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CORONARY ARTERY BYPASS GRAFTING: RED BLOOD CELL TRANSFUSIONS AND POST-OPERATIVE INFECTIONS

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ABSTRACT

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INTRODUCTION: Multiple studies have suggested blood red blood cell transfusions to be individual markers of post-operative outcomes, including infectious complications. This study set out to examine statistical relationships between red blood cell transfusions and infections following coronary artery bypass grafting surgery,in a retrospective cohort design following patients undergoing CABG in Tampere University Hospital in 2014 and 2015.
METHODS: Preoperative and intraoperative variables were collected in the study, as well as data on intraoperative transfusions. Transfusions of red blood cells were considered an ordinal variable, with stratification following number of units of RBCs transfused. Study outcome variables included development of post-operative pneumonia, mediastinal surgical site infection, or serious nosocomial infection (SNI). Univariate analysis was the mainstay of statistical analysis of collected data. Relevant percentages and p-values were calculated for comparisons of study variables and outcomes.
RESULTS: A total of 461 patients undergoing CABG where included in the study. Red blood cell transfusions where significantly associated with development of post-operative mediastinitis. Totally, 38 patients received 2 units of RBCs, of which mediastinitis presented in 4 cases or 10% of cases in the group ($p = 0.03$). No statistically significant correlation was observed in the comparison of RBC transfusions and pneumonia or serious nosocomial infection rates. Female sex in patients was significantly associated with development of pneumonia (6 cases of pneumonia, covering 7% of total female patients, compared to 7 cases of pneumonia, accounting for 2 % of male patients, $p = 0.007$). Obesity (BMI > 30 kg/m^2) was associated with a decreased rate of pneumonia (0 pneumonias, or 0% in obese patients, compared to 13 pneumonia patients, representing 4% of the non-obese group, $p = 0,024$) and SNI (3 cases, or 2% of patients in the obese group, versus 25 cases or 7% in the non-obese group, $p = 0,048$).
CONCLUSIONS: Statistical analysis revealed an association between transfusion of 2 red blood cell units and mediastinitis post-operation. The study also produced surprising results pertaining to development of infections in obese and female patients. A number of factors limit the reliability of study results, including modest sample size and restriction of analysis to the univariate level. Optimization of intraoperative patient blood management should continue to be an object of further studies.

Keywords: cardiac surgery, coronary artery bypass, blood transfusion, blood products, platelet transfusion, post-operative infections

CONTENTS

1 INTRODUCTION

1.1 Blood transfusion in cardiac surgery

Transfusion of blood products remains commonplace in heart surgery. In the United States, an estimated 10-20% of all blood transfusions are used in the perioperative care of patients undergoing cardiac surgical procedures (1,2). Despite the perceived blood product needs of cardiosurgical patients, significant post-operative complications associated with transfusion have been highlighted in both evidence, and guidelines published by the American College of Cardiology and the European Association of Cardiothoracic Surgery. The same guidelines stress that conservative strategies in administration of blood products may have both financial and medical benefits to liberal transfusion strategies (1,3). Nevertheless, both the complexity of cardiac procedures and prevalence of preoperative patient comorbidity pose problems in the management of anemic and bleeding patients. In addition to these obstacles, lack of evidence-based triggers for transfusion and poorly understood causal mechanisms further confound the choice of strategy for the practicing physician (4). This is especially seen in multicenter studies which show that variance in individual transfusion practices, on the institutional level, has been significant. In lack of concrete understanding, practices in many cases are being influenced by both local conventions and individual standards, besides evidence (5,6).

1.2 Indications for Red Blood Cell transfusion

The theoretical goal and accepted indication for transfusion of red blood cells (RBCs) is the prevention of injury related to inadequate tissue oxygenation (7), presenting as a consequence of significant bleeding or anemia (8). Patients undergoing coronary artery bypass grafting (CABG), the most common type of heart operation (9), constitute a group of notably heightened risk for these outcomes. Typical baseline characteristics for this

population include advanced age, BMI>25 kg/m2, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, prior acute coronary syndromes, and regular use of potent anticoagulants (10-12). Not surprisingly, the average incidence of bleeding alone as a complication has been observed to be as high as 30 % (13) in CABG patients. In particular, a retrospective cohort study found that major bleeding necessitating re-exploration was associated with 3 times higher mortality rates and significantly longer in-hospital length of stay following operation, for patients undergoing CABG (14). A subsequent study further solidified massive blood loss as a strong, independent risk factor for in-hospital mortality, following multivariate analysis (15).

Preoperative anemia, the second important determinant of RBC transfusion (16), defined on basis of blood hemoglobin concentration, is an additional factor thought to be associated with adverse outcomes in cardiac surgery. An anemic state, preceding operation, is common in cardiosurgical patients. This anemia can be either hospital-acquired, related to coronary angiography preceding surgery, or associated with iron-deficiency or comorbidities (e.g. chronic renal disease) (17). An independent association between preoperative anemia and postoperative morbidity and mortality has been recorded in multiple publications and meta-analyses of evidence. Associated outcomes include postoperative stroke (18,19), acute kidney failure (AKI) (19-21), infection (21) and mortality (21,22).

