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Predictors and Economic Impact of Red Blood Cell Transfusion in Cardiac Surgery: A Simulated Cost Reduction Model for Preoperative Anemia Management

Preditores e Impacto Económico da Transfusão de Glóbulos Vermelhos em Cirurgia Cardíaca e Simulação de Redução de Custos Através da Abordagem Pré-operatória da Anemia

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ABSTRACT

Introduction: Red blood cell (RBC) transfusions are frequent in cardiac surgery and are associated with higher morbidity, mortality, prolonged hospitalization, and increased healthcare costs. Several patient- and procedure-related factors have been identified as transfusion predictors. Studying these predictors in specific populations allows more accurate risk stratification and tailored clinical decision-making. RBC transfusions represent a significant economic burden for healthcare systems due to increased resource utilization and hospital costs overall. The aim of this study was to identify independent risk factors of RBC transfusion, evaluate its economic impact, and estimate potential cost savings from eliminating preoperative anemia.

Methods: We conducted a retrospective cohort study at a tertiary hospital in Portugal, including 661 adults who underwent elective cardiac surgery between April 2020 and April 2021. The primary outcome was the need for at least one RBC transfusion during hospitalization. Secondary outcomes included 30-day mortality, infection, acute kidney injury, prolonged mechanical ventilation, intensive care unit stay, hospital length of stay (LOS), and hospital costs. Independent risk factors were identified using multivariable logistic regression. An economic analysis compared costs between transfused and non-transfused patients. To estimate potential cost reductions, a simulation model was developed assuming the elimination of preoperative anemia and applying the observed transfusion patterns of non-anemic patients to the entire cohort.

Results: Red blood cell transfusion occurred in 41.3% of patients. The identified predictors were preoperative anemia (OR 3.67; 2.00 - 6.74), female sex (OR 2.06; 1.22 - 3.48), higher EuroSCORE II (OR 1.15; 1.03 - 1.29), longer cardiopulmonary bypass time (OR 1.01; 1.00 - 1.02) and lower intraoperative nadir hemoglobin (OR 0.48; 0.40 - 0.58), after adjusting for postoperative hemorrhage. Transfused patients had longer hospital stays (median 10 *vs* 8 days) and higher costs (median increase of €2264.44). After adjustment for infection and prolonged ventilation, transfusion was no longer independently associated with LOS. Eliminating preoperative anemia could prevent 47 transfusions, reduce 94 hospital days, and save €106 429 over 13 months overall.

Conclusion: Red blood cell transfusion was associated with longer hospital stays, likely due to higher infection rates and prolonged mechanical ventilation. Correcting preoperative anemia could potentially reduce transfusion rates and related hospital costs in cardiac surgery.

Keywords: Anemia/prevention and control; Cardiac Surgical Procedures; Costs and Cost Analysis; Erythrocyte Transfusion/economics; Hospital Costs; Length of Stay

RESUMO

Introdução: As transfusões de glóbulos vermelhos (GV) são frequentes em cirurgia cardíaca e estão associadas a maior morbimortalidade, tempo de internamento e custos hospitalares. Diversos fatores relacionados com o doente e com o procedimento têm sido identificados como preditores de transfusão. O estudo destes preditores em populações específicas permite uma estratificação de risco mais precisa. Este estudo teve como objetivo identificar fatores de risco independentes de transfusão de GV na nossa amostra, avaliar o seu impacto económico e estimar as potenciais poupanças de custos decorrentes da eliminação da anemia pré-operatória.

Métodos: Realizou-se um estudo de coorte retrospetivo, num hospital terciário em Portugal, incluindo 661 adultos submetidos a cirurgia cardíaca eletiva entre abril de 2020 e abril de 2021. O *outcome* primário foi a necessidade de pelo menos uma transfusão de GV durante o internamento. *Outcomes* secundários incluíram mortalidade aos 30 dias, infeção, lesão renal aguda, ventilação mecânica prolongada, tempo de internamento hospitalar e custos hospitalares. Os fatores de risco independentes foram identificados através de regressão logística multivariável. Uma análise económica comparou os custos entre doentes transfundidos e não transfundidos. Para estimar a redução de custos, desenvolveu-se um modelo de simulação assumindo a eliminação da anemia pré-operatória e aplicando os padrões de transfusão observados nos doentes não anémicos à coorte.

Resultados: A prevalência de transfusão foi 41,3%. Os preditores identificados foram a anemia pré-operatória (OR 3,67; 2,00 - 6,74), sexo feminino (OR 2,06; 1,22 - 3,48), EuroSCORE II mais elevado (OR 1,15; 1,03 - 1,29), maior tempo de *bypass* cardiopulmonar (OR 1,01; 1,00 - 1,02) e menor hemoglobina nadir intraoperatória (OR 0,48; 0,40 - 0,58), após ajuste para hemorragia pós-operatória. Doentes transfundidos apresentaram maior tempo de internamento (mediana de 10 *vs* 8 dias) e custos superiores (aumento mediano de €2264,44). Após ajuste para infeção e ventilação prolongada, a transfusão deixou de estar independentemente associada ao tempo de internamento. A eliminação da anemia pré-operatória poderia evitar 47 transfusões, reduzir 94 dias de internamento e poupar €106 429 em 13 meses.

