.34	0.40 (0.20, 0.78)	Reduction of fracture of pelvis or femur	0.73	0.44	2.07 (0.88, 4.91)
Colectomy	0.08	0.25	1.09 (0.67, 1.76)	Removal of intracranial lesion	-0.88	0.33	0.41 (0.21, 0.80)
Complete nephrectomy	0.11	0.36	1.12 (0.56, 2.25)	Repair of incisional hernia	-1.19	0.38	0.31 (0.14, 0.65)
Cystectomy	2.12	0.29	8.34 (4.75, 14.63)	Repair procedures on liver	2.29	0.51	9.9 (3.61, 27.14)
Decompression of lumbar spinal canal	-0.91	0.34	0.40 (0.21, 0.79)	Replacement of aortic arch and ascending thoracic aorta	2.76	0.35	15.73 (7.87, 31.46)
Endarterectomy	0.55	0.28	1.74 (1.01, 2.99)	Replacement of aneurysm with graft	2.74	0.29	15.53 (8.81, 27.36)
Endoscopic insertion or removal of ureteric stent	-1.85	0.36	0.16 (0.08, 0.32)	Replacement of ascending thoracic aorta	2.23	0.39	9.29 (4.32, 19.97)
Endoscopic resection bladder lesion/tissue	-1.88	0.35	0.15 (0.08, 0.30)	Resection of small intestine	0.87	0.35	2.39 (1.21, 4.72)
Excision of lesion of SSCT	-1.66	0.30	0.19 (0.11, 0.34)	Revision arthroplasty of hip	1.69	0.25	5.42 (3.32, 8.84)
Excision proc on salivary gland or duct	-1.04	0.37	0.36 (0.17, 0.74)	Simple mastectomy	-1.33	0.28	0.26 (0.15, 0.45)
Excision procedures on liver	0.78	0.27	2.19 (1.29, 3.73)	Spinal fusion	0.40	0.26	1.48 (0.88, 2.49)
Excision procedures on other musculoskeletal sites	-0.71	0.27	0.49 (0.29, 0.84)	Subcutaneous mastectomy	-0.16	0.32	0.85 (0.46, 1.60)
Fixation of fracture of pelvis or femur	0.43	0.30	1.54 (0.85, 2.77)	Total proctocolectomy	1.47	0.35	4.33 (2.16, 8.69)
Free flap	1.60	0.40	4.97 (2.28, 10.80)	Transluminal balloon angioplasty	-2.01	0.27	0.13 (0.08, 0.23)
Kidney transplantation	0.23	0.29	1.26 (0.72, 2.22)	Transplantation of heart or lung	5.18	1.09	178.55 (21.26, 1499.26)
Lobectomy of lung	-0.85	0.38	0.43 (0.20, 0.91)	Transplantation of lung	4.58	0.47	97.29 (38.60, 245.19)
Mitral valve annuloplasty	1.81	0.32	6.09 (3.28, 11.30)	Transcatheter embolisation of blood vessels	-2.10	0.35	0.12 (0.06, 0.24)
Nephroureterectomy	0.55	0.39	1.73 (0.81, 3.69)				
Oesophagectomy by abdominal and transthoracic mobilisation	-0.04	0.39	0.96 (0.44, 2.08)				
Open prostatectomy	1.49	0.28	4.45 (2.59, 7.66)				

\*Model effect estimates and standard errors from multiple imputation models pooled using Rubin's Rules. CABG: coronary artery bypass graft surgery; SSCT: skin and subcutaneous tissue.

### Sensitivity analysis

A sensitivity analysis performed on complete cases in the original dataset yielded very similar results to the median values over our imputed datasets. The AUC for Model 1 was 0.866 (95% CI 0.858, 0.872), and the AUC for Model 2 was 0.863, (95% CI 0.856, 0.870).

### Probability cut-off

The accuracy, sensitivity, specificity, positive predictive value, and negative predictive values of Model 2 at various probability cut-offs for the 20 imputed datasets are presented in Online Supplementary Content, Table SIV. After applying our weighted error rate  $1/([1.83 \times \text{false negatives}] + \text{false positives})$  we determined that the optimal probability cut-off value was 0.4. At this cut-off the median accuracy, sensitivity, specificity, positive predictive, and negative predictive values from the multiple imputations were 0.934, 0.257, 0.986, 0.573, and 0.946 respectively (Table IV).

### DISCUSSION

Our results demonstrate that red cell transfusion can be predicted with very good accuracy in the elective surgery setting. In our most simple statistical model we were able to demonstrate that two factors known prior to admission (pre-admission hemoglobin level and surgical procedure) performed as well as the more complicated model, and can be used to identify patients at risk of receiving a red cell transfusion (AUC=0.86).

