Association between anemia and blood transfusion with long-term mortality following cardiac surgery

Running Head: Preoperative anemia and cardiac surgery

Hari Padmanabhan,[1] MRCP

Matthew J. Brookes,[1] PhD

Alan M. Nevill [2] PhD

Heyman Luckraz, [4] FRCS

Departments of [1]Gastroenterology, Heart & Lung Centre, Wolverhampton, WV10 0QP United Kingdom, [2]Research Professor in the Faculty of Education Health and Wellbeing, University of Wolverhampton, Walsall, United Kingdom and [4]Cardiothoracic Surgery Department, Heart Centre, American Hospital Dubai, Oud Metha, Dubai, United Arab Emirates.

Funding: None

Conflicts of Interest: none

Word count: 4759

Corresponding author: Hari Padmanabhan, MRCP
Consultant, Department of Gastroenterology, Royal Wolverhampton NHS Trust
Wolverhampton, WV10 0QP
Phone: + 44 1902694112   Fax: + 44 1543 576957
Email: Hari.Padmanabhan@nhs.net

Abstract

Background

Preoperative anaemia and red blood cell (RBC) transfusion are both associated with in-hospital mortality after cardiac surgery. The aim of this study was to investigate the interactions between preoperative anaemia and RBC transfusion, and their effect on the long-term survival of patients undergoing cardiac surgery.

Methods

Between 2005 and 2012, 1,170 patients with anaemia who underwent elective or urgent cardiac surgery were included. A matched group of 1,170 non-anaemic patients was used as a control group. A binary logistic regression model was used.

Results

The median follow-up period was 64 (range 0-127) months. Anaemic patients had higher mortality (45%, n=526) than non-anaemic patients (32%, n=374; p<0.001). Preoperative anaemia was independently associated with long-term mortality (odds ratio [OR]: 1.70; 95% confidence interval [CI]: 1.46-2.1; p<0.001), with both moderate (OR: 2.27; 95% CI: 1.72-2.99; p<0.001) and mild anaemia (OR: 1.39; 95% CI: 1.13-1.71; p=002) contributing significantly. RBC transfusion was not associated with long-term mortality (OR: 1.07; 95% CI: 0.88-1.31; p=0.49). There was no interaction between preoperative anaemia and RBC transfusion (p=0.947).

Conclusion

Long-term mortality is significantly high in patients who are anaemic, regardless of their transfusion status. Preoperative anaemia is a strong, independent predictor of mortality and therefore should be managed prior to cardiac surgery.

Introduction

Preoperative anaemia is common, and a previous study at our center showed that 16% of patients who underwent elective cardiac surgery had preoperative anaemia [1]. In the last two decades, several observational studies have shown that preoperative anaemia was associated with adverse outcomes postoperatively [1-10]. Although there are disparities in small studies[11-13] that did not demonstrate a relationship between anaemia and in-hospital mortality, large published studies found this association [1, 2, 6, 10, 14]. A recent meta-analysis by Fowler et al. showed that anaemia was associated with an increased risk of in-hospital death for patients undergoing cardiac surgery [15]. In addition to anaemia, patients undergoing cardiac surgery may have other established risk factors such as advanced age, female sex, small body surface area, poor left ventricular ejection fraction, renal function impairment, congestive heart failure, and unstable angina, which may affect short-term mortality [2, 7]. In addition to being a risk factor, preoperative anaemia could be a marker of underlying disease. Propensity matching allows for a comparison of anaemic and non-anaemic patients who have the same preoperative and intraoperative risk profile. Using this method, three large studies have shown that preoperative anaemia is associated with short-term mortality [1-3, 16]. However, there is a paucity of data on long-term outcomes that are associated with preoperative anaemia.

Red blood cell (RBC) transfusion depends not only on the volume of perioperative blood loss but also on the preoperative presence of anaemia. There is evidence to support that intraoperative RBC transfusion is associated with both short- and long-term adverse outcomes[17-19]. However, the relative contribution of preoperative anaemia and RBC transfusion to, as well as their effect on, long-term mortality is uncertain.

