

Preoperative Anemia is Associated with Increased Intraoperative Mortality in Patients Undergoing Cardiac Surgery

Arwa Z. Al-Riyami¹, Balan Baskaran², Sathiya M. Panchatcharam³ and Hilal Al-Sabti^{2,4*}

¹Department of Hematology, Sultan Qaboos University Hospital, Muscat, Oman

²Department of Surgery, Division of Cardiothoracic Surgery, Sultan Qaboos University Hospital, Muscat, Oman

³Research Section, Medical Simulation and Skills Development Centre, Oman Medical Specialty Board, Muscat, Oman

⁴Oman Medical Specialty Board, Muscat, Oman

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ABSTRACT

Objectives: We sought to investigate the incidence of preoperative anemia in cardiac surgery and its association with outcomes. **Methods:** A retrospective review of clinical, laboratory, and transfusion data for all patients who underwent cardiac surgery at Sultan Qaboos University Hospital between 2008 and 2014 was performed. Patients were divided into two groups, anemic and non-anemic, with anemia defined as hemoglobin levels < 13 g/dL (males) and < 12 g/dL (females). Clinical variables were compared using chi-square and independent *t*-test. Factors influencing preoperative mortality were analyzed using multivariate binary logistics regression.

Results: A total of 599 patients (69.9% males and 30.1% females) were included in the study; 69.3% underwent coronary artery bypass surgery. Preoperative anemia was found in 76.1% of females and 26.7% of male patients. Rates of intraoperative red blood cell transfusions were higher among anemic patients (75.9% vs. 52.3%, *p* < 0.001). Anemic patients had a worse risk profile with higher incidence of diabetes mellitus (53.8% vs. 38.9%, *p* < 0.001), congestive heart failure (51.4% vs. 28.3%, *p* < 0.001), arrhythmia (16.5% vs. 8.6%, *p* = 0.004), and cerebrovascular disease (10.0% vs. 4.9%, *p* = 0.015). In addition, they had a higher risk of overall mortality (6.4% vs. 2.6%, *p* = 0.023). Preoperative anemia remained a risk factor for intraoperative mortality after logistic regression (odds ratio = 4.08, 95% confidence interval: 1.43–11.66; *p* = 0.009). **Conclusions:** Preoperative anemia in cardiac surgery is independently associated with increased intraoperative mortality and early readmission rates post-surgery.

Cardiac surgery is associated with significant bleeding and major transfusion demand. While some recommend blood transfusion in severely anemic patients with myocardial injury undergoing cardiac surgery,¹ Red blood cell (RBC) transfusion was shown to be associated with increased morbidity and mortality.^{2,3} Preoperative anemia was associated with increased mortality, morbidity, and postoperative admission to the intensive care unit.⁴ We lack studies that address the risk associated with preoperative anemia in populations from the Arabian Peninsula. We aim to investigate the incidence of anemia in patients undergoing cardiac surgery in our institution and its association with patient outcomes.

METHODS

We conducted a retrospective review of a database for all patients who underwent elective cardiac surgery between 2008 and 2014 at Sultan Qaboos University Hospital in Muscat, Oman. We assessed the clinical, laboratory, and transfusion details of the patients. All patients are transfused intraoperatively and postoperatively as per the previously described local transfusion and blood management protocols.^{5,6} Intraoperative allogeneic RBC transfusion is performed aiming at a hematocrit (Hct) level of > 23%. Patients' demographics included patients' age, gender, height, weight, and underlying comorbidities. Anemia was defined based on the World Health Organization (WHO) criteria as hemoglobin (Hb) < 13 g/dL in males and < 12 g/dL in females.⁷

*Corresponding author: dralsabti@gmail.com

Based on the Hb level and the criteria used, patients were divided into anemic and non-anemic groups. Underlying comorbidities were assessed in both groups, including the presence of diabetes mellitus (DM), congestive heart failure (CHF), arrhythmia, cerebrovascular disease (CVD), smoking history, baseline European System for Cardiac Operative Risk Evaluation (EuroSCORE) 4 or more, baseline ejection fraction (EF), systemic hypertension (HTN), pulmonary HTN, hypercholesterolemia, angina, myocardial infarction (MI), and peripheral vascular disease (PWD). History of use of aspirin or clopidogrel \leq 7 days after surgery was examined. Operative variables assessed included: type of surgery, urgency (elective or not), use of inotropes, use of cardiopulmonary bypass (CPB), CPB time (in minutes), and aortic cross-clamp time. Laboratory investigations compared between the anemic and non-anemic groups included preoperative Hct, preoperative Hb, and preoperative platelet count. Transfusion requirements throughout the intraoperative and the postoperative period up to 24 hours post-surgery were assessed. We assessed the rate of in-hospital morbidity, including renal failure, infection, multisystem failure, in-hospital length of stay, re-exploration surgery, and early readmission rate (within 30 days of surgery). Intraoperative and overall mortality were reviewed. This study was approved by the local ethics committee at the College of Medicine and Health Sciences at the University (MREC #1785).