These results are consistent with Roubinian *et al.*<sup>16</sup> who demonstrated that admission hemoglobin along with patient age, sex, comorbid conditions, admission type (emergency or elective), and admission diagnosis resulted

in an AUC of 0.86 for predicting hospital transfusion. One key difference with our study is that they included all hospitalised patients, and grouped all admissions into one of five medical and surgical categories. As our study focused on patients presenting for elective surgery we were able to include more detailed information by adding the surgical procedure to our statistical model. Of note, Roubinian *et al.* reported that the most important predictor for red cell transfusion was the admission hemoglobin level, and that contrary to common belief the patient’s severity of illness and comorbidities play a relatively minor role. Our prediction models provide the same conclusion about comorbidity.

One of the earliest studies to draw attention to the predictors of red cell transfusion was the Austrian Benchmark study<sup>11</sup>. This study reported that pre-operative anaemia, blood loss, and nadir hemoglobin were strong predictors for red cell transfusion (AUC=0.97). For comparative purposes we presented the results of a prediction model with pre-operative hemoglobin level and hemoglobin decrease (as a measure of blood loss), which also resulted in an AUC of 0.97. These results are significant as pre-operative anaemia, blood loss, and level of nadir hemoglobin are modifiable risk factors. However, the aim of our research was to predict transfusion from data available prior to admission and therefore intraoperative blood loss and nadir hemoglobin were not included in our prediction models.

A strength of our study was that it included six years of elective surgical patients presenting to four major public

**Table IV - Model 2 (red cell transfusion=admission hemoglobin + surgical procedure) median accuracy, sensitivity, specificity, positive predictive value, and negative predictive value at various probability cut-off values**

Probability cut-off	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0.1	0.833	0.706	0.843	0.253	0.974
0.2	0.904	0.507	0.934	0.369	0.962
0.3	0.926	0.353	0.970	0.469	0.952
0.4	0.934	0.257	0.986	0.573	0.946
0.5	0.936	0.177	0.993	0.656	0.941
0.6	0.935	0.118	0.997	0.725	0.937
0.7	0.933	0.070	0.999	0.785	0.934
0.8	0.932	0.036	1.000	0.867	0.932
0.9	0.930	0.009	1.000	0.885	0.930

metropolitan hospitals. In addition, data were sourced from the Western Australia Patient Blood Management data system, which combines data from five core hospital systems, including the laboratory information system and the transfusion medicine database, to create a detailed view of patient characteristics and outcomes associated with anaemia and transfusion practices<sup>17</sup>.

A limitation of our study was the number of patients with missing pre-operative hemoglobin levels, consistent with other studies<sup>18</sup>. These missing values may be a result of pre-admission investigations conducted in the primary care setting (and therefore not captured in our datasets), or it may indicate pre-admission testing was not conducted. We applied multiple imputation techniques to account for missing data, and our complete-case sensitivity analysis produced near identical results, strengthening our confidence in the results. Another limitation of our study was that our dataset did not contain information that may assist in better predicting blood loss, such as the results of coagulation screening, bleeding history, or anticoagulant and antiplatelet use. In addition, while our elective surgical patient population is generalisable to other health services, a high variability in transfusion practice does exist between hospitals. Part of this variability can be explained by factors included in our statistical model, such as pre-operative hemoglobin level. However, other reasons, like a department's pre-transfusion hemoglobin threshold policies, were not included in our model. Despite this, there is remarkable consistency between our prediction results and the results of researchers from other health care systems<sup>11,16</sup>, adding to our confidence that red cell transfusion in elective surgery is predictable and its risk factors are modifiable with the three pillars of patient blood management.

The results of our statistical modelling have great potential for use by clinical teams to better target patients for pre-operative screening and treatment. For example, the Australian Patient Blood Management Guidelines suggest screening of patients who are booked for elective surgical procedures where substantial blood loss is expected<sup>19</sup>. While studies have demonstrated the cost-effectiveness of pre-operative screening and treatment of anaemia prior to elective surgery<sup>20,21</sup>, some perioperative teams may lack the human resources required to screen all patients booked for surgical procedures with anticipated blood loss. Under

these circumstances our model can be applied to generate an automated list of patients booked for surgery ranked by the greatest risk of receiving a transfusion. This may provide clinicians with a tool to better focus their patient blood management efforts, thus making efficient use of limited resources.

The potential impact of clinical prediction models for transfusion is considerable. Current practice often results in hospitalised patients receiving a red cell transfusion after reaching a hemoglobin threshold indicated in published clinical trials. However, prediction models for transfusion in the elective surgical setting have the potential to proactively identify patients at risk and trigger the application of patient blood management strategies to reduce that risk. Given that blood transfusions are recognised as a top five overused therapy<sup>17</sup>, and are associated with negative patient outcomes and increased health care costs<sup>3,22</sup>, the implications for health care systems are considerable.

Future research efforts are needed to assess the feasibility of combining the results of continuous non-invasive monitoring devices connected to hospitalised patients collecting real-time data on vital signs (heart rate, blood pressure, respiration rate, and oxygen saturation), hemoglobin results, risk factors for bleeding, and other available measures to develop early prediction models for transfusion.