Therefore, we investigated the impact of preoperative anaemia and RBC transfusion on long-term mortality in a large, well-defined, propensity-matched cohort of patients with extended follow-up who underwent elective or urgent cardiac surgery.

Methods

This study was approved by our institutional review board, and the need to obtain informed consent from the patients was waived. This was an observational, retrospective, propensity matched, case-control study of prospectively collected data that were retrieved from our cardiac surgery database (PATS/Dendrite). Patients undergoing elective or urgent cardiac surgery (isolated coronary artery bypass grafting [CABG], isolated valve, combined valve and CABG, and other complex cardiac surgeries) between 2005 and 2012 were included in this study. Patients who had emergency procedures were excluded from the analysis.

Patients were considered to have anaemia based on the World Health Organization's (WHO) criteria: a preoperative hemoglobin level less than 13 g/dL for men and less than 12 g/dL for women. Anaemic patients were sub-classified as having mild (men: 110-129 g/dL; women: 110-119 g/dL), moderate (men: 80-109 g/dL; women: 80-109 g/dL), or severe anaemia (men: <80 g/dL; women: <80 g/dL) using the WHO recommendations. These patients were matched with non-anemic (control) using a logistic regression model. The latter was used to generate a propensity score for each patient. The exposure variables included age, sex, chronic obstructive pulmonary disease, pre-operative neurological dysfunction, extracardiac arteriopathy, previous cardiac surgery, active endocarditis, recent myocardial infarction, critical preoperative state, unstable angina requiring either intravenous nitrates and / or heparin, left ventricular dysfunction, pulmonary hypertension, urgency of the procedure, cardiac procedure, surgery on the thoracic aorta, Cardiopulmonary bypass time (CPB) and Euroscore. CPB time, pre-operative haemoglobin and EuroScore were log transformed prior to entry into the model. For each patient in the anaemic group, an individual was selected in the non-anaemic group by matching on the log of the estimated propensity score, using a nearest neighbour matching algorithm with callipers (an interval) of maximum width of 0.2 standard deviations (SDs). The distribution of all model factors was compared in the two groups to assess the success of the propensity score model. In line with recommendations, the balance in the covariates across the two groups was considered achieved if the standardised differences were less than 10%.

Participants in both the anaemic and non-anaemic groups were sub-classified into four groups: 1. anaemic patients undergoing RBC transfusion, 2. non-anaemic patients undergoing RBC transfusion 3. anaemic patients who did not undergo RBC transfusion, and 4. non-anaemic patients who did not undergo RBC transfusion. Patients in this cohort were followed-up until death or December 31, 2016, whichever occurred first. The median follow-up period was 64 (range 0-127) months. Combined procedures include the following procedures: CABG + valve (aortic, mitral, tricuspid), multiple valve surgeries (Aortic, mitral, tricuspid) CABG +/- valve along with procedures on the aorta, and valve +/- CABG + atrial fibrillation ablation treatment). Patients who were operated upon during the same hospital admission but not within 24 hours after admission were categorized as having an “urgent” procedure.

The primary aim was to investigate the association between preoperative anaemia and long-term mortality for patients undergoing cardiac surgery. The impact of various levels of anaemia (mild, moderate, and severe) on long-term mortality was also examined. Data on deaths that were registered between 2005 and 2016 were obtained from the National Institute for Cardiovascular Outcomes Research (NICOR) and the UK National Health Service Summary Care Records. We also studied the effect of the established risk factors of anaemia (age, female sex, renal replacement therapy, diabetes, and arteriopathy) on long-term mortality. The secondary aims were to explore the association between blood transfusion (zero, one or two, and > two units of blood) and long-term mortality and to determine the relative contribution of preoperative anaemia and RBC transfusion and their interactions on long-term mortality.