Conclusão: A transfusão de GV foi associada a maior tempo de internamento, provavelmente devido a maiores taxas de infeção e ventilação mecânica prolongada. A correção da anemia pré-operatória poderá potencialmente reduzir as taxas de transfusão e os custos hospitalares relacionados com a cirurgia cardíaca. Estes resultados reforçam a relevância e económica da anemia pré-operatória.

Palavras-chave: Anemia/prevenção e controlo; Custos e Análise de Custo; Custos Hospitalares; Procedimentos Cirúrgicos Cardíacos; Tempo de Internamento; Transfusão de Eritrócitos/economia

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KEY MESSAGES

- Preoperative anemia emerged as the strongest modifiable predictor of red blood cell transfusion, reinforcing patient blood management strategies.
- Transfusion was associated with longer hospitalization and higher costs, with effects on hospital length of stay possibly through higher infection rates and prolonged ventilation.
- Transfusions imposed an economic burden, with a median cost increase of €2264.44 per patient. A simulation model illustrated potential cost savings from eliminating preoperative anemia.
- This study integrates clinical and economic analyses in a real-world cardiac surgery cohort, strengthening its translational relevance.
- Limitations include retrospective single-center design, simplified cost modeling, and absence of costs related to anemia treatment.

INTRODUCTION

Cardiac surgery is frequently associated with red blood cell (RBC) transfusions. In Europe, transfusion rates for cardiac surgery vary widely, ranging from 40 to as high as 90%,[1] and cardiac surgery accounts for 20% of all blood transfusions.[2]

Despite their life-saving potential, RBC transfusions carry risks and exhibit a dose-dependent association with adverse outcomes, including infection, acute kidney injury (AKI), prolonged mechanical ventilation and reintubation.[3-5] Additionally, RBC transfusion is an independent risk factor for both short- and long-term mortality.[6-11] Furthermore, patients who undergo transfusion exhibit significantly prolonged intensive care unit (ICU) and hospital length of stay (LOS),[5,12-14] contributing to increased healthcare resource use and substantial financial burden.[15-17]

Over the past few years, the concept of patient blood management (PBM) has gained increasing prominence globally. It is a multidisciplinary, evidence-based approach aimed at optimizing the management of blood in all patients, particularly those undergoing major surgery. It promotes the appropriate use of blood products, its components and derivates, while also recommending strategies to prevent or minimize the need for transfusion, thereby improving clinical outcomes and resource use.[18]

A cornerstone of this multidisciplinary approach involves the identification of patients at increased risk of requiring transfusion, thereby enabling the timely implementation of targeted interventions to reduce transfusion burden and improve clinical outcomes. This identification is supported by several predictive scores designed to estimate preoperative transfusion risk.[19-25] These scores incorporate well-established patient- and procedure-related variables consistently recognized in the literature as predictors of RBC transfusion, as detailed in Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23502/15874).[19,26–37] Although these predictors are well established in the literature, we consider it important to examine them within our own population to gain a more nuanced understanding of our specific context and to enable more accurate, contextually relevant comparisons with other centers.

This also creates the opportunity to adjust local clinical practice in response to population-specific findings.

Furthermore, there is a relative paucity of studies that have incorporated postoperative bleeding as an adjustment variable in transfusion risk prediction models – a gap we intended to address in the scope of this study.

In addition to clinical impact, the economic implications of RBC transfusion represent a major concern for healthcare systems. Hospitalization costs associated with transfusion-related morbidity and prolonged length of stay contribute substantially to overall resource use. Therefore, an economic analysis was integrated in this study to quantify the financial impact of RBC transfusion in cardiac surgery and to simulate a potential cost reduction scenario concerning the elimination of preoperative anemia, one of the most relevant and modifiable predictors of transfusion.

Therefore, the main objectives of this study were to identify predictors of red blood cell transfusion in elective cardiac surgery while adjusting for postoperative bleeding, in order to evaluate the economic impact of transfusion, and to estimate a potential cost reduction achievable through a simulated scenario in which preoperative anemia is eliminated.

METHODS

A retrospective cohort study was conducted with the necessary approvals from the ethics committees of São João Local Health Unit and University of Porto's Faculty of Medicine (No. 158/21). The requirement for informed consent was waived due to the retrospective nature of the study. The study design and conduct followed the STROBE guidelines.

The study population consisted of patients aged ≥ 18 years who underwent cardiac surgery between April 1st, 2020, and April 30th, 2021, in a level III hospital within the

Portuguese National Health Service. Patients who underwent non-elective surgery or who were previously included in the study were excluded from the analysis.

Data collection

Data was gathered from electronic health records and physician notes, covering the period from approximately 24 hours before surgery until hospital discharge or death.