1.3 Problematics of RBCs

Roughly 50 % of patients undergoing CABG receive allogeneic red blood cell transfusions (23). This is largely done for the prevention of the potentially ischemic complications described above (24). In some cases indeed, such as hemorrhagic shock, the efficacy of allogeneic RBCs in reducing negative outcome has been justified, and transfusion of patients with hemoglobin levels of 6 g/dL or less has been called reasonable, in guidelines, and potentially life-saving. (25)

On the other hand, the safety of RBC transfusions has lately been a subject of scientific scrutiny. A growing body of publications in the last two decades has identified a positive and independent correlation between blood product usage and adverse results, following

cardiac surgery. Studies have reported transfusions to be linked to a substantially greater hazard for post-operative events like infections (26-31) such as pneumonia or mediastinitis, ischemic kidney injury (12,26,28,30) and cardiac complications (26,12, 30, 31), with corresponding influence on long-term patient mortality, in 1- and 5-year cohorts following operation (32-34). Adjusted hazard ratios for short term post-operative mortality have also consistently indicated at least 50% greater chances of death following transfusion in cardiac surgery (12,26,27,30,35), and worsened functional outcome (36). What is worse, results following multivariate analysis have also shown transfusions to increase the already acknowledged probability for adversity in anemic and bleeding patients, in a multiplicative manner on previously observed hazard ratios (37,38).

Attempts at interpretation of these results have presented a long-known immunomodulatory response (TRIM) of transfusion recipients to allogeneic blood products, as a probable contributor for infectious post-operative events (4,39). Besides scarce evidence on immunomodulation's actual impact on post-operative pathology in non-immunocompromised individuals, this conception has led to a widespread international adoption of pre-storage depletion of white blood cells from RBCs products, with the exception of the United States (40). This has been done to ensure that potential yet-to-be-proven negative effects are prophylactically reduced. RCTs comparing leukoreduced blood products to standard issue transfusions, however, have not given conclusive results and have only testified to their relative safety and in only some cases, to the reduction of infections (41).

In order to respond to the compelling findings surrounding transfusions, surgical and anesthesiological guidelines are being adapted to the state of evidence. Focus of patient blood management has transitioned to the overall reduction of transfusion requirements, and the development of new protocols for the evaluation of this requirement during operations (3,42). Such protocols include decision making algorithms based on point-of-care thromboelastography (TEG) or thromboelastometry (TEM). While these strategies have proven effective in the reduction of overall blood transfusions, they have not been shown to significantly improve odds for adverse outcome, when compared to conventional transfusion strategies (43). The true benefit has thus been a reduction in the considerable costs incurred by unnecessary transfusion of blood products (26).

Currently both European and North American guidelines agree in the choice of restrictive transfusion strategies during perioperative patient management, and the same statements recognize the increased risk of transfused patients for complications (3,27). Restrictive strategies are usually defined by a set blood hemoglobin concentration threshold, above which transfusions are not recommended (typically 8 g/dL) (4). Still, concrete findings have not yet been made on their efficacy (44,45).

1.4 Additional questions and study hypothesis

Multiple articles have referenced a progressive relationship between the amount of RBCs transfused and adverse outcome (26,27,29,30,34). However, reliable transfusion thresholds or evidence-based preferential strategies for intraoperative patient blood management in cardiac surgery patients do not yet exist. This fact stands out, as some publications have recorded even singe units of RBCs having potentially severe associations with postoperative outcomes (38,46). Little consensus exists on what threshold of transfusion (if existent) carries heightened risk of complications, while some studies have reported 4 or 5 units of RBCs as a potential cutline of transfusion safety for some outcomes (33,35). The investigation of a dose-dependent relationship between blood products and adverse events following surgery has notable importance, since transfusion of 1 -2 U of RBCs is considered low-risk when compared to potential benefit, and in some instances has been called “discretionary” (46).

The current study set out to examine red blood cell transfusions in the context of infectious outcomes. Recent publications have focused on and exclusively referenced notable associations between administration of intraoperative RBCs and pneumonia (47), mediastinitis, and/or severe septicaemia (27). Special focus will be taken into the examination of a proposed dose-dependent relationship between RBC transfusions and infections presenting as post-operative complications. As part of the study, analysis and evaluation of pre-operative patient population features will be also factored into the development of the results.

2 METHODS

2.1 Systematic review

2.1.1 Purpose and study identification

A systematic review of the current evidence was conducted for the purposes of the study. Data extracted from the systematic review was utilized in the design of the retrospective cohort study and the evaluation of its results.

Searches were conducted in the following databases: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)". The default Ovid Technologies, Inc. search engine was used, from a computer with access to University of Tampere's license for scientific publications.

The inclusion criteria for the studies were defined as follows. Only original studies that included adult cardiac surgery patients as their main study population were selected. Cardiac surgery was defined as either coronary artery bypass or heart valve surgery. Selected studies had to have postoperative complications as their main outcome variables. The selected studies also had to be in the English language and have transfusion of blood products as their main intervention or part of their main interventions. Furthermore, studies describing autologous blood transfusion as their main intervention were not included in the review, due to difficulty in comparison of their study populations with allogeneic transfusion studies' populations. Other reviews, patient series, case reports, letters and other non-original studies were excluded from this review, as well as articles which were only available in abstracts.