Categorical data are expressed as percentages, and differences between the two groups were assessed using the χ^2 test of independence. Continuous variables are expressed as the mean (standard deviation) or median (range) for Gaussian and skewed distributed data, respectively. Likewise, the groups were compared using the t-test or a non-parametric (Mann-Whitney U) test. The association between preoperative anaemia and long-term mortality was analyzed using a logistic regression analysis. The following confounding factors were entered in a multivariate logistic model to assess the relationship between preoperative anaemia and outcomes: age, sex, preoperative hemoglobin level, diabetes status, logistic EuroSCORE score, cardiopulmonary bypass time, arteriopathy, re-exploration, blood transfusion, and body mass index (BMI) (entered together with the inverted BMI to detect the presence of a nadir) [20]. The logit model predicting the odds of mortality contained the terms “a x BMI” and “b/BMI”. Elementary differential calculus was used to predict when mortality was at a minimum, expressed as BMI = Sqrt (b/a). The statistical analyses were performed using SPSS version 15 software (SPSS Inc., Chicago, IL, USA). An interaction term was added to the regression model to expand our understanding of the relationship between preoperative anaemia and blood transfusion, resulting in four combinations: mild anaemia/one or two units of transfusion, mild anaemia/> two units of transfusion, moderate anaemia/one or two units of transfusion, and moderate anaemia/>two units of transfusion.

Results

During the study period, 7,150 patients underwent elective or urgent cardiac surgery. A total of 1,170 patients (16%) had anaemia. Using the propensity score matching method, we extracted data on 1,170 non-anaemic patients from the original dataset. The preoperative characteristics of the matched anaemic (n=1,170) and non-anaemic (n=1,170) patients who had cardiac surgery are shown in Table 1. As per the WHO classification, 771 (65.9%) patients had mild anaemia, 393 (33.6%) patients had moderate anaemia, and only 6 patients with severe anaemia underwent cardiac surgery. Of the total population of 2,340 patients, 47.7% (n=1,115) received transfusions, and less than half of these (n=455) received either one or two units of transfusion. The proportion of patients in the anaemia group requiring blood transfusion and the number of units that were transfused were significantly higher than in those in the non-anaemia group (57.4% and 38%, respectively, $p<0.01$; and 3,534 vs. 1,978 units, respectively, $p<0.01$).

Nine hundred (38.5%) patients died during the extended follow-up period (median 64 (range 0-127) months). Anaemic patients had higher mortality (45%, n=526) than non-anaemic patients (32%, n=374; $p<0.001$). After controlling for risk factors (age, sex, BMI, diabetes, logistic EuroSCORE score, renal replacement therapy, arteriopathy, cardiopulmonary bypass time, re-exploration, preoperative hemoglobin level, and amount of blood transfusion), the binary logistic regression analysis demonstrated that preoperative anaemia was independently associated with long-term mortality (odds ratio [OR]: 1.70; 95% confidence interval [CI]: 1.46-2.1; $p<0.001$) (Table 2). The subgroup analysis of participants with anaemia displayed that mild and moderate anaemia were significant predictors of mortality, with ORs of 1.39 (95% CI: 1.13-1.71; p=002) and 2.27 (95% CI: 1.72-2.99; $p<0.001$), respectively (Table 3).

The logistic regression analysis also demonstrated that blood transfusion was not associated with long-term mortality (OR: 1.07; 95% CI: 0.88-1.31; p=0.49) (Table 2). The subgroup analysis of patients who underwent transfusion showed that transfusion of more than two units of blood increased the risk of death by 1.3-fold (95% CI: 1.03-1.66; p=0.02).

However, transfusion of either one or two units of blood did not seem to be associated with mortality (OR: 0.86; 95% CI: 0.67-1.11; p=0.26) (Table 3).

