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Increased long-term mortality with plasma transfusion after coronary artery bypass surgery

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Abstract *Purpose:* Patients undergoing cardiac surgery often require transfusions of red blood cells, plasma and platelets. These components differ widely in both indications for use and composition. However, from a statistical point of view there is a significant colinearity between the components. This study explores the relation between the transfusion of different blood components and long-term mortality. *Methods:* A retrospective single-centre study was performed including 5,261 coronary artery bypass grafting patients, excluding patients receiving more than eight units of red blood cells, those suffering early death (7 days) and emergency cases. Patients were followed up for a period of up to 7.5 years. A broad spectrum of potential risk factors was analysed using Cox proportional hazards survival regression. Non-significant risk factors were removed by step-wise elimination, and transfusion of red blood cells, plasma and platelets was forced to remain in the model. *Results:* The transfusion of red blood cells was not associated with decreased long-term mortality (HR = 1.007, $p = 0.775$), whereas the transfusion of plasma was associated with decreased long-term survival (HR = 1.060, $p < 0.001$), and the transfusion of platelets was associated with increased long-term survival (HR = 0.817, $p = 0.011$). The risk associated with transfusion of plasma was mainly attributed to patients receiving large amounts of plasma. All hazard ratios are per unit of blood product transfused. *Conclusions:* No association was found between the transfusion of red blood cells and mortality during the study period. However, transfusion of plasma was associated with increased mortality while transfusion of platelets was associated with decreased mortality during the study period.

Keywords Cardiac surgery · Transfusion · Plasma · Red blood cells · Mortality

Introduction

The benefits and risks of blood transfusions during and after cardiac surgery are the subject of considerable debate in both academic and clinical setting. Associations between blood transfusion and decreased long-term survival have been reported in several retrospective studies [1–8], while other studies have revealed conflicting results [9]. Furthermore, in a previous study, we found that the risk associated with RBC transfusion was almost completely eliminated by introducing preoperative haemoglobin levels and renal function into the model [10].

In most of the publications mentioned above only red blood cell (RBC) transfusion was studied, whereas in reality many patients also receive transfusions of plasma and platelets as well. From a clinical and statistical point of view, there is significant colinearity between these different types of transfusions, but from an immunological standpoint, these different blood components differ in many ways [11]. Few studies have been carried out on the effects of the transfusion of different blood components other than RBCs. Koch et al. reported platelet transfusion to have a beneficial effect [3, 12], while Ranucci et al. reported that platelet transfusion was associated with increased in-hospital mortality and that plasma transfusion had a negative effect [3, 12].

The aim of the present study was to evaluate the effects of the transfusion of different blood components on long-term mortality. Our goal was to create a more robust model by including additional risk factors and all types of transfusions.

Methods

Study design

The study protocol was approved by the local ethics committee. The patients included in this study had undergone cardiac surgery at the Department of Thoracic Surgery at the University Hospital in Lund, Sweden, from 1 January 2002 to 31 December 2008. Data were collected from four principal sources. Clinical data were retrieved from the in-house clinical database in which relevant clinical information is collected on perioperative care during the patients' hospital stay. The databases of the hospital's clinical chemistry laboratory and blood bank served as the second and third sources of data. Time of death was obtained from the Swedish tax authority in May 2009, defining the follow-up period of 0.5–7.5 years. When data were missing or extreme outliers were identified, patient records were read in a first attempt to complete the data.

Patient inclusion and exclusion

Data were gathered on all patients who had undergone coronary artery bypass grafting (CABG) as their sole cardiac procedure ($n = 5{,}922$). Patients who had undergone emergency surgery, defined as surgery within 1 h of the decision to operate, were excluded ($n = 121$), as were those who died during the first 7 days following surgery ($n = 34$) and those who had received 8 or more units of RBCs ($n = 506$). Eight units was chosen since, together with plasma, this represents more than half the blood volume in most adult patients and indicates massive bleeding, in which case the transfusion was life-saving. A total of 5,261 patients were finally included in the analysis.