Variables were presented as means or medians if continuous or proportions if categorical. Based on the Hb level, patients were divided into anemic and non-anemic groups. The baseline characteristics were compared using Student's *t*-test or Mann-Whitney test for continuous variables based on the data distribution and chi-squared test for categorical variables. The impact of anemia on morbidity and mortality was assessed using univariate logistic regression and further adjusted using multivariate logistic regression with other factors. In the multivariable models, collinearity was assessed using variance inflation factor, and none of the variables had a value > 10 . The *p*-value of < 0.050 was considered statistically significant. In addition, the effect of preoperative anemia on the major postoperative complications and outcomes was examined using univariate logistic regression. Cross-clamp time was dealt with as a continuous variable.

Transfusion was compared as a categorical variable between the anemic and non-anemic groups, and the number of RBC units transfused in both groups was analyzed. All descriptive and analytical statistics were performed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 599 patients were included, with a mean age of 58.6 ± 11.8 years. The majority of patients (69.3%) underwent coronary artery bypass graft (CABG) surgery. Cell salvage was used in 62.0% and 80.0% of the cohort. Preoperative anemia, as defined by WHO criteria, was found in 249 (41.6%) patients of whom 56.4% presented with mild anemia (Hb: 11.0–12.9 g/dL), 43.0% with moderate anemia (Hb: 8.0–10.9 g/dL), and 1.0% with severe anemia (Hb < 8.0 g/dL). Surgical and operative characteristics were similar between the anemic and non-anemic groups [Table 1]. Patients who were anemic had significantly lower preoperative Hct and Hb levels with a mean Hct of 34.3 ± 3.8 and mean Hb level of 10.9 ± 1.1 g/dL, respectively [Table 2]. On the other hand, preoperative platelet count was statistically higher in the anemic cohort. The cause of the anemia in the enrolled patients could not be assessed due to the lack of investigations. Intraoperative transfusion of blood products was required in 36.9% of patients. Preoperative anemia was associated with a significantly increased risk of exposure to blood products intraoperatively. Rates of intraoperative RBC transfusions were higher among anemic patients when compared to non-anemic patients (75.9% vs. 52.3%, *p* < 0.001). The median number and range of RBC units transfused was 2 (1,4) in the anemic group and 0 (0,2) in the non-anemic group. Anemic patients had a median in-hospital length of stay of nine days (7.8). Preoperative anemia was a risk factor for early readmission post-surgery (odds ratio (OR) = 2.50, 95% confidence interval (CI): 1.44–4.34; *p* = 0.001). The re-exploration rate was 4.4% in anemic and 2.0% in the non-anemic group, but the difference did not reach statistical significance.

Upon univariate analysis, anemic patients had a worse risk profile before surgery with a higher incidence of DM (53.8% vs. 38.9%, OR = 1.8; *p* < 0.001), CHF (51.4% vs. 28.3%, OR = 2.7; *p*

Table 1: Baseline variables in anemic and non-anemic patients as per the World Health Organization definition for anemia (N = 599).