The four-group logistic regression analysis demonstrated that anaemic patients who received blood transfusion (OR: 1.87; 95% CI: 1.46-2.40; p<0.001) had approximately the same risk of death as anaemic patients who did not receive blood transfusion (OR: 1.62; 95% CI: 1.24-2.11; p<0.001) (Table 4). There was no interaction between preoperative anaemia and RBC transfusion (p=0.95). The assessments of various combinations between preoperative anaemia and RBC transfusion were as follows: mild preoperative anaemia and receiving one or two units of RBC transfusion (OR: 1.03; 95% CI: 0.60-1.78; p=0.91), mild preoperative anaemia and receiving > two units of RBC transfusion (OR: 1.03; 95% CI: 0.63-1.69; p=0.89), moderate preoperative anaemia and receiving one or two units of RBC transfusion (OR: 1.23; 95% CI: 0.58-2.60; p=0.59), and moderate preoperative anaemia and receiving > two units of RBC transfusion (OR: 0.81; 95% CI: 0.44-1.49; p=0.49) (Table 5).

In addition, long-term mortality was also influenced by age, sex, diabetes status, logistic EuroSCORE score, use of renal replacement therapy, peripheral vascular disease, and cardiopulmonary bypass time (Table 2). There was a “U”-shaped association between BMI and mortality with mortality lowest at around BMI=27 and increased mortality is associated with relatively low and high BMI values (p=0.04) (Table 4). The long-term survival of patients, depending on anaemia and/or transfusion, was plotted as a Kaplan-Meier curve (Figures 1 & 2).

Discussion

This study showed that preoperative anaemia was independently associated with long-term mortality, regardless of whether or not they received RBC transfusion. On the other hand, blood transfusion was not associated with mortality. There was no interaction between preoperative anaemia and blood transfusion on long-term mortality.

Several studies have shown that preoperative anaemia adversely affects in-hospital or 30-day mortality after cardiac surgery [1, 2, 5, 16]. van Straten et al. found that late mortality (all-cause mortality beyond 30 days) after CABG was considerably higher in patients with preoperative anaemia than in those without (43.8% vs. 18.1%, respectively, $p<0.001$) [6]. von Heymann et al. performed a 6-year observational cohort study showing that even mild anaemia not only influences short-term mortality but also affects long-term survival (OR: 1.44; 95% CI: 1.20-1.73; $p<0.001$) [21]. Likewise, our study, which had a follow-up period of up to 11 years, confirmed that mild and moderate anaemia were associated with poor long-term survival.

Our analysis did not show any association between blood transfusion and mortality, in general, while transfusion of more than two units of blood increased the risk of death by 1.3-fold. In contrast, Paone et al. showed that transfusion of one to two units of blood was associated with increased mortality and morbidity in their patient population [22]. However, the patients in this study who did not receive transfusion were young and had a higher BMI, higher preoperative hemoglobin level, lower prevalence of various co-morbidities, more elective procedures, and higher ejection fraction than those who received one to two units of transfusion.

To separate the effects of anaemia and blood transfusion, we studied the interaction between these two factors with respect to mortality. Preoperative anaemia appeared to be detrimental for long-term survival, because anaemic patients who received transfusion had the same increase in long-term mortality as anaemic patients who did not receive transfusion. In contrast, patients who were non-anaemic and received blood transfusion did not experience an increase in risk of death, suggesting that blood transfusion is probably safe.

In addition to preoperative anaemia, long-term mortality is also associated with other risk factors that include age, sex, diabetes status, logistic EuroSCORE score, renal replacement therapy, peripheral vascular disease, cardiopulmonary bypass time time and having either excessively high or low BMI (Figure 1) that identified the nadir to be marginally overweight at 27 kg.m-2). Preoperative anaemia is the strongest risk factor that is modifiable, although it is not currently included in risk stratification models such as the EuroSCORE scoring system and Society of Thoracic Surgeons prediction of the risk of mortality. The present findings support the addition of preoperative anaemia to future risk models.

The main assets of this study lie in the number of patients who were included and its detailed data collection. Anaemic patients were matched against non-anaemic patients using propensity score methods to adjust for confounders, and we used statistical methods such as a binary logistic regression analysis. However, this study had some limitations. First, it was a retrospective study that relied on the completeness or accuracy of recorded information. Second, despite the use of a propensity-score matching method and a sophisticated logistic regression analysis, our data were observational and may still be prone to unknown confounders. Third, it was not feasible to study either the cause of preoperative anaemia or the reasons for blood transfusion in this study.