Completeness and reliability of the data

Perioperative information was entered into the in-house clinical database by each surgeon (100 % completion rate). Information on deaths was obtained from the Swedish tax authority, which lacks data only in exceptional cases such as emigration. The emigration rate for all Swedes in this age category is approximately 0.1 % per year [14]. Preoperative creatinine values were missing from the chemistry laboratory data for 104 patients and were imputed based on levels on the first postoperative day [10]. Preoperative haemoglobin concentrations were not available for 21 patients, and a standard mean value substitution method was employed.

The postoperative renal function of the patients was categorised using the RIFLE criteria (Risk-Injury-Failure-Loss-End Stage) based on the preoperative creatinine level and the maximum creatinine level during the hospital stay [15]. Renal function was also expressed as the estimated glomerular filtration rate (eGFR) and calculated according to the MDRD formula (Modification of Diet in Renal Disease) [16]:

$$\text{eGFR} = 32,788 \times \text{Serum creatinine}^{1.154} \times \text{Age}^{-0.203} \times (0.742\,\text{if female})$$

where eGRF is expressed as (ml/min/1.73 m^2), serum creatinine in μmol/l and age in years.

Surgery and postoperative care

Surgery was performed in a standardised manner. The use of aprotinin and tranexamic acid was left to the discretion of the individual surgeon. During the patient's stay in the intensive care unit (ICU), extra aprotinin, protamine, tranexamic acid or desmopressin was administered based on coagulation analyses or clinical assessment. No predefined limits for RBC transfusion or reoperation for bleeding were used during the period, and indications for transfusion of blood products were determined by the physician in charge of the ICU or the ward after clinical judgement.

Selection of outcome variables and statistical analysis

The variables used for survival analysis were based on frequently found predictors for decreased survival in recent survival studies focusing on renal function or RBC transfusion in cardiac surgery [1–4, 9, 17–19]. In addition, we included other potential risk factors and preoperative laboratory parameters that could reflect the preoperative morbidity of importance for long-term survival. The following variables were entered as dichotomous variables: gender, diabetes, chronic obstructive pulmonary disease

(COPD), history of cerebrovascular disease, peripheral vascular disease, left ventricular ejection fraction (LVEF) 30–50 %, LVEF <30 %, recent myocardial infarction, known pulmonary hypertension (systolic pressure >60 mmHg), acute coronary symptoms, previous CABG, previous percutaneous coronary intervention (PCI), use of cardiopulmonary bypass, intra-aortic balloon pump (IABP) before surgery, IABP after surgery, postoperative sepsis, postoperative stroke, postoperative atrial fibrillation, perioperative myocardial infarction, and re-operation for bleeding or mediastinitis. Perfusion time, age, time on the ventilator in the ICU and BMI were entered as continuous variables. Renal function (expressed as preoperative eGFR), haemoglobin, plasma C-reactive protein, plasma alanine aminotransferase, plasma leukocyte count and platelet count were entered as continuous variables. For the 195 patients who underwent off-pump surgery, the perfusion time used in the analysis was the mean value for the other 5,066 patients. Transfusion of blood products was defined as a transfusion during surgery or during the postoperative stay and was entered as a continuous variable representing units of blood products transfused.

The Cox proportional hazard model was used to determine which factors affected long-term survival, and the Wald test was used to determine the strength of the relation. For missing data, mean substitution was used. A backward stepwise elimination procedure was used starting with the above-mentioned variables. Variables with $p < 0.05$ were retained in the model together with transfusion of blood products regardless of their level of significance. Variables with $p > 0.05$ were removed in order of strength as defined by the level of significance. After all non-significant variables had been removed, they were entered one at the time to confirm that they were not relevant to the model. To check the linearity of the risk associated with plasma transfusion, plasma was categorised in four different categories and four new variables were created (no plasma transfusion, 1–2, 3–4, 5–6 or more that 6 units of plasma transfused) and entered into the model instead of plasma as continuous variable. The interaction between different types of transfusion was evaluated by creating eight variables (RBC transfusion yes/no, plasma transfusion yes/no and platelet transfusion yes/no). These variables were then entered in the final model, and the continuous variables for units of blood products were removed from the model. Student's t test was used for group comparisons, where numbers were large and the distributions not strongly skewed; otherwise the Wilcoxon-Mann-Whitney test was performed. Unless otherwise stated, the results are presented as the mean ± 1 SD. The R-project software (version 2.13.0) with the survival package was used to test the proportional hazards assumption for a Cox regression model fit. All other statistical calculations were performed using Statistica, version 8 (StatSoft inc, Tulsa, OK, USA).