The study included the following variables:

(I) Preoperative data - age, sex, body surface area (BSA); comorbidities such as type 2 diabetes *mellitus*, arterial hypertension (HTN), active smoking, chronic pulmonary obstructive disease (COPD), pulmonary hypertension [classified as moderate (PSAP 31 - 55 mmHg) or severe (PSAP ≥ 55 mmHg)], atrial fibrillation, heart failure (according to the New York Heart Association classification), angina (according to the Canadian Cardiovascular Society classification), and coronary artery disease (at least 70% of stenosis on at least one artery); additional factors such as the need for insulin, anticoagulation, antiplatelet or dual antiplatelet therapy, history of previous cardiac surgery, EuroSCORE II value; laboratory parameters such as anemia (defined as less than 13.0 g/dL and less than 12.0 g/dL of hemoglobin in men and women, respectively), serum creatinine, estimated glomerular filtration rate (calculated by Cockgroft-Gault equation), need for dialysis, and value of left ventricular ejection fraction (LVEF).

(II) Intraoperative data - procedure complexity (according to EuroSCORE II – CABG as baseline; one non-CABG procedure; two procedures; ≥ three procedures), thoracic aorta involvement, cardiopulmonary bypass (CPB) and aortic cross-clamping times (zero minutes recorded for off-pump surgeries), need for blood transfusions during the procedure and intraoperative nadir hemoglobin level.

(III) Postoperative data - need for blood transfusions during ICU and ward stay, 12-hour postoperative bleeding, 30-day mortality, infection (defined as the need for antibiotic therapy), AKI (defined as an increase from baseline of ≥ 0.3 mg/dL of postoperative creatinine or an increase of more than 1.5 times the preoperative creatinine within 48 h), prolonged mechanical ventilation (defined as the requirement for intubation exceeding 24 hours), prolonged ICU LOS (defined as more than five days), and total hospital LOS.

The primary outcome was the need for at least one RBC transfusion during hospital stay. Secondary outcomes included 30-day mortality, infection, AKI, prolonged ventilation, prolonged ICU LOS, total hospital LOS and hospital costs.

Statistical analysis

The normality of the distribution of continuous variables was assessed through graphical visualization of histograms and the Kolmogorov-Smirnov test. Continuous variables were not normally distributed and are thus presented as median with interquartile ranges (IQR), while categorical variables are expressed as absolute and relative frequencies.

Predictors of red blood cell transfusion

Comparison between patients who did not receive RBC transfusions and patients who received at least one RBC transfusion was performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

A backward stepwise-selection logistic regression model was developed using variables significantly associated with RBC transfusion ($p < 0.05$) in the univariate analysis and/or variables with clinical relevance, while also adjusting for postoperative hemorrhage. Variables showing evident collinearity (e.g., eGFR and serum creatinine) or a variance inflation factor (VIF) exceeding 10 were excluded to mitigate multicollinearity and ensure model stability. A likelihood ratio with a p-value > 0.1 was used as the cut-off for variable removal. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test, while its discriminative performance was assessed by the area under the receiver operating characteristic curve (AUROC).

The results of the multivariable model are presented as β coefficients, adjusted odds ratios (ORadj) with corresponding 95% confidence intervals (CI), and p-values.

Red blood cell transfusion and hospital length of stay

The impact of RBC transfusion on hospital LOS, along with the underlying mechanisms, were evaluated using two generalized linear models employing a gamma distribution with a log link function. The first model treated RBC transfusion as the primary independent variable and adjusted for potential confounders, including age, preoperative anemia, EuroSCORE II value, CPB time, aortic cross-clamping time, intraoperative nadir hemoglobin level, postoperative bleeding at 12 hours and postoperative acute kidney injury.

The second model incorporated all variables from the first model and further adjusted for the postoperative complications most frequently associated with RBC transfusion in the literature, namely, infection and prolonged mechanical ventilation.

Economic analysis and potential cost reduction

The economic analysis was limited to the costs incurred by the hospital during the study period. The average daily costs for cardiac surgery patients were obtained from the hospital's financial department; however, it was not possible to differentiate between ward and ICU costs. Costs encompassed personnel, medical supplies and consumables, pharmaceuticals, diagnostics and laboratory services, operating room and procedure expenses, room and board, as well as indirect costs, including administrative and infrastructure expenses. A univariate comparative analysis of hospitalization costs between non-transfused and transfused patients was performed using non-parametric tests. Hedges's g estimation was used to determine the incremental

Table 1 – Demographics, comorbidities, procedure characteristics and binary analysis (section 1 of 2)