In conclusion, our findings suggest that anaemia is a serious condition that negatively impacts the long-term survival of patients who undergo cardiac surgery. We have previously shown that anaemic patients experience worse outcomes and potentially consume significantly more resources during their cardiac surgical stay than non-anaemic patients [1]. We emphasize the need for future randomized studies to treat patients with preoperative anaemia, because its correction could improve the outcomes of cardiac surgery.

Disclosures

The research department of M.J.B. has received grant support from Syner-Med (UK) and Vifor Pharma (Switzerland). M.J.B. has received honoraria and travel support for consulting or lecturing from Vifor Pharma and Merck Sharp and Dohme Limited (UK). H.L, H.P and A.M.N have no conflict of interests to declare in relation to this study. The views expressed are those of the authors only.

Acknowledgement

We would like to express our gratitude to all staff (nurses, perfusionists, para-medical staff, Junior Doctors, anaesthetists and surgeons) of the cardiothoracic surgical Unit of the Heart & Lung Centre, Wolverhampton for their contribution in the management of patients treated at our institution. We would also like to acknowledge the help of Sarah Pickford (Senior Cardiac Audit Officer) and NICOR in providing the data for the long-term survival.

References

1. Padmanabhan H, Aktuerk D, Brookes MJ et al. Anaemia in cardiac surgery: next target for mortality and morbidity improvement? *Asian Cardiovasc Thorac Ann* 2016; 24: 12-17.

2. Ranucci M, Di Dedda U, Castelvecchio S, Menicanti L, Frigiola A, Pelissero G. Impact of preoperative anaemia on outcome in adult cardiac surgery: a propensity-matched analysis. *Ann Thorac Surg* 2012; 94: 1134-1141.

3. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anaemia in cardiac surgery: a multicenter cohort study. *Circulation* 2008; 117: 478-484.

4. Zindrou D, Taylor KM, Bagger JP. Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. *Lancet* 2002; 359: 1747-1748.

5. Hung M, Besser M, Sharples LD, Nair SK, Klein AA. The prevalence and association with transfusion, intensive care unit stay and mortality of pre-operative anaemia in a cohort of cardiac surgery patients. *Anaesthesia* 2011; 66: 812-818.

6. van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. *Circulation* 2009; 120: 118-125.

7. Kulier A, Levin J, Moser R et al. Impact of preoperative anaemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation* 2007; 116: 471-479.

8. De Santo L, Romano G, Della Corte A et al. Preoperative anaemia in patients undergoing coronary artery bypass grafting predicts acute kidney injury. *J Thorac Cardiovasc Surg* 2009; 138: 965-970.

9. Boening A, Boedeker RH, Scheibelhut C, Rietzschel J, Roth P, Schonburg M. Anaemia before coronary artery bypass surgery as additional risk factor increases the perioperative risk. *Ann Thorac Surg* 2011; 92: 805-810.

10. Klein AA, Collier TJ, Brar MS et al. The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK - the first Association of Cardiothoracic Anaesthetists national audit. *Anaesthesia* 2016; 71: 627-635.

11. Munoz M AD, Gomez-Ramirez S, Hernandez P, Garcia-Erce JA, Leal-Noval SR. Preoperative anaemia in elective cardiac surgery: prevalence, risk factors, and influence on postoperative outcome. *Transfus Altern Transfus Med* 2010; 11: 47–56.

12. Carrascal Y, Maroto L, Rey J et al. Impact of preoperative anaemia on cardiac surgery in octogenarians. *Interact Cardiovasc Thorac Surg* 2010; 10: 249-255.

13. Kim CJ, Connell H, McGeorge AD, Hu R. Prevalence of preoperative anaemia in patients having first-time cardiac surgery and its impact on clinical outcome. A retrospective observational study. *Perfusion* 2015; 30: 277-283.