Results

Study population

Patients were followed for between 152 and 2,706 days (mean 1,423 days). During follow-up there were 503 deaths. Among the patients, 2,618 (49.8 %) received RBC transfusion, 1,533 (29.1 %) received plasma transfusion and 418 (7.9 %) received platelets (Fig. 1). Patient characteristics are described in Table 1.

Analysis of patients receiving plasma transfusions

Patients who received plasma showed more preoperative comorbidity (Table 1) and more postoperative complications (Table 2) than patients not receiving plasma. The patients given plasma received on average 4.2 ± 4.0 units of plasma, and 80.7 % also received an average of 3.0 ± 2.1 units of RBCs.

Cox analysis

Stepwise elimination of non-significant variables in the Cox proportional hazards ratio analysis left 16 variables in the model: age (per year), COPD, diabetes, history of cerebrovascular disease, peripheral vascular disease,

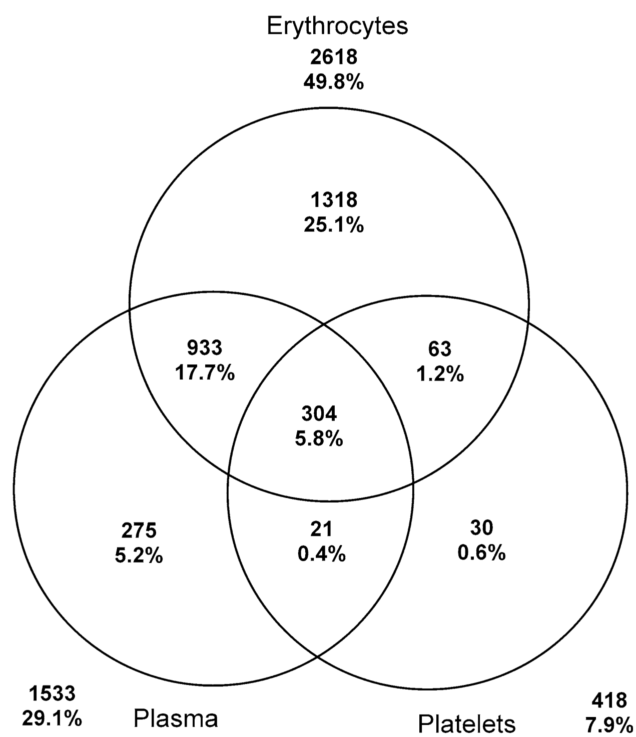


Fig. 1 Venn diagram of the covariance of transfusion of different blood products in the study population: number and percentage (of entire population of 5,261 patients) receiving products