## **CONCLUSIONS**

A small number of variables available prior to admission can predict red cell transfusion with very good accuracy. Our model can be used to flag high-risk patients most likely to benefit from pre-operative patient blood management measures.

## **ACKNOWLEDGEMENTS**

Kevin Trentino is supported by the Australian Government Research Training Program (RTP).

## **AUTHORSHIP CONTRIBUTION**

KT conceived the work, designed, developed, and refined the study protocol with contributions from all Authors. He was responsible for running the analysis and drafting the manuscript. FS, ML, SF, KM contributed to the design, development and refining of the study protocol, contributed to the interpretation of the data for the work,

critically revised the draft, and approved the final version to be published. HM, AL contributed to the interpretation of the data for the work, were involved in critically revising the draft, and approved the final version to be published.

### **DISCLOSURE OF CONFLICTS OF INTEREST**

HM, AL, FS, ML, KM have nothing to disclose. SLF reports support for attending meetings and/or travel from the National Blood Authority (Australia), Scientific Associate with the International Foundation for Patient Blood Management (unpaid), Executive Committee member of the Western Australia Patient Blood Group, University of Western Australia, (unpaid), outside the submitted work; KMT reports honoraria from the International Foundation for Patient Blood Management, outside the submitted work.

### **REFERENCES**

1. Trentino KM, Farmer SL, Leahy MF, et al. Systematic reviews and meta-analyses comparing mortality in restrictive and liberal haemoglobin thresholds for red cell transfusion: an overview of systematic reviews. *BMC Medicine* 2020; **18**: 154.
2. Trentino KM, Mace HS, Leahy MF, et al. Appropriate red cell transfusions are often avoidable through Patient Blood Management. *Blood Transfus* 2021; **19**: 177-8.
3. Trentino KM, Farmer SL, Swain SG, et al. Increased hospital costs associated with red blood cell transfusion. *Transfusion* 2015; **55**: 1082-9.
4. Jalali A, Lonsdale H, Zamora LV, et al. Machine learning applied to registry data: development of a patient-specific prediction model for blood transfusion requirements during craniofacial surgery using the Pediatric Craniofacial Perioperative Registry Dataset. *Anesth Analg* 2021; **132**: 160-71.
5. Liu LP, Zhao QY, Wu J, et al. Machine learning for the prediction of red blood cell transfusion in patients during or after liver transplantation surgery. *Front Med (Lausanne)* 2021; **8**: 632210.
6. Liu S, Zhou R, Xia XQ, et al. Machine learning models to predict red blood cell transfusion in patients undergoing mitral valve surgery. *Ann Transl Med* 2021; **9**: 530.
7. de Boer WJ, Visser C, van Kuijk SMJ, de Jong K. A prognostic model for the preoperative identification of patients at risk for receiving transfusion of packed red blood cells in cardiac surgery. *Transfusion* 2021; **61**: 2336-46.
8. Walczak S, Velanovich V. Prediction of perioperative transfusions using an artificial neural network. *PLoS One* 2020; **15**: e0229450.
9. Mukhtar SA, Leahy MF, Trentino K, et al. Effectiveness of a patient blood management data system in monitoring blood use in Western Australia. *Anaesth Intensive Care* 2013; **41**: 207-15.
10. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015; **350**: g7594.
11. Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. *Transfusion* 2007; **47**: 1468-80.
12. Mitterecker A, Hofmann A, Trentino KM, et al. Machine learning-based prediction of transfusion. *Transfusion* 2020; **60**: 1977-86.
13. James G, Witten D, Hastie T, Tibshirani R. *An introduction to statistical learning: with applications in R*. New York: Springer; 2013.
14. Steyerberg EW. *Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating*. New York, NY: Springer; 2009.
15. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. *Biochem Med (Zagreb)* 2016; **26**: 297-307.
16. Roubinian NH, Murphy EL, Swain BE, et al. Predicting red blood cell transfusion in hospitalized patients: role of hemoglobin level, comorbidities, and illness severity. *BMC Health Serv Res* 2014; **14**: 213.
17. Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. *Transfusion* 2017; **57**: 1347-58.
18. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011; **378**: 1396-407.
19. National Blood Authority (Australia). Patient Blood Management Guidelines: Module 2 - Perioperative. 2012. Available at: [www.blood.gov.au](http://www.blood.gov.au). Accessed on 01/12/2019.
20. Trentino KM, Mace H, Symons K, et al. Associations of a Preoperative anemia and suboptimal iron stores screening and management clinic in colorectal surgery with hospital cost, reimbursement, and length of stay: a net cost analysis. *Anesth Analg* 2021; **132**: 344-52.
21. Trentino KM, Mace HS, Symons K, et al. Screening and treating pre-operative anaemia and suboptimal iron stores in elective colorectal surgery: a cost effectiveness analysis. *Anaesthesia* 2021; **76**: 357-65.
22. Isbister JP, Shander A, Spahn DR, et al. Adverse blood transfusion outcomes: establishing causation. *Transfus Med Rev* 2011; **25**: 89-101.