14. Bell ML, Grunwald GK, Baltz JH et al. Does preoperative hemoglobin independently predict short-term outcomes after coronary artery bypass graft surgery? *Ann Thorac Surg* 2008; 86: 1415-1423.

15. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015; 102: 1314-1324.

16. Joshi SS, George A, Manasa D, Savita HM, Krishna PT, Jagadeesh AM. Propensity-matched analysis of association between preoperative anaemia and in-hospital mortality in cardiac surgical patients undergoing valvular heart surgeries. *Ann Card Anaesth* 2015; 18: 373-379.

17. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; 116: 2544-2552.

18. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg* 2002; 74: 1180-1186.

19. Koch CG, Li L, Duncan AI et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006; 34: 1608-1616.

20. Durazo-arvizu R, McGee D, Li Z, Cooper R. Establishing the nadir of the body mass index-mortality relationship: a case study. *J Am Stat Assoc* 1997; 92: 1,312-319.

21. von Heymann C, Kaufner L, Sander M et al. Does the severity of preoperative anaemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? *J Thorac Cardiovasc Surg* 2016; 152: 1412-1420.

22. Paone G, Likosky DS, Brewer R et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg* 2014; 97: 87-93; discussion 93-84.

Tables

Table 1 Pre- & intra-operative characteristics of the patients in the two groups

Patient characteristics	**Anaemic (n=1170)**	**Non-anaemic (n=1170)**	**p-Value**
Preoperative Haemoglobin* (g/dl)	11.2 (1.0)	13.9 (1.1)	<0.01
Age* (years)	68.7 (10.6)	69.9 (9.4)	0.1
Male (n, %)	868 (74%)	833 (71%)	0.1
Peripheral vascular disease (n, %)	271 (23%)	300 (26%)	0.2
Non- smoker (n, %)	433 (37%)	468 (40%)	0.3
COPD (n, %)	196 (17%0	208 (18%)	0.5
Impaired left ventricle (n, %)	481 (41%)	511 (44%)	0.3
Elective surgery (n, %)	576 (49%)	621 (53%)	0.06
Re-exploration Surgery (n, %)	65 (5.6%)	49 (4.2%)	0.07
Use of IV nitrates till surgery (n, %)	81 (6.9%)	76 (6.5%)	0.8
OPCAB (n, %)	97 (8.3%)	83 (7.1%)	0.6
CPB time* (minutes)	106 (62)	106 (63)	0.7
Log Euroscore**	6.2 (0.9, 75.5)	6.2 (0.9, 74.4)	0.99

*denotes mean (SD)

**denotes median (range)

COPD: chronic obstructive pulmonary disease; OPCAB: off-pump coronary artery bypass grafting;

CPB: cardiopulmonary bypass

Table 2 Association between preoperative anaemia and blood transfusion, and late mortality after cardiac surgery, analyzed using binary logistic regression analyses

Variables	**p value**	**OR**	**95% CI**
Age (years)	<0.001	1.053	1.041-1.064
Gender (female)	0.057	0.812	0.656-1.006
Diabetes	0.008	1.325	1.075-1.632
Logistic EuroSCORE	<0.001	1.032	1.020-1.044
Renal replacement therapy	<0.001	2.667	1.937-3.663
Peripheral vascular disease	0.014	1.321	1.057-1.647
Cardiopulmonary bypass time	0.016	1.002	1.000-1.004
Re-exploration	0.748	1.058	0.750-1.494
Body mass index	0.739	1.003	0.984-1.023
Preoperative anaemia	<0.001	1.768	1.460-2.140
Blood transfusion	0.492	1.073	0.878-1.311

The baseline category/group included male patients who did not have diabetes, renal replacement, re-exploration, peripheral vascular disease, anaemia, or blood transfusion.

OR, odds ratio; 95% CI, 95% confidence interval.