Table 1 Perioperative characteristics of the study population

Variable	n	All	Plasma transfusion		p
			No $n = 3,728$	Yes $n = 1,533$	
Age (year)	5,261	67 (9.7)	66.4 (9.6)	68.4 (9.6)	<0.0001
Female gender	5,261	1,155 (22 %)	798 (21.4 %)	357 (23.3 %)	0.1340
Body mass index	5,256	27.2 (4)	27.3 (4)	26.8 (3.9)	<0.0001
Diabetes	5,261	1,180 (22.4 %)	868 (23.3 %)	312 (20.4 %)	0.0206
History of cerebrovascular disease	5,261	460 (8.7 %)	300 (8 %)	160 (10.4 %)	0.0053
COPD	5,261	483 (9.2 %)	326 (8.7 %)	157 (10.2 %)	0.0876
Peripheral vascular disease	5,261	741 (14.1 %)	497 (13.3 %)	244 (15.9 %)	0.0143
Neurological dysfunction	5,261	88 (1.7 %)	63 (1.7 %)	25 (1.6 %)	0.8793
Previous vascular surgery	5,261	113 (2.1 %)	52 (1.4 %)	61 (4 %)	<0.0001
Critical preoperative state	5,261	160 (3 %)	54 (1.4 %)	106 (6.9 %)	<0.0001
Pulmonary hypertension	5,261	24 (0.5 %)	6 (0.2 %)	18 (1.2 %)	<0.0001
LVEF 30–50 %	5,261	1,435 (27.3 %)	933 (25 %)	502 (32.7 %)	<0.0001
LVEF <30 %	5,261	309 (5.9 %)	150 (4 %)	159 (10.4 %)	<0.0001
Recent myocardial infarction	5,261	2,261 (43 %)	1,478 (39.6 %)	783 (51.1 %)	<0.0001
Previous CABG	5,261	98 (1.9 %)	46 (1.2 %)	52 (3.4 %)	<0.0001
Previous PCI	5,261	636 (12.1 %)	448 (12 %)	188 (12.3 %)	0.8033
Euroscore—additive	5,261	4.6 (3.1)	4.2 (2.9)	5.6 (3.5)	<0.0001
NYHA					
I	5,261	1,294 (24.6 %)	1,002 (26.9 %)	292 (19 %)	<0.0001
II	5,261	1,764 (33.5 %)	1,305 (35 %)	459 (29.9 %)	0.0004
III	5,261	1,620 (30.8 %)	1,094 (29.3 %)	526 (34.3 %)	0.0004
IV	5,261	582 (11.1 %)	327 (8.8 %)	255 (16.6 %)	<0.0001
CCS					
I	5,261	203 (3.9 %)	160 (4.3 %)	43 (2.8 %)	0.0109
II	5,261	1,786 (33.9 %)	1,357 (36.4 %)	429 (28 %)	<0.0001
III	5,261	2,265 (43.1 %)	1,630 (43.7 %)	635 (41.4 %)	0.1256
IV	5,261	1,003 (19.1 %)	579 (15.5 %)	424 (27.7 %)	<0.0001
Urgency					
Elective (>1 week)	5,261	3,403 (64.7 %)	2,538 (68.1 %)	865 (56.4 %)	<0.0001
Prioritized (<1 week)	5,261	1,509 (28.7 %)	1,026 (27.5 %)	483 (31.5 %)	0.0037
Urgent (<24 h)	5,261	349 (6.6 %)	164 (4.4 %)	185 (12.1 %)	<0.0001
Emergency (<1 h)	5,261	0 (0 %)	0 (0 %)	0 (0 %)	<0.0001
Use of CBP	5,261	5,066 (96.3 %)	3,589 (96.3 %)	1,477 (96.3 %)	0.8951
Perfusion time (min)	5,066	79.5 (24.8)	76.9 (23.1)	85.7 (27.5)	<0.0001
Cross clamping time (min)	5,066	47.4 (16.7)	46.5 (16.4)	49.7 (17.2)	<0.0001
IABP before surgery	5,261	131 (2.5 %)	41 (1.1 %)	90 (5.9 %)	<0.0001
IABP after surgery	5,261	117 (2.2 %)	38 (1 %)	79 (5.2 %)	<0.0001
Preop haemoglobin (g/l)	5,241	133.2 (15.5)	133.7 (15.3)	131.9 (15.9)	0.0002
Preop creatinine (μmol/l)	5,260	86.5 (36.1)	85.1 (34.7)	90 (39.2)	<0.0001
Preop eGFR (ml/min/1.73 m^2)	5,260	84.3 (23.6)	85.4 (22.8)	81.4 (25.2)	<0.0001
Preop platelets (10^9/l)	4,841	238.5 (67.2)	240.6 (66.5)	233.5 (68.9)	0.0008
Preop ALAT (μkat/l)	4,855	1.02 (5.9)	1.03 (6)	0.98 (5.4)	0.7603
Preop leukocytes (10^9/l)	4,838	7.7 (4)	7.5 (2.6)	8.1 (6.2)	<0.0001
Preop CRP (mg/l)	4,787	9.3 (21.3)	8.1 (18.7)	12.4 (26.3)	<0.0001
30-day mortality	5,261	20 (0.4 %)	10 (0.3 %)	10 (0.7 %)	0.0397

Data are presented as the mean (standard deviation) for continuous variables, or number (percent) for dichotomous variables, together with a comparison between patients receiving plasma and patients not receiving plasma