	Total n = 661		No RBC transfusion n = 388		≥ 1 RBC transfusions n = 273		*p*-value
Demographics							
Age, y (IQR)	69	(60 - 76)	69	(59 - 75)	72	(65 - 78)	< 0.001
Sex							< 0.001
Male, n (%)	393	59.5	267	68,8	126	46.2	
Female, n (%)	269	40.5	121	31.2	147	53.8	
BSA, m² (IQR)	1.82	(1.70 - 1.96)	1.75	(1.88 - 1.99)	1.75	(1.64 - 1.90)	< 0.001
	Total n = 661		**No RBC transfusion** n = 388		**≥ 1 RBC transfusions** n = 273		***p*-value**
Comorbidities							
Obesity, n (%)	197	29.8	125	32.2	72	26.4	0.106
DM2, n (%)	197	29.8	111	28.6	86	31.6	0.406
DM2 on insulin, n (%)	31	4.7	13	3.4	18	6.6	0.051
Arterial hypertension, n (%)	479	72.5	276	71.1	203	74.6	0.321
Active smoker, n (%)	49	7.4	41	7.9	8	5.5	0.324
COPD, n (%)	49	7.4	31	7.9	18	6.6	0.5
Pulmonary hypertension							0.007
No, n (%)	398	60.1	252	64.9	146	53.5	
Moderate, n (%)	202	30.5	108	27.8	94	34.4	
Severe, n (%)	57	8.6	26	6.7	31	11.4	
Atrial fibrillation, n (%)	103	15.6	53	13.6	50	18.3	0.1
Heart failure (NYHA)							0.764
1, n (%)	300	45.4	177	45.6	123	45.1	
2, n (%)	263	39.8	158	40.7	105	38.5	
3, n (%)	93	14.1	50	12.9	43	15.8	
4, n (%)	5	0.8	3	0.8	2	0.7	
Angina (CCS)							0.236
1, n (%)	549	83.1	331	85.3	218	79.9	
2, n (%)	78	11.8	38	9.8	40	14.7	
3, n (%)	25	3.8	16	4.1	9	3.3	
4, n (%)	6	0.9	3	3	3	1.1	
Coronary disease, n (%)	352	88.7	199	51.3	153	56	0.241
Anticoagulation therapy, n (%)	166	25.1	84	21.6	82	30	0.013
Antiplatelet therapy, n (%)	242	36.6	145	37.4	97	35.5	0.629
Dual antiplatelet therapy, n (%)	13	1.9	10	2.6	3	1.1	0.178
Previous cardiac surgery, n (%)	51	7.7	21	5.4	30	10.9	0.008
EuroSCORE II (IQR)	1.92	(1.07 - 3.85)	1.56	(0.94 - 2.89)	2.89	(1.41 - 5.51)	< 0.001

costs associated with RBC transfusion.

A simulation was conducted to estimate the potential economic impact of preoperative anemia management. A scenario was created in which all anemic patients were optimized before surgery with no patients presenting with preoperative anemia; therefore, a simulated redistribution of patients was generated by applying the relative risk of transfusion observed among non-anemic individuals to the entire cohort. Based on this adjusted probability, the expected number of transfused and non-transfused patients was recalculated. Group-specific simulated costs were then estimated by multiplying the number of patients in each category (transfused/non-transfused) by the corresponding median hospitalization cost per patient observed in the real cohort. The total simulated expenditure was subsequently compared with the observed total cost to estimate the potential cost savings associated with the elimination of preoperative anemia.

This analysis focused exclusively on hospital costs related to hospital length of stay and did not include the expenses associated with preoperative anemia management.

RESULTS

Study sample

A total of 661 patients were included in the cohort, of whom 388 (58.7%) did not require RBC transfusion, while 273 (41.3%) received at least one unit.

A sensitivity analysis for missing data was not conducted as the proportion of missing values was minimal [maximum missing data: 2.9% - Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/23502/15874)]. Given this low percentage, the risk of bias introduced by missingness was considered negligible, and the assumption of missing completely at random (MCAR) was deemed reasonable, minimizing the potential impact on model validity and inference. Missing data was handled using complete case analysis (listwise deletion).

Table 1 – Demographics, comorbidities, procedure characteristics and binary analysis (section 2 of 2)

	Total n = 661		No RBC transfusion n = 388		≥ 1 RBC transfusions n = 273		*p*-value
Preoperative analytical data							
Preoperative anemia, n (%)	119	18	32	8.2	87	31.9	< 0.001
Serum creatinine, mg/dL (IQR)	0.8	(0.67 - 1.01)	0.8	(0.68 - 0.96)	0.82	(0.67 - 1.12)	0.125
eGFR, mL/min/1.73m^2 (IQR)	89.9	(72.3 - 104.2)	79.7	(61.9 - 102.1)	67.9	(46.6 - 88.9)	< 0.001
On dialysis, n (%)	8	1.2	0	0	8	2.9	< 0.001
LVEF (%)							0.304
21% - 30%, n (%)	13	2	6	1.5	7	2.6	
31% - 50%, n (%)	62	9.4	32	8.2	30	10.9	
> 50%, n (%)	586	88.7	350	90.2	236	86.4	
	Total n = 661		**No RBC transfusion** n = 388		**≥1 RBC transfusions** n = 273		***p*-value**
Procedure characteristics							
Procedure complexity							0.045
Isolated CABG, n (%)	103	15.6	67	17.3	36	13.2	
1 non-CABG, n (%)	220	33.3	140	36.1	80	29.3	
2 procedures, n (%)	213	32.2	117	30.2	96	35.2	
≥ 3 procedures, n (%)	125	18.9	64	16.5	61	22.3	
Procedure on thoracic aorta, n (%)	98	1.5	61	15.7	37	13.6	0.44
CPB time, min (IQR)	90	(63.0 - 124.0)	85	(58.0 - 110.0)	104	(71.5 - 143.0)	< 0.001
Cross-clamping time, min (IQR)	64	(44.0 - 87.0)	59	(39.25 - 79.0)	71	(50.0 - 100.0)	< 0.001
Intraoperative nadir Hb, g/dL (IQR)	8.6	(7.4 - 10.0)	9.4	(8.3 - 10.6)	7.6	(7.0 - 8.3)	< 0.001
	Total n = 661		**No RBC transfusion** n = 388		**≥1 RBC transfusions** n = 273		***p*-value**
Postoperative bleeding							
12h postoperative bleeding, mL (IQR)	400	(270.0 - 637.5)	360	(260.0 - 550.0)	500	(290.0 - 820.0)	< 0.001

