

# Does Preoperative Anemia Predict Adverse Outcomes after Cardiac Surgery?

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**Abstract:** ***Objective:** Preoperative anemia is now emerging as a potential risk factor after cardiac pulmonary bypass. The aim of this study is to evaluate whether anemia has been associated with worse outcomes following open heart surgery. **Methods:** In this retrospective study, 1836 adult patients who underwent open heart surgery between January 1994 and December 2012. Among them 475 (25.8%) have preoperative anemia defined as per world health organization guidelines as hemoglobin (Hb) <13 g/dl in men and Hb <12g/dl in women Patients with chronic renal failure, unknown hemoglobin level was excluded. Univariate and multivariate analysis were used to determine the relationship between preoperative anemia and worse outcomes. **Results:** In hospital mortality rate was 8.8% in anemic patients vs 3.3% in non anemic patients ( $p<0.0001$ ). In multivariate regression analysis, longer surgical time, prolonged respiratory support, longer ICU stay, use of excessive dose of inotropic agents and postoperative renal failure were identified as predictor of death in anemic patients. Major cardiac and non cardiac complications were significantly higher with lower preoperative hemoglobin concentration. **Conclusion:** The negative effect of preoperative anemia on immediate results after cardiac surgery, suggests that its correction before CPB might reduce poor outcomes.*

## 1. Introduction

The effect of preoperative anemia in cardiac surgery remains controversial. Some previous studies found a significant association between low hemoglobin level and adverse outcome (death, stroke, renal impairment) in patients undergoing cardiac and non-cardiac surgery<sup>1 2 3 4</sup>.

However other investigations failed to demonstrate significant impact of preoperative anemia on morbidity and mortality after cardiac surgery [5-6]. Also cardiac surgery is known to be potentially hemorrhagic procedure because of excessive use of heparin and fibrinolysis, in this condition it is potentially most sensitive to the impact of low hemoglobin levels<sup>2 7 8 9</sup>.

Recent data showed that patients with preoperative anemia required more red blood cell (RBC) transfusion<sup>10</sup>.

The purpose of the present study was to determine the effect of preoperative anemia on overall short-term morbidity and mortality in patients undergoing open heart surgery.

## 2. Patients and methods

This is a retrospective study of collected data on patients who underwent cardiac surgery at author's institute between January 1994 and December 2012. Our study was approved by local committee.

2060 adult patients underwent cardiac surgery. We evaluate the influence of preoperative anemia on immediate results of cardiac surgery under cardio pulmonary bypass (CPB).

This study included patients undergoing valve surgery, coronary surgery, combined procedure, surgery for thoracic aortic disease, adult congenital defect and other heart diseases.

The patients were divided into two groups: group with anemia (n=475), group without anemia (n=1361). The data

collection included demographic informations, preoperative data and postoperative results. We excluded patients with following criteria: age<18 years, unknown preoperative hemoglobin level, preoperative critical state, acute and chronic renal insufficiency. (Figure: 1)

Finally, 1836 cases were enrolled in the present study of which 475 (25.8%) had preoperative anemia. The patients were divided into two categories: group with anemia (n=475) and group without anemia (n=1361).

All patients received 1mg/kg of Hydroxyzin for premedication. Anesthetic induction used Fentanyl 5µg/kg, Propofol 3mg/kg, Cisatracurium 0.15mg/kg. The maintenance of anesthesia was performed with continuum injection of Propofol 6-12mg/kg/h and Sevoflurane 1 to 2%.

Statistical analysis was conducted with SPSS 19.0

Continuous variables were expressed as mean  $\pm$  SD (standard deviation) and categorical variables as a real number and percentages. Differences between two groups (anemic group vs non anemic group) were compared using  $\chi^2$  test or fisher's exact test when appropriate, and the student's t-test or mann-whitney for continuous variables.

Multivariate logistic regression analysis was performed to determine the predictors of mortality and major morbidity. All statistical tests with two-sided, p value< 0.05 were considered statistically significant.

## 3. Results

This study included 1836 patients who underwent open cardiac surgery. Of these 475 patients (25.8%) presented with anemia before surgery. There was no difference of gender and mean age between the groups (48.5 $\pm$ 14.6 vs 47.5 $\pm$ 13.6.  $p=0.22$ ). the mean hemoglobin concentration was 11.2 $\pm$ 1.2 g/dl in anemic group vs 14.3 $\pm$ 1.2 g/dl in non anemic group  $p<0.0001$ . the demographic and preoperative characteristics are summarized in table 1.