COPD chronic obstructive pulmonary disease, *LVEF* left ventricular ejection fraction, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *NYHA* New York Heart Association, *CCS* Canadian Cardiovascular Society, *CPB* cardiopulmonary bypass, *IABP* intra-aortic balloon pump, *eGFR* estimated glomerular filtration rate, *ALAT* alanine transaminase, *CRP* C-reactive protein

female gender, previous myocardial infarction, LVEF <30 %, previous CABG, perfusion time (per min), permanent stroke, preoperative haemoglobin (per g/l), preoperative eGFR (per ml/min/1.73 m^2), transfusion of RBC (per unit), transfusion of plasma (per unit) and transfusion of platelets (per unit). Transfusion of the three different blood products was forced to remain in the model. RBC transfusion gave a hazard ratio (HR) of 1.007 (95 % CI 0.96–1.06, $p = 0.775$), transfusion of plasma gave a HR of 1.060 (95 % CI 1.04–1.09, $p < 0.001$) and transfusion of platelets gave a HR of 0.817 (95 % CI 0.70–0.96, $p = 0.011$) for each unit transfused (Table 3).

When plasma was entered in the analysis as a categorical variable, the HR for 1–2 plasma transfusions

Table 2 Postoperative outcome

Variable	*n*	All	Plasma transfusion		*p*
			No	Yes	
		n = 5,261	*n* = 3,728	*n* = 1,533	
Hours in the ICU	5,157	22 (19–24)[a]	22 (18–23)[a]	23 (20–44)[a]	<0.0001
Time on ventilator (min)	5,161	360 (255–540)[a]	330 (240–450)[a]	502 (350–840)[a]	<0.0001
Postop heart failure	4,672	154 (3.3 %)	34 (1 %)	120 (9.1 %)	<0.0001
Postop myocardial infarction	4,672	70 (1.5 %)	27 (0.8 %)	43 (3.3 %)	<0.0001
Postop sepsis	4,672	38 (0.8 %)	11 (0.3 %)	27 (2 %)	<0.0001
Postop permanent stroke	4,672	23 (0.5 %)	13 (0 %)	10 (1 %)	0.104
Postop transient cerebral ischaemia	4,672	28 (0.6 %)	17 (0.5 %)	11 (0.8 %)	0.194
Postop atrial fibrillation	4,672	1,139 (24.4 %)	754 (22.5 %)	385 (29.2 %)	<0.0001
Re-operation for bleeding	5,258	123 (2.3 %)	0 (0.1)	0.1 (0.3)	<0.0001
Postoperative mediastinitis	5,258	56 (1.1 %)	33 (1 %)	23 (2 %)	0.049
Haemoglobin at discharge (g/l)	5,190	103 (11.2)	102.8 (11.4)	103.2 (11)	0.247
RIFLE—risk at discharge	5,228	500 (9.6 %)	320 (9 %)	180 (12 %)	<0.0001
RIFLE—injury at discharge	5,228	117 (2.2 %)	74 (2 %)	43 (3 %)	0.07
RIFLE—failure at discharge	5,228	95 (1.8 %)	50 (1 %)	45 (3 %)	<0.0001
Units of RBC transfused	5,261	1.6 (1.9)	0.96 (1.4)	2.98 (2.1)	<0.0001
No. receiving RBCs	5,261	2,618 (49.8 %)	1,381 (37 %)	1,237 (80.7 %)	<0.0001
Units of plasma transfused	5,261	1.2 (2.9)	0 (0)	4.2 (4)	<0.0001
No. receiving plasma	5,261	1,533 (29.1 %)	0 (0 %)	1,533 (100 %)	<0.0001
Units of platelets transfused	5,261	0.2 (0.7)	0.1 (0.3)	0.5 (1)	<0.0001
No. receiving platelets	5,261	418 (7.9 %)	93 (2.5 %)	325 (21.2 %)	<0.0001

Legend: postoperative outcome of the study population presented as the mean (standard deviation) for continuous variables or number (percent) for dichotomous variables together with a comparison between patients receiving red blood cells and those not receiving red blood cells