Table 3 Association between levels of preoperative anaemia and blood transfusion (1 or 2 units Vs > 2 units), and late mortality after cardiac surgery, analyzed using binary logistic regression analyses

Variables	**p value**	**OR**	**95% CI**
Age (years)	<0.001	1.054	1.042-1.066
Gender (female)	0.015	0.762	0.613-0.948
Diabetes	0.011	1.312	1.063-1.618
Logistic EuroSCORE	<0.001	1.028	1.017-1.040
Renal replacement Therapy	<0.001	2.488	1.801-3.436
Peripheral vascular disease	0.011	1.335	1.067-1.667
Cardiopulmonary bypass time	0.028	1.002	1.000-1.004
Re-exploration	0.823	0.961	0.677-1.364
Body mass index	0.779	1.003	0.983-1.023
No Preoperative anaemia	Reference		
Mild Preoperative anaemia	0.002	1.389	1.126-1.713
Moderate Preoperative anaemia	<0.001	2.270	1.724-2.988
No blood transfusion	Reference		
Blood transfusion 1 or 2 units	0.302	0.874	0.677-1.128
Blood transfusion > 2 units	0.027	1.307	1.031-1.656

The baseline category/group included male patients who did not have diabetes, renal replacement, re-exploration, peripheral vascular disease, anaemia, or blood transfusion.

OR, odds ratio; 95% CI, 95% confidence interval

Table 4 Association between preoperative anaemia and blood transfusion, and late mortality (analyzed using four-group logistic regression analyses)

Variables	**p value**	**OR**	**95% CI**
Age (years)	<0.001	1.054	1.042-1.065
Gender (female)	0.034	0.792	0.638-0.983
Diabetes	0.008	1.326	1.076-1.634
Logistic EuroSCORE	<0.001	1.032	1.020-1.044
Renal replacement Therapy	<0.001	2.674	1.946-3.676
Peripheral vascular disease	0.011	1.335	1.068-1.667
Cardiopulmonary bypass time	0.018	1.002	1.000-1.004
Re-exploration	0.758	1.056	0.748-1.491
Body mass index	0.035	1.080	1.006-1.160
Body mass index	0.036	1.006	1.000-1.011
No Anaemia/ No Transfusion	Reference		
Anaemia/ Transfusion	<0.001	1.873	1.463-2.397
No Anaemia/ Transfusion	0.944	0.990	0.745-1.315
Anaemia/ no Transfusion	<0.001	1.620	1.243-2.111

The baseline category/group included male patients who did not have diabetes, renal replacement, re-exploration, peripheral vascular disease, anaemia, or blood transfusion.

OR, odds ratio; 95% CI, 95% confidence interval.

Table 5 Interaction between preoperative anaemia and blood transfusion on long-term mortality, and late mortality (analyzed by adding interaction term to the logistic regression analyses)

Variables	p value	OR	95% CI
Age (years)	<0.001	1.054	1.042-1.065
Sex (female)	0.014	0.759	0.610-0.945
Diabetes	0.013	1.305	1.057-1.610
Logistic EuroSCORE	<0.001	1.028	1.017-1.040
Renal replacement Therapy	<0.001	2.475	1.795-3.425
Peripheral vascular disease	0.012	1.333	1.066-1.667
Cardiopulmonary bypass time	0.029	1.002	0.982-1.022
Re-exploration	0.809	0.958	0.674-1.360
Body mass index	0.843	1.002	0.982-1.022
Interaction between mild anaemia and one or two units of RBC transfusion	0.914	1.031	0.596-1.783
Interaction between mild anaemia and > two units of RBC transfusion	0.893	1.034	0.633-1.688
Interaction between moderate anaemia and one or two units of RBC transfusion	0.587	1.231	0.582-2.603
Interaction between moderate anaemia and > two units of RBC transfusion	0.491	0.807	0.438-1.486

The baseline category/group included male patients who did not have diabetes, renal replacement, re-exploration, peripheral vascular disease, anaemia, or blood transfusion.

OR, odds ratio; 95% CI, 95% confidence interval.

Legends

Figure 1

Long-term survival of patients depending on presence or absence of anaemia are illustrated as Kaplan-Meier curves

Figure 2

Long-term survival of patients depending on anaemia and/or transfusion are illustrated as Kaplan-Meier curves