2.1.2 Search strategy

The search strategy utilized is presented in detail in Table 1. Searches were structured using the "PICO" search strategy template. Patient population (P) was defined with search #5 ("Cardiovascular surgical procedures (MeSH)" OR "Coronary Artery Bypass (MeSH)" OR "CABG (All fields)" OR "Coronary Artery Bypass (All fields)"). The intervention (I) was formulated using non-MeSH and MeSH-terms for "Blood transfusion", "Platelet transfusion", "Erythrocyte transfusion", as well as "All fields"-searches for the terms "cryoprecipitated plasma", "blood products" and "frozen plasma" (search #15). Complication (C) and outcome (O) were defined by combining search #22 ("complications (all fields)" AND "postoperative (all fields)") with the main expected complication in these patient groups (hemorrhage) expressed in MeSH and non-MeSH terms ("hemorrhage (all fields)" OR "Hemorrhage (MeSH)" OR "Postoperative Hemorrhage (MeSH)"). The combined results for the target outcome were produced with search #23.

Finally, results for the defined patient population, intervention, and outcome were combined with the AND command (search #24). The result was 997 potentially relevant articles.

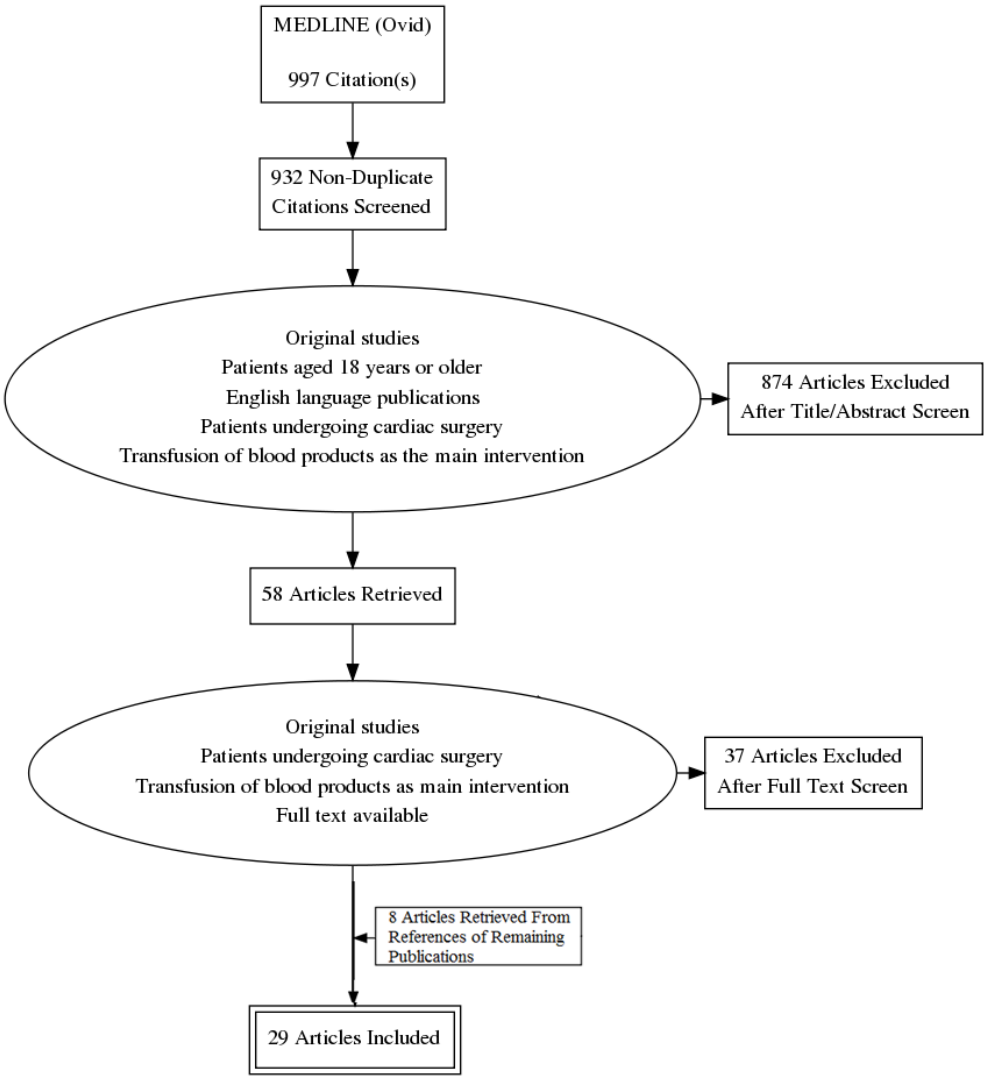
Table 1. *Utilized search strategy*

1. Cardiovascular surgical procedures (MeSH)	13. cryoprecipitated plasma (all fields)
2. Coronary Artery Bypass (MeSH)	14. frozen plasma (all fields)
3. CABG (All fields)	15. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
4. Coronary Artery Bypass (All fields)	16. Hemorrhage (MeSH)
5. 1 OR 2 OR 3 OR 4	17. Hemorrhage (all fields)
6. Blood transfusion (MeSH)	18. Postoperative Hemorrhage (MeSH)
7. Blood transfusion (All fields)	19. 16 OR 17 OR 18
8. Platelet transfusion (MeSH)	20. complications (all fields)
9. Platelet transfusion (All fields)	21. postoperative (all fields)
10. Erythrocyte transfusion (MeSH)	22. 20 AND 21
11. Erythrocyte transfusion (All fields)	23. 19 AND 22
12. Blood products (all fields)	24. 5 AND 15 AND 23