RIFLE risk-injury-failure-loss-end stage, *RBCs* red blood cells

[a] Outcome variables that are strongly skewed are presented as the median and the range between first and third quartiles

Table 3 Cox proportional hazard model

	HR	95 % CI	Wald	*p*
Age (years)	1.051	1.04–1.06	68.5	<0.001
COPD	1.669	1.33–2.10	19.5	<0.001
Diabetes	1.518	1.25–1.84	18.3	<0.001
History of cerebrovascular disease	1.296	1.01–1.67	4.1	0.044
Peripheral vascular disease	1.651	1.34–2.03	22.5	<0.001
Female gender	0.623	0.50–0.78	17.6	<0.001
Previous myocardial infarction	1.315	1.09–1.58	8.4	0.004
LVEF <30 %	2.178	1.69–2.81	36.1	<0.001
Previous CABG	1.686	1.06–2.69	4.8	0.029
Perfusion time (min)	1.005	1.00–1.01	6.2	0.013
Permanent stroke	2.810	1.25–6.31	6.3	0.012
Preoperative haemoglobin (g/l)	0.985	0.98–0.99	21.4	<0.001
Preoperative eGFR (ml/min/1.73 m^2)	0.990	0.99–0.99	20.3	<0.001
RBC transfusion	1.007	0.96–1.06	0.1	0.775
Plasma transfusion	1.060	1.04–1.09	23.1	<0.001
Platelet transfusion	0.817	0.70–0.96	6.4	0.011

Legend: results of Cox proportional hazard analysis. *HR* hazard ratio, *COPD* chronic obstructive pulmonary disease, *CABG* coronary artery bypass grafting, *eGFR* estimated glomerular filtration rate, *RBC* red blood cell

became 1.18 (95 % CI 0.91–1.54, $p = 0.212$), the HR for 3–4 plasma transfusions became 1.28 (95 % CI 0.95–1.75, $p = 0.107$), the HR for 5–6 plasma transfusions became 1.142 (95 % CI 0.70–1.87, $p = 0.599$), and the HR for 7 or more plasma transfusions became 1.710 (95 % CI 1.21–2.42, $p = 0.003$, Fig. 2).

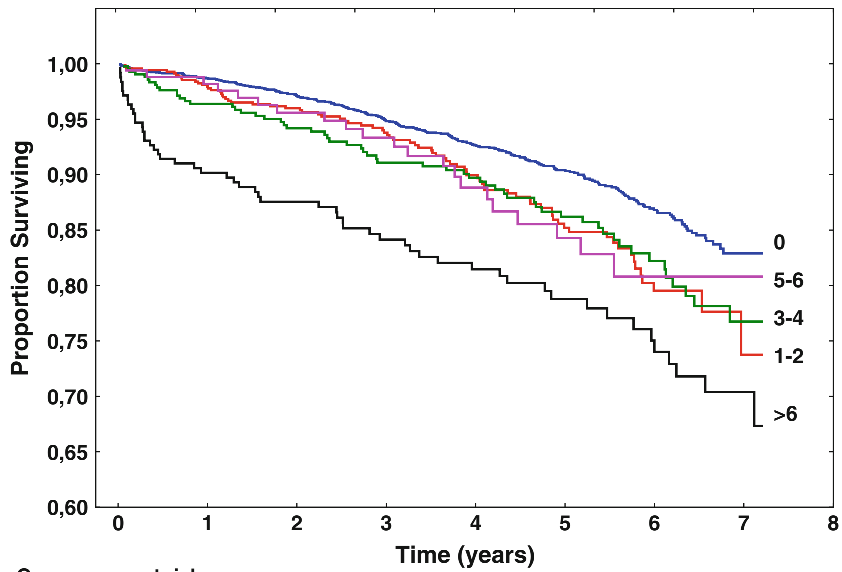
The result of the interaction analysis only revealed one significant interaction, and it was the group that received RBC and plasma transfusion, but not platelet transfusion, with a HR of 1.52 (95 % CI 1.20–1.95, $p = <0.001$). The group that received only RBC transfusion had a HR of 1.15 (95 % CI 0.89–1.48, $p = 0.266$). None of the other groups were significant (Table 4).