Predictors of red blood cell transfusion

Univariate analysis (Table 1) identified multiple clinical and procedural factors significantly associated with RBC transfusion. Among patient-related variables, older age, female sex, lower BSA, pulmonary hypertension, anticoagulation therapy, and prior cardiac surgery were significantly correlated with transfusion. Additionally, higher EuroSCORE II value, preoperative anemia and impaired renal function (lower GFR and dialysis requirement) were also significantly associated with increased transfusion rates.

Regarding surgical factors, procedure complexity, CPB time, and aortic cross-clamping duration were significantly associated with RBC transfusion. Lower intraoperative nadir hemoglobin and increased postoperative bleeding at 12 hours were also significantly associated with transfusion requirement. Diabetes *mellitus* with insulin therapy was marginally associated with the need for RBC transfusion (p = 0.051).

The final multivariate logistic regression model (Table 2) confirmed that female sex (ORadj: 2.055, 95% CI: 1.215 - 3.475, p = 0.007), higher EuroSCORE II value (ORadj: 1.152, 95% CI: 1.031 - 1.287, p = 0.012), preoperative anemia (ORadj: 3.672, 95% CI: 2.000 - 6.741, p < 0.001), longer CPB time (ORadj: 1.009, 95% CI: 1.004 - 1.015, p < 0.001) and lower intraoperative nadir hemoglobin (ORadj: 0.48, 95% CI: 0.397 - 0.581, p < 0.001) were all independently associated with RBC transfusion, after adjusting for the degree of postoperative bleeding.

Interestingly, higher procedure complexity was associated with a lower transfusion risk (ORadj: 0.73, 95% CI: 0.541 - 0.986, p = 0.04).

Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test (p = 0.239), indicating an adequate fit. The model demonstrated excellent discriminative ability, with an AU-ROC of 0.89 (95% CI: 0.86 - 0.91).

Red blood cell transfusion and other outcomes

Outcomes associated with RBC transfusion were also assessed and are reported in Table 3.

The overall 30-day mortality rate was 1.8% (n = 12). Four patients died from sudden refractory cardiac arrest, three from refractory cardiogenic shock, two from septic shock, and two from intestinal ischemia. Additionally, one patient died intraoperatively. Transfusion requirement was significantly associated with 30-day mortality (p-value < 0.001) in univariate analysis (Table 3). No deaths occurred among non-transfused patients.

Unadjusted analysis for other outcomes assessed (AKI, infection, prolonged ventilation and prolonged ICU stay) showed a statistically significant association with RBC transfusions as well, with p-values < 0.001.

Regarding hospital LOS, the overall median LOS was eight days. Transfused patients had a significantly prolonged LOS compared to non-transfused patients (median: 10 *vs* 8 days, p < 0.001). In the first generalized linear model (Table 4), RBC transfusion remained an independent risk factor of increased hospital LOS after adjusting for potential confounders (age, EuroSCORE II value, preoperative

Table 2 – Multivariate analysis for predictors of RBC transfusion

Variable	B	OR adj	95% CI	*p*-value
Female	0.72	2.055	(1.215 - 3.475)	0.007
eGFR	-0.008	0.992	(0.984 - 1.000)	0.065
EuroSCORE II	0.142	1.152	(1.031 - 1.287)	0.012
Preoperative anemia	1.301	3.672	(2.000 - 6.741)	< 0.001
Procedure complexity	-0.314	0.73	(0.541 - 0.986)	0.04
CPB time	0.009	1.009	(1.004 - 1.015)	< 0.001
Intraoperative nadir Hb	-0.733	0.48	(0.397 - 0.581)	< 0.001
12h postoperative bleeding	0.003	1.003	(1.002 - 1.004)	< 0.001