2.1.3 Assessment of results and final study selection

Figure 1 presents the selection process for the 997 articles acquired through the search strategy. Screening for duplicates produced 932 relevant publications. Title based screening excluded 874 studies from the review, based on previously defined inclusion criteria. A total of 58 studies where screened based on text, and following exclusion of articles not compliant to the inclusion criteria and removal of studies only available as abstracts through the University's license, a total of 21 articles remained for inclusion in the review. References of these publications where also examined, and an additional 8 acceptable articles where extracted, making for a total of 29 original studies which were used for the review of evidence in the introduction (9–16,19–21,25–39,42,46,47). Generic commentary of the status quo in clinical practice was supplemented with independently indexed references, which account for additional bibliography in this study.

Figure 1. *Flow chart for study selection process*



2.2 Retrospective Cohort Study

2.2.1 Study materials

The present study set out to retrospectively examine patients undergoing coronary artery bybass grafting surgery in Tampere University Hospital in the years 2014 - 2015. The collection of patient data for the purposes of the study received approval from the Heart Hospital, Tampere University Hospital in 2018.

Patient information and perioperative variables from CABG operations in the years 2014 – 2015 were manually processed from the University Hospital's electronic patient information database, MD-Uranus (CGI Group Inc. Finland). Intraoperative transfusion records and anesthesiological data were retrieved from physical patient records. Patients with incomplete medical information on the performed operation were not included in the study. Data was initially collected and tabulated into Microsoft Office Excel (Microsoft Corp., version 2016), and later imported and further analysed in SPSS Statistics (IBM Corp., version 24).

2.2.2 Collection and classification of baseline patient characteristics

Baseline characteristics of study population were collected followingly. Patients were stratified with respect to age into two classes, namely patients with 65 or above years of age, and patients with less than 65 years of age. Sex was recorded as either male or female. Through patient data on height and preoperative weight, patients' preoperative body-mass indeces (BMI) were calculated and used to classify patients into either obese, for a BMI above 30 kg/m2, and non-obese, for a correspondingly lower BMI. Smoking as a health habit was recorded as a categorical variable, into classes "Yes", for an active smoker, "No" for a patient that had never smoked, and "Ex-smoker" for a former smoker that had quit, based on clinical history taking documented into patient electronic records.

Patients' long term diagnoses were also collected, and treated as dichotomous variabes. These included diagnosed arterial hypertension, diabetes mellitus (insulin-dependent or not), peripheral arterial disease, chronic obstructive pulmonary disorder (COPD). Patient data was also similarly collected on previous stroke history and previously performed percutaneous coronary intervention.

Cardiac function was documented in the study as an ordinal variable, based on left ventricular ejection fraction percentage, as measured though cardiac ultrasonography by a practicing University Hospital cardiologist. Cardiac function was classified as either "≥ 50 %; Normal", "30 – 50 %; Compromised" and "≤ 30%; Severe".

Tampere University Hospital also calculated numerical EuroSCORE II evaluations (European System for Cardiac Operative Risk Evaluation) for all patients undergoing CABG. The EuroSCORE values for study patients were included in the study, and stratified into three ordinal classes, "0 – 2 ", "2 – 5" and "> 5".

2.2.3 Classification of perioperative and outcome variables

The urgency of the indication for CABG was documented for the purposes of the present study, and categorized as either "Elective" for non-, "Hastened" for CABG occuring within 2 – 4 days following decision for surgical intervention, and "Emergency" for CABG performed within 24 hours of patient presentation to the Hospital's Emergency Department.

Anesthesiological technique during operation was considered as either "on-pump" or "off-pump", pertaining to the usage of mechanical cardiopulmonary bypass or not, respectively.

Intraoperative blood product transfusions were included in the study in the following way. Transfusion of red blood cells was considered an ordinal variable, stratified according to the number of standard units used during operation. Classes were defined "None", for no transfusion, and "1 Unit", "2 Units", "3 Units" and "≥ 4 Units", on the basis of the number of

used units, respectively. Likewise, transfusion of blood platelets was considered in tems of standard units transfused, with patient being classified into 3 groups, termed “None”, for no platelets transfused, “2 Units” for transfusion of 2 standard units and “> 2 Units” for transfusion of platelets exceeding aforementioned amount. Blood products used in Tampere University Hospital are procured by the Finnish Red Cross Blood Service, and standard units used during operation are defined by the Blood Service. One unit of red blood cells is reported as roughly amounting to 300 milliliters of product, while one unit of platelets is reported to amount to roughly 250 milliliters of product (48). Usage of blood product derivatives, such as Octaplas®, Octaplex®, or Fibrogammin®, were not included in the study.

The study’s primary outcomes, namely post-operative infections, were considered dichotomous variables, indicating presence or not of the infectious complication. Infections considered were bacterial pneumonia, mediastinitis, and serious nosocomial infection. In the University Hospital, diagnoses of pneumonia and mediastinitis are made based on the combination of clinical and radiographic evidence of localized bacterial infection. A post-operative complication of septicaemia was considered a serious nosocomial infection, when evidence of systemic inflammatory response to infection was observed along with evidence of organ failure. Interpretation of aforementioned evidence followed Finnish national practice guidelines where applicable, and hospital approved guidelines were followed where national guidelines were not applicable.