Discussion

Two principal findings were made in this study. First, we found an association between plasma transfusion and increased long-term mortality. Secondly, we found no association between RBC transfusion and long-term survival. These findings challenge the current view on transfusion after cardiac surgery.

The finding that there was no significant correlation between RBC transfusion and long-term survival is in contrast to the results of the majority of studies published to date. Previous studies have reported hazards ratios for long-term mortality between 1.03 and 2.4, depending on the study design and whether transfusion was entered as a dichotomous variable or continuous variable [1, 2, 4, 6–8,

Fig. 2 Unadjusted Kaplan-Meier *curves* divided into patients receiving different amounts of plasma (0 = no plasma transfusion, 1–2, 3–4, 5–6 refers to corresponding units of plasma given, >6 refers to 7 or more units transfused)



Group	no. at risk							
0	3728	3409	2842	2263	1700	1157	648	138
1-2	701	633	531	426	337	228	112	17
3.4	420	371	331	283	256	188	117	52
5-6	167	160	137	117	86	64	29	9
>6	245	213	191	165	142	103	72	36
Total	5261	4786	4032	3254	2521	1740	978	252

Table 4 Interaction analysis

	n	HR	95 % CI	Wald	*p*
RBC yes/PLA yes/TRC yes	304	0.95	0.61–1.47	0.06	0.812
RBC yes/PLA yes/TRC no	933	1.52	1.20–1.95	11.6	<0.001
RBC yes/PLA no/TRC yes	63	1.19	0.48–2.93	0.14	0.705
RBC yes/PLA no/TRC no	1,318	1.15	0.89–1.48	1.23	0.266
RBC no/PLA yes/TRC yes	21	1.98	0.49–8.01	0.91	0.339
RBC no/PLA no/TRC yes	30	0.81	0.1–5.80	0.04	0.831
RBC no/PLA yes/TRC no	275	1.22	0.83–1.79	0.32	0.320

Interaction between different types of transfusion (*RBC* red blood cells, *PLA* plasma, *TRC* platelets) when the variables were added to the final Cox model. Number of patients in each group is also presented

10, 20, 21]. In a previous study on the same cohort, we found a hazard ratio of 1.10 when using a model similar to that in other studies, but when we included preoperative eGFR and haemoglobin levels the hazard ratio decreased to 1.05 and was no longer significant [10]. By increasing the number of potential risk factors and including all types of transfusion, the present study revealed a hazard ratio of 1.007 for RBC transfusion with a confidence interval of 0.96–1.06, thereby further diminishing any risk associated with RBC transfusion. From a statistical point of view, it appears that RBC transfusion and plasma transfusion interact strongly. When including plasma transfusion in the model, the risk associated with RBC transfusion was further decreased, since our model revealed that the associated risk from RBC transfusion actually belonged to plasma transfusion. In an editorial, Engoren commented on our previous article and concluded that just showing that transfusion of RBC is not dangerous may not be enough [10, 22]. Instead, we should try to find improved outcomes of transfusions in these patients. The findings of this study take at least one step in that direction.

The results of the present study indicate that plasma transfusion in cardiac surgery is associated with decreased long-term survival and that this risk is found in patients receiving many plasma transfusions. Similar findings that plasma transfusion is associated with worse outcome have been reported in a few studies on patient populations mostly receiving massive transfusions. A study based on the trauma-associated severe haemorrhage (TASH) score [23], which was used to objectively determine which patients would benefit or exhibit increased complications as a result of a high plasma:RBC ratio after severe trauma, demonstrated that the outcome was indeed dependent on the TASH score, where a high plasma:RBC ratio was associated with an adverse outcome [24]. However, in a recent meta-analysis, plasma transfusion was associated with a reduction in the risk of death and multiorgan failure in patients undergoing massive transfusions. The results were based on studies judged to have “very-low-quality” evidence [13]. Plasma transfusion also significantly reduced the risk of multiorgan failure, but increased the risk of acute lung injury [13]. In patients undergoing cardiac surgery without the need for massive transfusions, plasma transfusion was found to markedly increase short-term mortality [12, 25]. Our finding that plasma transfusion is associated with decreased long-term survival seems to be in agreement with the reports of other authors on short-term outcome. However, no one has yet been able to ascertain whether it is the plasma per se or the need for plasma transfusion that carries the risk. Significant risk were only found in patients receiving seven or more units of plasma, and in these patients the high rate of plasma transfusion might be explained by a comorbidity and not a bleeding. Therefore, we should be careful in drawing any far-reaching conclusions from this finding.