Table 3 – Univariate analysis: RBC transfusion and secondary outcomes

	Total n = 661		No RBC Transfusion n = 388		≥ 1 RBC Transfusions n = 273		*p*-value
30-day mortality, n (%)	12	1.8	0	0	12	4.4	< 0.001
AKI, n (%)	95	4.2	24	6.2	71	26	< 0.001
Infection, n (%)	53	8	14	3.6	39	14.3	< 0.001
Prolonged ventilation, n (%)	49	7.6	4	1	45	16.5	< 0.001
Prolonged ICU stay, n (%)	81	12.2	35	6.8	46	31.7	< 0.001
Hospital LOS, days (IQR)	8	(7 - 12)	8	(7 - 9)	10	(8 - 16)	< 0.001

anemia, CPB and cross-clamping duration, postoperative bleeding, intraoperative nadir hemoglobin and postoperative AKI), with transfused patients experiencing a 39.3% longer LOS compared to non-transfused patients [Exp(B) = 1.393, 95% CI: 1.243 - 1.562, $p < 0.001$]. However, after adjusting for postoperative infection and prolonged mechanical ventilation on the second model (Table 5), the effect of RBC transfusion on LOS was no longer statistically significant [Exp(B) = 1.034, 95% CI: 0.936 - 1.132, $p = 0.511$].

Economic analysis and potential cost reduction

Cost comparison between transfused and non-transfused patients is presented in Table 6. The average hospitalization daily cost per patient, reported by the hospital's financial department, was €1132.22. In the observed cohort, the median cost per non-transfused patient was €9057.76, while for transfused patients, it was €11 322.22. The incremental median cost for each transfused patient was €2264.44 (IQR: 1132.22 - 7925.54), with a *p*-value < 0.001 and Hedges g' estimate of 0.272, indicating a small to moderate effect size. With a total of 388 non-transfused and 273 transfused patients, the overall hospital expenditure amounted to €6 605 371.

A cost simulation was then performed to estimate the potential economic impact of eliminating preoperative anemia, assuming that all 119 anemic patients had been optimized before surgery (Table 6). Applying the relative transfusion risk observed in non-anemic patients (34%) to the entire cohort resulted in a simulated redistribution of 435 non-transfused and 226 transfused patients – 47 fewer transfusions overall, equivalent to approximately 0.39 fewer transfusions per optimized anemic patient.

Based on this simulated redistribution, the total hospital expenditure was recalculated by multiplying the simulated number of patients in each group (transfused and non-transfused) by their respective observed median cost per patient. The projected total hospital cost under this scenario was €6 498 943, representing a potential cost reduction of approximately €106 429 over the 13-month study period.

DISCUSSION

The aim of this study was to identify predictors of RBC transfusion in our population, the results being in line with recent literature.

Table 4 – Generalized linear model with log link function and gamma distribution for hospital length of stay according to transfusion status

Variable	B	Exp(B)	95% CI	*p*-value
RBC transfusion	0.332	1.393	(1.243 - 1.562)	< 0.001
Age	0.006	1.006	(1.002 - 1.010)	0.001
Preoperative anemia	-0.074	0.929	(0.814 - 1.060)	0.272
EuroSCORE II	-0.009	0.991	(0.973 - 1.008)	0.304
CPB time	0.001	1.001	(0.999 - 1.003)	0.490
Cross-clamping time	0	1.000	(0.998 - 1.003)	0.842
12h postoperative bleeding	0	1.000	(1.000 - 1.001)	< 0.001
Intraoperative nadir Hb	0.022	1.022	(0.992 - 1.054)	0.152
AKI	0.051	1.052	(0.915 - 1.211)	0.476

Table 5 – Generalized linear model with log link function and gamma distribution for hospital length of stay according to transfusion status, including the variables infection and prolonged ventilation

Variable	B	Exp(B)	95% CI	*p*-value
RBC transfusion	0.038	1.034	(0.936 - 1.132)	0.511
Age	0.005	1.006	(1.002 - 1.009)	< 0.001
Preoperative anemia	-0.023	0.977	(0.878 - 1.087)	0.977
EuroSCORE II	0.006	1.006	(0.991 - 1.021)	0.423
CPB time	-0.001	0.999	(0.998 - 1.001)	0.27
Cross-clamping time	0	1.001	(0.999 - 1.003)	0.409
12h postoperative bleeding	0.001	1.000	(1.000 - 1.001)	< 0.001
Intraoperative nadir Hb	0	1.000	(0.970 - 1.020)	0.69
AKI	-0.033	0.968	(0.864 - 1.084)	0.573
Infection	0.907	2.476	(2.077 - 2.951)	< 0.001
Prolonged Ventilation	0.568	1.764	(1.404 - 2.274)	< 0.001

Table 6 – Economic analysis

	No RBC Transfusion n = 388		≥ 1 RBC Transfusions n = 273		***p*-value**
Median cost per patient (€)	9057.76	(7925.54 - 10 189.98)	11 322.22	(9057.76 – 18 115.52)	< 0.001
Total median cost (€)	9057.76 x 388 + 11 322.22 x 273 = 6 605 371				
Median cost difference per patient (€)	Cost per patient (RBC transfusion) - Cost per patient (No RBC transfusion) = 2 264.44 (1132.22 - 7925.54)				
Total median cost without anemia (€)	9057.76 x 435 + 11 322.22 x 226 = 6 498 943				
Potential cost reduction by eliminating anemia (€)	6 605 371 – 6 498 943 = 106 429				