2.2.4 Statistical analysis of data

Data was analysed in SPSS Statistics version 24. Univariate analysis of study variables was the principal method of statistical evaluation. With respect to the classification of variables, none were considered continuous. Variables were analysed as categorical, ordinal or dichotomous. Dichotomous variables were evaluated in relation to ordinally categorized ones by utilizing the Wilcoxon-Mann-Whitney test, whereas testing of variables with 3 categories or above with ordinal variables was done with Kruskal Wallis tests. Statistical comparison of dichotomous variables with other dichotomous varibles was made with conventional chi-squared tests where at least 5 instances existed of each variable. In cases where this term was not fulfilled, Fisher’s exact test was used. This

same procedure was also used when comparing variables considered non-ordinal and having three categories or above with other variables considered non-ordinal. For the purposes of the study, p-values from each statistical test were tabulated along with rounded percentages for the representative instances of the study variables' statistics.

3 RESULTS

3.1 Descriptive statistics of study population

In total, characteristics and perioperative information from 461 patients were included in the study. A total of 41 patients were excluded from the study, due to incomplete or missing records of hospitalization and treatment. Baseline characteristics of patients included in the study are presented in Table 2. Patients of age equal to or above 65 years and male sex were characteristically in majority of the study population, totalling 301 (65 %) and 378 (82 %) of patients, respectively. Comorbidity included hypertension in 73 %, diabetes mellitus in 32%, peripheral arterial disease in 9 %, and chronic obstructive lung disease in 10 % of CABG patients. Of all patients, 28 % were considered obese, and 17 % were active smokers while awaiting operation, while non-smokers represented 52 % of the study population, and ex-smokers 31 %. Patients that had suffered stroke in their history accounted for 9 %, while 3 % of patients undergoing CABG had previously been subjects of PCI. 70 % of patients were evaluated as having normal cardiac ejection fraction, 27 % had compromised left ventricular ejection fraction, while 3 % had severe impairment of cardiac function, with an LVEF of below 30 %. Individuals with calculated EuroSCOREs below 2 accounted for 58 % of the population, while 28 % had a calculated EuroSCORE between 2 and 5, and 14 % scored above 5 in EuroSCORE. Of all operations, 15 % represented surgical intervention in the emergency setting, while 34 % of operations were considered hastened. 51 % were elective and non-emergency. 5 % of all operations were performed without cardiopulmonary bypass.

Intraoperative transfusions occurred as follows. 93 % of patients received no platelet transfusions, while 6 % received 2 Units of platelets, leaving 1 % of patients as having received above 2 Units of platelets. In terms of red blood cells, 84 % of patients were not deemed in need of intraoperative transfusion, 2 % of patients were transfused with 1 Unit of red blood cells. Patients that received 2 Units of RBCs accounted for the majority of transfusions at 8 %, while 2 % received 3 Units and 3 % received 4 Units or above of RBCs, respectively.

Variables	Patients (%) (n=461)
Age	
≥ 65 years	301 (65)
< 65 years	160 (35)
Sex	
Male	378 (82)
Female	83 (18)
Hypertension	338 (73)
Diabetes Mellitus	147 (32)
PAD	43 (9)
Obesity	127 (28)
Smoking	
Ex-smoker	144 (31)
No	240 (52)
Yes	77 (17)
COPD	46 (10)
Stroke history	41 (9)
Previous PCI	15 (3)
Ejection Fraction (%)	
≥ 50(Normal)	322 (70)
30 – 50 (Compromised)	125 (27)
≤ 30 (Severe)	14 (3)
EuroSCORE	
0-2	269 (58)
2-5	127 (28)
>5	65 (14)

Variables	Patients (%) (n=461)
Indication for CABG	
Elective	237 (51)
Hasty	156 (34)
Emergency	68 (15)
Technique (off-pump)	25 (5)
Transfusion	
Thrombocytes	
> 2 Units	4 (1)
2 Units	30 (6)
None	427 (93)
Red Blood Cells	
1 Unit	9 (2)
2 Units	38 (8)
3 Units	9 (2)
≥ 4 Units	16 (3)
None	389 (84)

Table 2. Baseline characteristics of study population. (Abbreviations:, PAD = Peripheral Arterial Disease, COPD = chronic obstructive pulmonary disorder, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting)

3.2 Results of statistical analysis

3.2.1 Effect of baseline characteristics on transfusion

Results of comparative statistical evaluation of baseline characteristics to intraoperative transfusions are presented in table 3. Relevamt percentages are displayed in respect to row variables. Significant associations where noted between preoperative left ventricular ejection fraction ($p < 0.001$), previous percutaneous coronary intervention ($p = 0,044$), urgency of indication for surgery ($p = 0,049$) and red blood cell transfusions. Within patients with compromised LVEF, 22% were given transfusion of red blood cells, while severely lowered LVEF was associated with transfusion in 43 % of patients, compared to transfusions occuring only in 12 % of patients with normal cardiac function. Patients with previous percutaneous intervention in history were subject to transfusions in 33 % of cases, compared to 15 % in the group with no previous PCI. Patients operated with an elective indication for intervention were administered RBCs in 16 % of cases, while transfusions in hastened operations were represented in 19 % of patients. Only 6 % of patients undergoing emergency CABG were given red blood cell transfusions. Transfusions of thrombocytes where also significantly associated with RBC transfusions ($p < 0.001$), as is to be expected in the management protocols of intraoperative bleeding.