Variables	Parameter	Results		p-value
		Total N = 599	Anemic 249 (41.6)	Non-anemic 350 (58.4)
Age, years*	58.6 ± 11.8	59.6 ± 12.6	58.0 ± 11.3	0.092
Weight, kg*	68.5 ± 14.9	65.3 ± 15.1	70.7 ± 14.4	< 0.001
Gender				
Male	419 (69.9)	112 (45.0)	307 (87.7)	< 0.001
Female	180 (30.1)	137 (55.0)	43 (12.3)	
Comorbidities				
Diabetes mellitus	270 (45.1)	134 (53.8)	136 (38.9)	< 0.001
CHF	227 (37.9)	128 (51.4)	99 (28.3)	< 0.001
Arrhythmia	71 (11.9)	41 (16.5)	30 (8.6)	0.004
CVD	42 (7.0)	25 (10.0)	17 (4.9)	0.015
Smoking history^	98 (16.4)	23 (9.2)	75 (21.4)	0.356
EuroSCORE of 4 or more	63 (10.5)	33 (13.3)	30 (8.6)	0.031
Cardiogenic shock	18 (3.0)	14 (5.6)	4 (1.1)	0.002
Use of inotropes	25 (4.2)	17 (6.8)	8 (2.3)	0.007
Baseline EF*	50.7 ± 14.1	49.5 ± 15.1	51.2 ± 13.5	0.249
Systemic HTN	402 (67.1)	176 (70.7)	226 (64.6)	0.112
Pulmonary HTN	73 (12.2)	43 (17.3)	30 (8.6)	0.002
Hypercholesterolemia	375 (62.6)	146 (58.6)	229 (65.4)	0.104
Angina	420 (70.1)	164 (65.9)	256 (73.1)	0.057
MI	277 (46.2)	117 (47.0)	160 (45.7)	0.803
PVD	26 (4.3)	15 (6.0)	11 (3.1)	0.104
Circulatory arrest	11 (1.8)	4 (1.6)	7 (2.0)	1.000
Operations				
CABG	415 (69.3)	159 (63.9)	256 (73.1)	0.116
Valve surgery	101 (16.9)	49 (19.7)	52 (14.9)	
Combined CABG and valve surgery	63 (10.5)	31 (12.4)	32 (9.1)	
Other surgeries	20 (3.3)	10 (4.0)	10 (2.9)	

Data represent numbers and % unless otherwise specified.

*median and interquartile range.

[^]Data was measured for males only.

CHF: congestive heart failure; CVD: cerebrovascular disease; EF: ejection fraction; HTN: hypertension; MI: myocardial infarction; PVD: peripheral vascular disease; CABG: coronary artery bypass grafting.

< 0.001), arrhythmia (16.5% vs. 8.6%, OR = 2.1; $p = 0.004$), CVD (10.0% vs. 4.9%, OR = 2.2; $p = 0.015$) and EuroSCORE of ≥ 4 (40.7% vs. 25.9%, OR = 2.0; $p = 0.031$). Moreover, these patients are more likely to require inotropic support (6.9% vs. 2.3%, OR = 3.1; $p = 0.007$). Preoperative anemia was significantly associated with new renal failure (OR = 1.96, 95% CI: 1.20–3.20; $p = 0.008$) and multisystem failure (OR = 2.92, 95% CI: 1.23–6.94; $p = 0.018$). Anemic patients had a higher risk for overall mortality (OR = 2.1, 95% CI: 0.96–4.60; $p = 0.070$) and intraoperative mortality (OR = 2.59, 95% CI: 1.13–5.96; $p = 0.023$) although this did not reach statistical significance for the former.

Preoperative anemia remains as an independent predictor for intraoperative mortalities (OR = 4.08, 95% CI: 1.43–11.66; $p = 0.009$) and overall mortality (OR = 2.79, 95% CI: 1.09–7.19; $p = 0.033$) after adjustment for these risk factors in the multivariable logistic regression model [Table 3].

DISCUSSION

Preoperative anemia is an independent factor for increased postoperative morbidity and mortality in patients undergoing coronary artery CABG and cardiac surgeries.^{8–10} Despite this, preoperative anemia is not considered a potential predictor of

Table 2: Operative characteristics, transfusion requirements, and outcomes among anemic and non-anemic patients (N = 599).