The transfusion incidence was 41.3%, aligning with the commonly reported range of 40% to 90%.[1,38]

The female sex was the second strongest predictor in our study, with women exhibiting twice the risk of requiring RBC transfusion when compared to men. This aligns with the findings of Ter Woorst *et al*[30] reporting that women had 3.54 higher odds of being transfused and were exposed to significantly more units of RBC. Several factors may contribute to this, including lower preoperative hematocrit levels, smaller circulating blood volume,[39] higher prevalence of comorbid conditions, greater burden of advanced disease and poorer baseline functional status.[40] Although the World Health Organization (WHO) recommends a preoperative hemoglobin level of at least 12.0 g/dL for women, lower than the 13.0 g/dL threshold for men, Cavalli *et al*[31] found that both male and female patients should have hemoglobin levels of at least 13.0 g/dL to minimize the need for transfusion during cardiac surgery.

Based on these findings, our results suggest that using a preoperative hemoglobin threshold of 12.0 g/dL—per WHO guidelines—as a marker of adequate optimization in female patients may systematically disadvantage them in the perioperative setting.

The prevalence of preoperative anemia in adult patients undergoing elective cardiac surgery ranges from 16% to 54%.[41] Anemia in our sample had a prevalence of 19%, which falls on the lower end of the reported range. In our study, preoperative anemia emerged as the strongest predictor of RBC transfusion, with anemic patients exhibiting a 3.67-fold increased risk of requiring transfusion.

This finding concurs with previous studies identifying anemia as a key determinant of transfusion risk in cardiac surgery.

In a multicenter large-scale analysis of 23 800 patients undergoing all-type cardiac surgery, Klein *et al*[42] reported that anemic patients had 2.75 times higher odds of RBC transfusion. Taken together, these findings highlight the importance of recognizing preoperative anemia as one of the few modifiable risk factors that can significantly influence transfusion requirements in cardiac surgery.[18]

EuroSCORE II—the standard mortality risk prediction model in cardiac surgery—was also a significant predictor of transfusion in our study. This is unsurprising, as higher EuroSCORE II values reflect a greater comorbidity burden and poorer functional status, along with increased procedural complexity – factors that are often associated with a higher likelihood of transfusion.

Surgical aspects also played a significant role in transfusion risk. Lower intraoperative nadir hemoglobin and longer CPB time were also predictors, corroborating previous findings.[28,43] The Transfusion Requirements After Cardiac Surgery (TRACS) randomized controlled trial performed by Hajjar *et al*[28] demonstrated that the duration of cardiopulmonary bypass was a predictor of transfusion requirement. Hemodilution and intraoperative blood loss are the logically associated mechanisms.[37]

Renal dysfunction is a known predictor of transfusion in cardiac surgery.[37] Nevertheless, in our study, eGFR did not emerge as a significant factor. This may be explained by the relatively preserved renal function in our cohort (median eGFR: 89.9 mL/min/1.73m^2, IQR: 72.3 - 104.2), limiting our ability to detect an association.

Procedure complexity has also been associated with increased transfusion in the literature[19]; however, in our study, it unexpectedly emerged as a protective factor. One possible explanation is that more complex surgeries may have prompted the use of stricter blood conservation strategies, leading to fewer transfusions compared to simpler procedures.

Not many studies have their transfusion risk models adjusted for postoperative bleeding.

By incorporating this variable into our analysis, we sought to confirm the identified predictors and their relationship with transfusions, ensuring that these associations were not merely driven by increased postoperative blood loss.

In our cohort, the 30-day mortality was 1.8%, closely aligning with the EuroSCORE II predicted mortality of

1.92%. While RBC transfusion was significantly associated with mortality in the unadjusted analysis ($p < 0.001$), the adjusted analysis was not feasible due to complete separation in the data, as no deaths occurred in non-transfused patients. This strong unadjusted association supports previous evidence linking transfusion to excess mortality risk.[10] Regarding other secondary outcomes, the unadjusted analysis demonstrated significantly worse outcomes for patients who received at least one RBC transfusion, including increased incidence of acute kidney injury, higher infection rates, greater need for prolonged mechanical ventilation and longer ICU stays. These findings reinforce the well-documented relationship between RBC transfusion and adverse outcomes.[3-5,8] This relationship may be partially explained by direct mechanisms, including transfusion-related immunomodulation and exacerbated inflammatory response.[44] Additionally, impaired oxygen delivery due to a leftward shift of the oxygen dissociation curve and reduced erythrocyte deformability may further contribute to this effect.[45]

Prolonged hospital LOS is a critical aspect of cardiac surgery, as it is linked to increased healthcare costs and heightened clinical risk, including greater exposure to infections and iatrogenic events. It has been associated with transfusion, both in cardiac[14] and non-cardiac surgery.[15] In our study, transfused patients exhibited an extended hospital LOS (10 *vs* 8 days), an association that remained significant after adjusting for multiple potential confounders, such as age, preoperative anemia, EuroSCORE II, CPB and cross-clamping duration, nadir intraoperative hemoglobin, postoperative hemorrhage, and postoperative acute kidney injury with transfused patients having approximately 1.4 times longer LOS than non-transfused patients. However, after adjustment for infection and prolonged ventilation, RBC transfusion no longer retained statistical significance, indicating that its association with LOS may be primarily mediated by these postoperative complications.