Patients with anemia were likely to have a greater prevalence of advanced heart failure (17% vs 4.3%,  $p<0.0001$ ). New-York heart association NYHA functional class III-IV 55.4% vs 41.1%  $p<0.0001$ . Also anemic patients had more prevalence of redo cardiac surgery and more preoperative impaired left ventricular function ( $p=0.038$ ).

Perioperative and postoperative data are listed in table 2.

Cardiopulmonary bypass time and aortic clamp time were significantly longer in the anemic patients ( $p<0.0001$  and  $p=0.017$  respectively). Patients with preoperative anemia were ventilated longer than patients without anemia ( $p<0.0001$ ). ICU stay and hospital stay were also longer a There was more low output syndrome (LOS) in the anemic group (14.5% vs 6.5%,  $p<0.0001$ ).

Additionally, our results showed a negative impact of preoperative anemia on hospital outcomes. 30 day mortality rate and composite morbidity were significantly higher in patients with low levels of preoperative hemoglobin. Preoperative anemia was associated with a threefold increased in risk of death (8.8% vs 3.3%,  $p<0.0001$ ).

There was also a significant difference between anemic and non-anemic patients in the risk of major complications following surgery (28% vs 14.2%  $p<0.0001$ ).

Incidence of postoperative renal failure was higher in patients with lower preoperative hemoglobin level ( $p<0.0001$ ). Anemic patients were likely to require red blood cell (RBC) transfusion (42.9% vs 33%,  $p=0.007$ ).

Many factors were determinant of mortality in anemic patients when we used univariate analysis, but after adjusting for those variables, multivariate analysis showed that: longer surgical time, prolonged respiratory support, longer ICU, use of excessive inotropic drugs and postoperative renal failure were the most independent predictors of death [table3].

#### 4. Discussion

In cardiac surgery, most of postoperative complications are related to the patient's characteristics and history of previous disease such as a chronic anemia. Several investigations indicated that low preoperative hemoglobin levels may correlate to adverse outcomes after cardiac surgery<sup>2 11 12 13 14 15</sup>.

Consistent with these studies, our study found that preoperative anemia is a determinant risk factor for short-term complications in patients undergoing cardiac surgery. Overall mortality rate was almost 3-fold higher in anemic patients compared to non anemic (8.8% vs 3.3%  $p<0.0001$ ). the incidence of major postoperative complications was significantly higher in anemic patients 28% vs 14.2%  $p<0.0001$ .

Our results were similar to recent study published by Elmistekawy<sup>15</sup> (30 day mortality 8% vs 2.8%  $p<0.0001$ , composite morbidity 28% vs 11.2%  $p<0.0001$ ).

The relationship between preoperative anemia and increased in hospital death was observed by other investigators<sup>3 16 17</sup>. Nevertheless, other investigations failed to demonstrate a negative impact of preoperative anemia on short outcomes<sup>14 17 18</sup>. The prevalence of anemia in patients undergoing cardiac surgery vary widely. In recent meta-analysis of 153. 180 patients with heart failure across 34 published studies over seven year period (2001-2007), the prevalence of anemia was 37.2%<sup>19</sup>. Similarly. In a study of 576 patients undergoing elective cardiac surgery, Munoz<sup>20</sup> found that prevalence of preoperative anemia was 37%, also in a study of 2698 patients undergoing non emergent aortic valve surgery, Elmistekawy found that one third of them (32.2%) have a preoperative anemia<sup>15</sup>. In our cohort 25.8% of patients undergoing CPB were anemics, this is similar to Kulier<sup>17</sup> 28.1%, and karkouti<sup>2</sup> 26%.

Controversies exist about which complications occurred more in anemic patients: cardiac or non cardiac events ? valvular or coronary surgery? In this setting the opinions diverge. Finally, anemia has been found to be a major predictor of worse outcomes in patients undergoing valvular surgery, coronary artery bypass grafting (CABG) and both procedures<sup>21 22</sup>.

Despite cardiac pathologies requiring surgery in our sample are heterogenic (coronary artery bypass grafting, valvular surgery, aortic surgery, adult congenital defect), we found that anemia has independent harmful effects in patients undergoing cardiac surgery.