Parameters	Results			<i>p</i> -value
	Total N=599	Anemic 249 (41.6)	Non-anemic 350 (58.4)	
Operative parameters				
Non-elective	92 (15.4)	45 (18.1)	47 (13.4)	0.135
Use of CPB	459 (76.6)	185 (74.3)	200 (57.1)	0.095
CPB time, min*	104 (74,138)	104 (75,140)	104 (73,136)	0.512
Cross-clamp time, min*	58 (42,85)	58 (42,87)	57 (42,82)	0.512
History of aspirin or clopidogrel ≤ 7 days after surgery	275 (45.9)	163 (65.5)	112 (32.0)	0.740
Investigations				
Preoperative Hct# (0.35–0.45)	38.4 ± 5.1	34.3 ± 3.8	41.4 ± 3.7	< 0.001
Preoperative Hb (g/dL)* (11.5–15.5 g/dL)	12.5 ± 1.7	10.9 ± 1.1	13.7 ± 1.0	< 0.001
Preoperative PLT count* (140–400 × 10 ⁹ /L)	267.2 ± 84.1	282.2 ± 96.0	256.5 ± 72.7	0.002
Transfusion requirements				
Intraoperative blood products	221 (36.9)	150 (60.2)	71 (20.3)	< 0.001
RBC transfusion	372 (62.1)	189 (75.9)	183 (52.3)	< 0.001
RBC units transfused*	1 (0,3)	2 (1,4)	0 (0,2)	< 0.001
PLT transfusion	154 (25.7)	73 (29.3)	81 (23.1)	0.107
PLT units transfused*	0 (0,2)	0 (0,4)	0 (0,0)	0.247
Non-cardiac outcomes				
RF	73 (12.2)	41 (16.5)	32 (9.1)	0.008
Infection	95 (15.9)	45 (18.1)	50 (14.3)	0.256
Multisystem failure	24 (4.0)	16 (6.4)	8 (2.3)	0.018
Hospital stay*	8 (7,12)	9 (7,14)	8 (4,10)	< 0.001
Re-exploration rate	18 (3.0)	11 (4.4)	7 (2.0)	0.095
Early readmission rate (within first 30 days)	59 (9.8)	36 (14.5)	23 (6.6)	0.001
Intraoperative mortality	25 (4.2)	16 (6.4)	9 (2.6)	0.023
Overall mortality	27 (4.5)	16 (6.4)	11 (3.1)	0.072

Data represent numbers and % unless otherwise specified.

*median and interquartile range. #mean±standard deviation.

#Locally obtained normal range.

CPB: cardiopulmonary bypass; RBC: red blood cells; PLT: platelets; Hct: hematocrit; Hb: hemoglobin; PLT: platelet; RF: renal failure.

Table 3: Logistic regression analysis of factors for intraoperative mortality and overall mortality.

Variables	Intraoperative mortality			Overall mortality		
	β	<i>p</i> -value	OR (95% confidence interval)	β	<i>p</i> -value	OR (95% confidence interval)
Anemia	1.405	0.009	4.08 (1.43–11.66)	1.027	0.033	2.79 (1.09–7.19)
Cholesterol	0.180	0.726	1.20 (0.44–3.28)	0.459	0.353	1.58 (0.60 – 4.17)
Diabetes	0.539	0.327	1.71 (0.58–5.033)	0.367	0.481	1.44 (0.52 – 4.00)
Angina	0.950	0.076	2.59 (0.91–7.38)	0.857	0.091	2.36 (0.87–6.36)
Renal Failure	-0.968	0.070	0.38 (0.13–1.08)	-1.120	0.028	0.33 (0.12–0.88)
Cross-clamp time	0.008	0.183	1.01 (0.99–1.02)	0.013	0.025	1.01 (1.00 – 1.02)
Cardiovascular disease	-0.465	0.524	0.63 (0.15–2.63)	-0.293	0.692	0.75 (0.18 – 3.18)

β: beta; OR: odds ratio.

adverse outcomes in adult cardiac surgery in the most commonly used risk stratification scores; the EuroSCORE,¹¹ Society of Thoracic Surgeons predicted risk of mortality,¹² and age, creatinine, and EF predictor models.¹³ Studies addressing this aspect showed conflicting findings. In a recent study by Tauriainen et al,¹⁴ on patients undergoing coronary surgery, patients with preoperative anemia had an increased prevalence of significant comorbidities and a higher risk of early and late adverse events. However, when adjusted for perioperative bleeding, preoperative anemia was not associated with increased mortality. The authors hypothesized that the increased exposure to blood transfusion among anemic patients might result in poorer late survival.¹⁴ Other authors showed that several risk factors may occur concurrently with low Hb and that preoperative anemia was not a strong independent predictor for mortality and morbidity.¹⁵ Preoperative anemia is associated with several comorbidities and risk prediction, including older age, female gender, poorer left ventricular EF, impaired renal function, CHF, DM, and unstable angina.^{8,9} Such association makes it difficult to identify if anemia is an independent risk factor or simply a marker of a more severe and complex comorbid status in a patient undergoing cardiac surgery. In all these reports, the need for more studies in this area was expressed.