Contrarywise, no significant correlation was observed between other descriptive patient variables, such as age, sex, hypertension, obesity, tobacco smoking, COPD, peripheral arterial disease, diabetes mellitus or EuroSCORE.

	Patients (%)					
	RBC Transfusion					
Variable	0	1U	2U	3U	≥4U	p-value
Age						
<65 years	136 (85)	4 (3)	15 (9)	3 (2)	2 (1)	
≥65 years	253 (84)	5 (2)	23 (8)	6 (2)	14 (5)	0,666
Gender						
Female	72 (87)	0 (0)	3 (4)	2 (2)	6 (7)	
Male	317 (84)	9 (2)	35 (9)	7 (2)	10 (3)	0,689
Ejection fraction						
≥ 50 %	283 (88)	5 (2)	23 (7)	6 (2)	5 (2)	
30–50 %	98 (78)	3 (2)	14 (11)	2 (2)	8 (6)	
≤ 30 %	8 (57)	1 (7)	1 (7)	1 (7)	3 (21)	<0.001
Euroscore						
0–2	223 (83)	8 (3)	22 (8)	5 (2)	11 (4)	
2–5	105 (83)	1 (1)	12 (9)	4 (3)	5 (4)	
>5	61 (94)	0 (0)	4 (6)	0 (0)	0 (0)	0,069
Obesity						
No	279 (84)	9 (3)	27 (8)	8 (2)	11 (3)	
Yes	110 (87)	0 (0)	11 (9)	1 (1)	5 (4)	0,468
Smoker						
No	197 (82)	5 (2)	23 (10)	5 (2)	10 (4)	
Yes	66 (86)	1 (1)	4 (5)	3 (4)	3 (4)	
Ex	126 (88)	3 (2)	11 (8)	1 (1)	3 (2)	0,324
Stroke history						
No	350 (83)	8 (2)	38 (9)	8 (2)	16 (4)	
Yes	39 (95)	1 (2)	0 (0)	1 (2)	0 (0)	0,045
Hypertension						
No	108 (88)	2 (2)	8 (7)	2 (2)	3 (2)	
Yes	281 (83)	7 (2)	30 (9)	7 (2)	13 (4)	0,219
COPD						
No	350 (84)	8 (2)	36 (9)	8 (2)	13 (3)	
yes	39 (85)	1 (2)	2 (4)	1 (2)	3 (7)	0,986
PAD						
No	350 (84)	8 (2)	36 (9)	8 (2)	16 (4)	
Yes	39 (91)	1 (2)	2 (5)	1 (2)	0 (0)	0,21
DM						
No	264 (84)	5 (2)	27 (9)	7 (2)	11 (4)	
Yes	125 (85)	4 (3)	11 (7)	2 (1)	5 (3)	0,754

	Patients (%)					
	RBC Transfusion					
Variable	0	1U	2U	3U	≥ 4U	p-value
Previous PCI						
No	379 (85)	8 (2)	37 (8)	8 (2)	14 (3)	
Yes	10 (67)	1 (7)	1 (7)	1 (7)	2 (13)	**0,044**
Indication						
Elective	198 (84)	5 (2)	17 (7)	6 (3)	11 (5)	
Hastened	127 (81)	3 (2)	19 (12)	3 (2)	4 (3)	
Emergency	64 (94)	1 (1)	2 (3)	0 (0)	1 (1)	**0,049**
Technique						
Off-Pump	23 (92)	0 (0)	1 (4)	0 (0)	1 (4)	
On-Pump	366 (84)	9 (2)	37 (8)	9 (2)	15 (3)	0,306
Blood platelets						
No transfusion	372 (87)	8 (2)	33 (8)	8 (2)	6 (1)	
2U	16 (53)	0 (0)	5 (17)	0 (0)	9 (30)	
>2U	1 (25)	1 (25)	0 (0)	1 (25)	1 (25)	**<0.001**

Table 3. Analysis of baseline characteristics to red blood cell transfusions (Abbreviations: RBC = Red Blood Cell, PAD = Peripheral Arterial Disease, COPD = chronic obstructive pulmonary disorder, DM = Diabetes Mellitus, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting). Relevant p-values, describing probability of documented results for null hypothesis of correlation between row variables and red blood cell transfusions, are displayed in the right end of the table.

3.2.2 Infectious outcomes

Results of statistical analysis with respect to post-operative infections as outcomes, in relation to other study variables, are presented in Table 4. Relevant percentages are displayed in respect to row variables. Female sex was significantly associated with development of pneumonia, with 7 % of female individuals being diagnosed with pulmonary infection post operation, compared to 2 % in the male group (p = 0,007). No similar associations where found in the development of mediastinitis (p = 0,665) or serious nosocomial infection (p = 0,983). A statistically significant correlation between obesity and incidence of post-operative pneumonia and development of serious nosocomial infection was also observed in the study population. Out of 127 patients considered obese, based on BMI calculations, 0 % were cited as acquiring pneumonia, when compared to the non-obese patient group, where pneumonia developed in 4 % of cases (p = 0,024). Additionally, 2 % or 3 patients belonging to the obese group developed SNI, compared to the non-obese group where serious nosocomial infection was observed in 7 % of cases, or 25 patients (p = 0,048).