The existing literature on this topic is limited, highlighting the need for further research to evaluate this potential mediation effect.

Regardless of the exact mechanism through which transfusion prolongs hospitalization, the association between RBC transfusion and increased LOS remains clinically relevant – particularly given its implications for healthcare costs. In line with previous studies reporting increased hospital costs and resource use associated with transfusion,[16,17,46] our economic analysis highlights the financial burden associated with RBC transfusion, with an unadjusted incremental cost of €2264.44 for each transfused patient. The effect size estimated by Hedges' g (0.272) suggests a small to moderate impact which, at an individual level, might appear modest. However, when contextualized within the high prevalence of transfusions in cardiac surgery, even a seemingly moderate increase in cost per patient translates into a considerable financial impact at a healthcare system level.

Finally, our hypothetical cost-reduction model estimated that transforming anemic patients into non-anemic preoperatively would result in 47 fewer transfused patients, yielding a reduction of 94 days on hospital LOS, resulting in an estimated €106 429 reduction in total hospital costs over 13 months. This finding underscores the potential cost savings as another benefit of preoperative anemia management.

Although simplified and not adjusted for potential confounders, this economic model provides a conceptual framework for quantifying the financial implications of anemia correction in cardiac surgery. It merely relies on assumptions derived from the observed cohort and thus may not capture the full complexity of clinical and cost variability. Importantly, the analysis focused exclusively on hospitalization costs and did not account for the expenses associated with preoperative anemia management, which could influence the overall cost-effectiveness balance.

Despite these constraints, the results underscore the role of preoperative anemia management as a fundamental pillar of patient blood management programs and provide a basis for future more comprehensive cost-effectiveness analyses.

Limitations

This study has limitations that should be considered when interpreting the findings.

First, its retrospective design, which inherently restricts causal inferences, as confounding factors may not have been fully accounted for despite statistical adjustments. Moreover, the study was conducted at a single center, limiting the generalizability of the results to other healthcare settings with different transfusion protocols or patient populations.

Another important consideration is that our economic analysis estimated the financial impact of RBC transfusion based on average non-individualized daily hospitalization costs, which may limit the accuracy of value determination. Furthermore, it did not differentiate between ward and ICU daily costs, which would have allowed for a more detailed cost assessment.

A key limitation of the economic component, as mentioned above, is that the model did not include the costs related to preoperative anemia management (e.g., iron supplementation, erythropoietin therapy, diagnostic evaluation). This omission restricts the interpretation of the findings as a true cost-effectiveness analysis and should be regarded as the central limitation of this study.

In the hypothetical anemia elimination model, applying a uniform transfusion relative risk to all patients may fail to account for inter-individual variability in clinical response to anemia correction.

It also does not fully account for baseline differences between groups, such as comorbidities or overall clinical severity. The absence of a sensitivity analysis further limits the ability to assess the robustness of these assumptions.

Finally, a further limitation is that the study was conducted during the COVID-19 pandemic, which may have influenced both patient characteristics and healthcare costs. Although all patients undergoing elective surgery tested negative for COVID-19 upon admission, we did not assess if any patient developed the disease during hospitalization, potentially influencing clinical outcomes. Furthermore, the pandemic introduced fluctuations in hospital resource allocation and overall healthcare costs, which could have impacted the financial estimates in our analysis.

These factors should be considered when comparing our findings to studies from non-pandemic periods.

CONCLUSION

This study identified preoperative anemia, female sex, higher EuroSCORE II value, longer CPB time and lower intraoperative hemoglobin nadir value as independent risk factors for RBC transfusion in cardiac surgery in our sample, even after adjusting for postoperative hemorrhage. The increase in hospital costs for transfused patients resulted from their significantly longer hospital stay. This seems to be at the expense of an increased incidence of infection and prolonged mechanical ventilation.

Finally, eliminating preoperative anemia could potentially reduce transfusion rates and associated hospital costs. Although our economic model is simplified and does not account for the expenses of anemia correction, our findings reinforce the recognition of preoperative anemia management as a fundamental pillar of patient blood management programs, with potential clinical and economic benefits.

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The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

MCS: Data curation, methodology, formal analysis, writing – original draft, writing – review and editing.

JA: Conceptualization, data curation, writing – review.

ALRD: Methodology, formal analysis, writing – review.

CA: Conceptualization, data curation, methodology, formal analysis, writing – review.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

ALRD is a teaching assistant professor at the University of Porto's Faculty of Medicine and has given unpaid lectures at national congresses and at the trainees' booth of the European Anesthesiology Congress.

All other authors have no conflicts of interest to declare.

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