Our study demonstrates that preoperative anemia, as per the WHO definition, is a risk factor for mortality and morbidity in a patient undergoing cardiac surgery despite the higher level of Hb cutoff that defines anemia compared to what is commonly used in practice ($Hb \leq 10 \text{ g/dL}$). A low level of Hb increases the risk of death, postoperative renal outcomes, multisystem failure, prolonged length of hospital stay, and early readmission rates. Low Hb level was associated with doubling the risk of overall mortality. Moreover, preoperative anemia quadruples the risk of intraoperative mortality. The overall and intraoperative mortality of the anemic patients was significantly higher than the overall and intraoperative mortality of non-anemic patients. Clearly, patients with preoperative anemia had a significantly worse preoperative risk profile than non-anemic patients. That said, in our multivariable analysis, and after taking these risk factors into account, the results showed that preoperative anemia is an independent predictor for intraoperative and

overall mortality with this cutoff Hb level. This indicates that anemia is a risk factor on its own and not only an indicator for the clinical risk profile of patients undergoing cardiac surgery. This supports the need to correct preoperative Hb as a vital step for the outcome after cardiac surgeries.

In the past years, several observational studies have shown that preoperative anemia was associated with adverse outcomes postoperatively in cardiac surgery.^{8–10,16–22} It is hypothesized that anemia, especially during CPB, is associated with inadequate oxygen delivery intraoperatively, which may trigger multiorgan dysfunction.¹⁰ Many studies have studied the risk associated with anemia and adverse outcomes, including mortality and morbidity.^{14,15,18,19,23,24} The different results obtained in different studies can be related to the different Hb cutoff values used. Zindrou and coworkers⁸ defined anemia as hemoglobin $\leq 10 \text{ g/dL}$, while Magovern and coworkers defined anemia as $\leq 12.5 \text{ g/dL}$ for males and $\leq 11 \text{ g/dL}$ for females or the need for preoperative transfusion.²⁵ Others used the WHO criteria.²⁶ Kulier et al,⁹ showed that in multiple logistic regression, preoperative anemia and intraoperative RBC transfusion were both independent and additive risk factors for adverse outcomes. In addition, there was a direct relationship between the number of units transfused intraoperatively and the incidence of adverse effects.⁹ On the other hand, Tauriainen et al,¹⁴ showed that preoperative anemia is not associated with poorer survival when adjusted for baseline covariates and severity of perioperative bleeding. A meta-analysis showed that preoperative anemia as defined by WHO criteria was associated with an increased risk of poor outcomes, regardless of whether the patients received RBC transfusion or not. However, heterogeneity between the studies was significant.²⁷ Finally, anemia is the strongest predictor for blood transfusion, and it has been shown that transfusion increases mortality and morbidity in those patients.^{3,19} Considering that other retrospective studies have established an association between low preoperative anemia and increased postoperative morbidity and mortality, it is important to assess the association between preoperative anemia and morbidity and mortality without the confounding influence of transfusion. Moreover, the generalizability of the results of these studies to other populations is essential for study.

Our study has several strengths. We utilized a

relatively large cohort size, and both anemic and non-anemic groups were homogenous regarding the operative characteristics and the type of surgery required, controlling the additional risk associated with such a high-risk procedure. The study was conducted in a cohort of patients who had been transfused based on a pre-defined transfusion protocol. The study has a limitation of utilizing a retrospective cohort-based methodology, which does not eliminate the effect of other unmeasured confounding factors, including severely ill patients with high demand for blood transfusion. The study is based on data collected from a single institution. The cause of anemia has not been investigated, and therefore is unknown to the authors. The three most common causes of preoperative anemia in cardiac surgery are hospital-acquired anemia, iron-deficiency anemia, and anemia of chronic disease.²⁸ Although there are previous data to show a high prevalence of iron deficiency anemia among the adult Omani population,²⁹ the results of this study cannot be generalized due to the difference in the population characteristics. It is important to assess the cause of the anemia in preoperative patients. A study has shown that the highest proportion of moderately and severely anemic patients had microcytic anemia.³⁰ It was also noted that patients with normocytic anemia were older, and those with microcytic anemia were younger and more frequently women, likely inferring underlying iron deficiency. Type of anemia was associated with cardiac outcomes as normocytic anemia was associated with a higher risk of renal failure, other complications, and death.

CONCLUSION

Preoperative anemia in patients undergoing cardiac surgery is independently associated with increased intraoperative mortality risk, intraoperative RBC transfusion rates, and early readmission post-surgery. The findings of this study have important clinical implications. If the observed association between preoperative anemia and adverse outcomes in cardiac surgery is indeed causal, then diagnosing and correcting preoperative anemia will improve outcomes. Randomized controlled clinical trials are warranted to determine whether treating preoperative anemia improves outcomes in cardiac surgery patients. We advocate for clinical trials in our region to assess causes of preoperative anemia

in our patient population and the impact of well-structured patient blood management programs on the outcomes.

Disclosure

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