Transfusions of platelet products where significantly associated with patients acquiring post operational pneumonia. In the group receiving more than 2 units of platelets, 1 patient (25 %) developed pneumonia, while in the group receiving 2 units of platelets, 2 patients (7 %) were diagnosed with pneumonia. This was statistically significant (p = 0,01) when compared to the group receiving no platelet transfusions, in which 2 % or 10 patients developed pneumonia. No similar associations where seen in the cases of mediastinitis (p = 0,823) or SNI (p = 0,871). In patients that received no red blood cell transfusions, mediastinitis developed in 1,3 % of cases (5 patients), while mediastinitis was not observed in any patients receiving 1 unit, 3 units, or 4 units and above of red blood cells. Patients transfused with 2 units of RBCs developed mediastinitis in 10,5 % of cases, totaling 4 patients. In Fisher's exact test, this proved to be a statistically significant correlation between RBC transfusions and development of mediastinitis (p = 0,03). No statistical significance was observed between red blood cell transfusions and development pneumonia (p = 0,193) or SNI (p = 0,526).

	Patients (%)								
	Pneumonia			Mediastinitis			SNI		
	No	Yes	p-value	No	Yes	p-value	No	yes	p-value
Age									
<65 years	155 (97)	5 (3)		156 (97,5)	4 (2,5)		149 (93)	11 (7)	
≥65 years	293 (97)	8 (3)	0,773	295 (98,3)	5 (1,7)	0,725	284 (94)	17 (6)	0,599
Gender									
Female	77 (93)	6 (7)		80 (97,6)	2 (2,4)		78 (94)	5 (6)	
Male	371 (98)	7 (2)	**0,007**	371 (98,1)	7 (1,9)	0,665	355 (94)	23 (6)	0,983
Ejection fraction									
≥50 %	315 (98)	7 (2)		315 (97,8)	7 (2,2)		306 (95)	16 (5)	
30-50 %	120 (96)	5 (4)		122 (98,4)	2 (1,6)		114 (91)	11 (9)	
≤ 30 %	13 (93)	1 (7)	0,353	14 (100)	0 (0)	0,805	13 (93)	1 (7)	0,31
Euroscore									
0-2	261 (97)	8 (3)		262 (97,8)	6 (2,2)		258 (96)	11 (4)	
2-5	123 (97)	4 (3)		127 (100)	0 (0)		115 (91)	12 (9)	
>5	64 (98)	1 (2)	0,793	62 (95,4)	3 (4,6)	0,08	60 (92)	5 (8)	0,096
Obesity									
No	321 (96)	13 (4)		327 (98,2)	6 (1,8)		309 (93)	25 (7)	
Yes	127 (100)	0 (0)	**0,024**	124 (97,6)	3 (2,4)	0,712	124 (98)	3 (2)	**0,048**
Smoker									
No	237 (99)	3 (1)		237 (98,8)	3 (1,3)		227 (95)	13 (5)	
Yes	73 (95)	4 (5)		76 (98,7)	1 (1,3)		73 (95)	4 (5)	
Ex	138 (96)	6 (4)	0,096	138 (96,5)	5 (3,5)	0,277	133 (92)	11 (8)	0,636
Stroke history									
No	408 (97)	12 (3)		410 (97,9)	9 (2,1)		395 (94)	25 (6)	
Yes	40 (98)	1 (2)	1	41 (100)	0 (0)	1	38 (93)	3 (7)	0,729
Hypertension									
No	120 (98)	3 (2)		121 (98,4)	2 (1,6)		117 (95)	6 (5)	
Yes	328 (97)	10 (3)	1	330 (97,9)	7 (2,1)	1	316 (93)	22 (7)	0,661
COPD									
No	404 (97)	11 (3)		406 (98,1)	8 (1,9)		387 (93)	28 (7)	
yes	44 (96)	2 (4)	0,379	45 (97,8)	1 (2,2)	1	46 (100)	0 (0)	0,097
ASO									
No	406 (97)	12 (3)		408 (97,8)	9 (2,2)		392 (94)	26 (6)	
Yes	42 (98)	1 (2)	1	43 (100)	0 (0)	1	41 (95)	2 (5)	1
Diabetes Mellitus									
No	306 (97)	8 (3)		307 (97,8)	7 (2,2)		298 (95)	16 (5)	
Yes	142 (97)	5 (3)	0,606	144 (98,6)	2 (1,4)	0,726	135 (92)	12 (8)	0,199