Platelet transfusion was found to be associated with decreased mortality, although previous studies have reported conflicting results [3, 12, 26]. The clinical indication for platelet transfusion intra- and postoperatively in cardiac surgery is mainly bleeding, and platelets are often administered together with plasma and/or RBC transfusion, which makes the situation more complex. It was recently reported that fresh frozen plasma and platelet transfusion carry a higher risk of short-term mortality than transfusions of packed red blood cells [12]. Morphological, biochemical and functional changes occur in platelets during storage [27]. However, platelet storage time was not found to be associated with adverse short-term outcomes, decreased long-term survival or infections after cardiac surgery [28]. Our finding that platelet transfusion may be associated with better outcome is difficult to explain based on the information available from our studies and those of others, and could be a coincidental finding of little clinical relevance. However, one explanation could be that platelet transfusion is a surrogate marker for reduced or impaired platelet function, which may be pharmacologically induced or naturally low. The assumption that the need for platelet transfusion is related to lower platelet function and consequently associated with a lower incidence of future thromboembolic events, thereby increasing the chances of longer life, is, with the present knowledge, theoretical. In addition, we did not have access to information on preoperative antiplatelet therapy, further precluding any potential relation from being revealed.

This study has some limitations. First of all, a larger sample size would have been preferable to more accurately determine the relationship between transfusion and outcome. Secondly, some concern has been expressed about the storage time of RBCs and plasma and the effect on outcome after cardiac surgery. For example, van Straten et al. [29] have shown that a longer plasma storage time is a risk factor for early but not late mortality in CABG patients, while Koch found that the age of RBCs affected long-term survival negatively [30]. Unfortunately, we did not have access to the age of the blood products given. Thirdly, we did not distinguish between fresh frozen plasma, fresh plasma or leukocyte-depleted blood products in this study. The use of leukocyte-depleted blood products has been routine for several years in patients undergoing cardiac surgery at our clinic, but we cannot guarantee that some patients were given non-leukocyte-depleted transfusions. It could also be argued that by excluding patients receiving eight or more units of RBCs, we excluded the patients exposed to the largest transfusions, thereby missing relevant information. We therefore included the patients receiving more than eight units in a post hoc analysis, and while the hazard ratio for RBC transfusion remained virtually the same (1.005, 95 % CI 0.98–1.03), the value for plasma decreased from 1.060 (95 % CI 1.04–1.09) to 1.028 (95 % CI 1.02–1.04). However, we still believe that in this study it is not relevant to analyse the potential risks of transfusion in patients requiring a transfusion to survive. The aim of the present study was to investigate the long-term effects of blood product transfusion in cardiac surgery patients, and we therefore excluded patients who died within 7 days of surgery. In a post hoc analysis, the patients who died during the first week were included, and it did not change the results regarding transfusion and outcome. Moreover, patients dying during the first week are a heterogeneous group, often representing outliers in several ways, and may jeopardise the proportional hazard assumption. The relevant clinical question is whether a different transfusion regimen could have prevented any of the patients from dying within 7 days and changed the outcome of the analysis. This is a limitation in retrospective studies such as this. To shed some light on the issue, a separate analysis should be performed on this subgroup. On the other hand, one strength of the study is the completeness of the database, where important variables have a more than 99.5 % completion rate.

The results of this study emphasise the fundamental differences between different blood products by showing that long-term outcome differs depending on the type of transfusion given. Reliable and accurate data on the long-term risks of transfusions are paramount in making valid transfusion recommendations, and our findings may serve as a step in that direction as long as firmer evidence in form of randomised trials is lacking.

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Conflicts of interest Henrik Bjursten has a vested interest in ErySave AB. Lars Algotsson lectures for Orion Pharma AB and Abbott Scandinavia AB. The other authors have no conflicts of interest to report.

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