	Patients (%)								
	Pneumonia			Mediastinitis			SNI		
Variable	No	Yes	p-value	No	Yes	p-value	No	yes	p-value
Previous PCI									
No	433 (97)	13 (3)		437 (98,2)	8 (1,8)		418 (94)	28 (6)	
Yes	15 (100)	0 (0)	1	14 (93,3)	1 (6,7)	0,26	15 (100)	0 (0)	0,614
Indication									
Elective	228 (96)	9 (4)		234 (99,2)	2 (0,8)		224 (95)	13 (5)	
Hastened	152 (97)	4 (3)		150 (96,2)	6 (3,8)		149 (96)	7 (4)	
Emergency	68 (100)	0 (0)	0,242	67 (98,5)	1 (1,5)	0,105	60 (88)	8 (12)	0,096
Technique									
Off-Pump	25 (100)	0 (0)		25 (100)	0 (0)		21 (84)	4 (16)	
On-Pump	423 (97)	13 (3)	1	426 (97,9)	9 (2,1)	1	412 (94)	24 (6)	0,057
Thrombocytes									
No transfusion	417 (98)	10 (2)		418 (98,1)	8 (1,9)		401 (94)	26 (6)	
2U	28 (93)	2 (7)		29 (96,7)	1 (3,3)		28 (93)	2 (7)	
>2U	3 (75)	1 (25)	**0,01**	4 (100)	0 (0)	0,823	4 (100)	0 (0)	0,871
Transfusion RBCs									
No transfusion	379 (97)	10 (3)		384 (98,7)	5 (1,3)		364 (94)	25 (6)	
1 RBC	9 (100)	0 (0)		9 (100)	0 (0)		9 (100)	0 (0)	
2 RBC	37 (97)	1 (3)		34 (89,5)	4 (10,5)		37 (97)	1 (3)	
3 RBC	9 (100)	0 (0)		9 (100)	0 (0)		9 (100)	0 (0)	
≥4 RBC	14 (88)	2 (13)	0,193	16 (100)	0 (0)	**0,03**	14 (88)	2 (13)	0,526

Table 4. Analysis of infectious outcomes based on baseline characteristics and transfusions (Abbreviations: RBC = Red Blood Cell, PAD = Peripheral Arterial Disease, COPD = chronic obstructive pulmonary disorder, DM = Diabetes Mellitus, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting). Relevant p-values, describing probability of documented results for null hypothesis of correlation between row and column variables, are displayed in the column to the right of the column variable.

4 DISCUSSION

This study set out to examine rates of post-operative infectious complications, and compare them to rates of intraoperative blood product transfusions. Results suggested a strong association between transfusions of red blood cells in the operating room and development of mediastinal surgical site infections. However, mediastinal infections occurred only in the patient group receiving 2 units of red blood cells, which included a total of 38 patients, while similar outcomes where not observed in other patient groups receiving a differing number of red blood cells. Furthermore, no significant associations where observed in the development of pneumonia or serious nosocomial infections. These considerations pose a challenge in the interpretation of the role of transfusions as an independent marker of infectious complications. While 2 units of RBCs where statistically associated in a significant way with mediastinal infection, patient numbers in groups receiving a different unit quantity of RBCs were modest. In total, only 9 patients received 1 unit of red blood cells and 9 patients were transfused with 3 units. Transfusion of 4 RBC units or above was represented by only 16 patients in the study. Therefore, it is considered vital by the study author to highlight the study population limitations in the overall distribution of patient cases across different numbers of RBC units transfused in the operating room. In conclusion, while study results showcased an association between RBC transfusion and post-operative mediastinitis following CABG, clinical implications for a preventive cut-off value of RBC units transfused are severely limited by disproportionate patient representation in the study setting.

Overall study results do not fall in line with results from publications suggesting dose-dependent correlations between transfusions and infectious outcomes (27,47). Other studies have challenged this interpretation and argued that based on their analytic results, frequency of red blood cell transfusions could be serving more as a predictor of overall patient disease severity and thus increased risk for unfavorable outcome, and less so as an independent marker of complications (49). These views would primarily be in support of the 2017 consensus of the European Academy of Cardiothoracic Surgeons and Association of Cardiothoracic Anesthesiologists, which concluded that current evidence

comparing outcomes in restrictive and liberal transfusion strategies, has not showcased significant reduction in adverse outcomes through restrictive transfusion strategies (3).

In the broader scope of the study, a BMI of 30 kg/m^2 or above in patients was significantly associated with decreased rates of infectious outcomes. It may be noted that this directly contradicts results showcasing increased coincidence of infectious outcomes in obese patients, produced in other relevant publications (27,47). Further study may be indicated for the exploration of this analytic result. Alternatively, it may be argued that the relatively lower percentage of obese patients in the study population (28%) could be acting as a confounding element in the overall presentation of infectious complications in the study.

Critical evaluation of the results must also be placed in the context of limitations of the study. Specific indications for transfusions performed were not available for consideration in the study variables. Furthermore, transfusions performed post-operatively in the Intensive Care Unit of the Hospital could not be included for analysis due to technical limitations of the study. Similarly, variance in surgical technique is not possible to evaluate through electronical patient records. Modesty in the total population of patients included in the study is also to be considered as a factor limiting the broader applicability of study results. Study methods were also limited to only univariate analysis of data.

Understanding of causal mechanisms in post-operative outcomes is challenging to elucidate, given the extended multimorbid profile of cardiac surgery patients. Heterogeneity in both surgical technique and anesthesiologic management across institutions (12), all contribute to the difficulty in isolating the individual contributions of variables, such as transfusion, to outcomes (47). Nevertheless, international focus on the suspected effect of allogeneic red blood cells on surgical outcomes has still driven the development of progress in optimization of intraoperative patient blood management. Specifically, novel methods for evaluation of transfusion requirements during anesthesia, through thromboelastometry and thromboelastography, for example, allow for future prospects of reduced transfusion rates during surgery. These would in turn promise a more cost-effective anesthesiological management of cardiothoracic surgery patients in the future, as well as tighter scrutiny on intraoperative transfusion practices. Further

research is thus indicated in the examination of the use of blood products during cardiothoracic surgery.

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