The exact pathophysiological mechanism by which anemia might cause adverse outcome in cardiac surgery has not been fully elucidated. However, several studies suggest that impaired oxygen delivery to tissues causing tissue hypoxia plays the key role<sup>4 23 24 25</sup>.

Acute Kidney injury (AKI) is a common and prognostically important complication of cardiac surgery with cardiopulmonary bypass. Up to 30% of patients undergoing open heart surgery develop clinically significant acute renal failure and about 3% of them develop severe ARF that necessitates renal hemodialysis<sup>26 27 28</sup>. Our results indicate that anemic patients appear to be more susceptible to acute renal failure after CPB ( $p<0.0001$ ). this comforts the hypothesis that renal system was more sensitive than other organs to temporary relative hemoglobin deficiency<sup>29 30</sup>.

As previously reported, the pathophysiology of anemia in heart disease is multifactorial. In cardiac surgery, the 3 most common causes of preoperative anemia are, hospital acquired anemia, iron deficiency anemia and anemia secondary to chronic disease<sup>31</sup>.

Other investigators suggest that etiology of anemia is related in one third of cases to a global malnutrition or nutritional deficits affecting iron, folic acid or vitamin B12. Another third due to inflammatory disease renal disease or neoplasm and the remaining third is unknown<sup>32 33</sup>.

In our cohort, most of anemic patients were valvular, with poor socio-economic level and most of them were in advanced heart disease (congestive heart failure: 17% in

anemic patients vs 4.3% in non anemic patients  $p < 0.0001$ ). in addition we know that those categories of patients often experienced malnutrition combined to hypervolemia related to heart failure. Theoretically, those factors seem sufficient to explain the origin of anemia. Our results did not differ markedly from previous reports that demonstrate the strong relationship between anemia and postoperative morbidity and mortality and highlighting the question of whether the anemia should be treated prior to elective cardiac surgery.

As anemia is a modifiable risk factor, many investigators recommend its correction before surgery<sup>34, 35</sup>. Anemia may be treated with iron supplementation, erythropoietin or transfusion of packed red blood cells. However, the deleterious effects associated with transfusion therapy reduce its use<sup>28, 36</sup>. In our practice, we often minimize red blood cell transfusion and we try to treat the etiology or use the iron supplementation.

## 5. Conclusion

As most previous studies, we found that preoperative anemia has a negative impact on immediate results after cardiopulmonary bypass. We suggest that its correction should improve perioperative results.

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**Table 1 : preoperative patients characteristics**

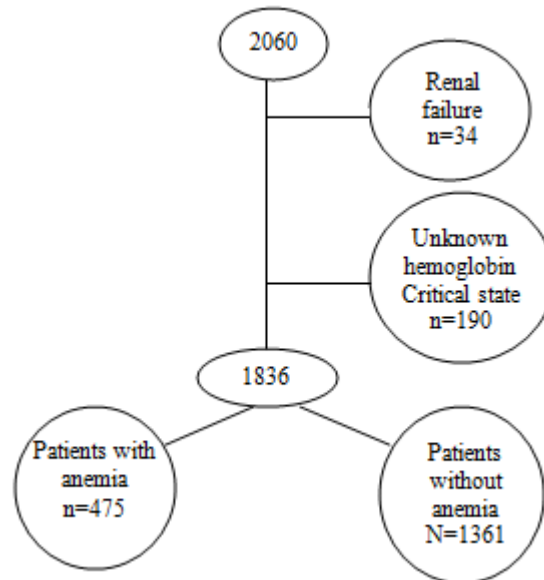
variable	Group with anemia n=475	Group without anemia n=1361	p value
Age (years)	48.5±14.6	47.5±13.6	0.22
Male/Female	297 (62.5%)	832 (61%)	0.62
BMI	23.9±5.5	24.7±4	
Arterial hypertension	95 (20%)	251 (18.5%)	0.45
Diabetes mellitus	102 (21.5%)	263 (19.3%)	0.31
Smoking	163 (34.3%)	476 (34.9%)	0.82
Dyslipidemia	53 (11.2%)	217 (15.9%)	0.011
CHF	81 (17%)	58 (4.3%)	0.000
COPD	34 (7.15%)	86 (18%)	0.52
Peripheral arteriopathy	51 (10.7%)	78 (5.7%)	0.004
Previous stroke	18 (3.8%)	60 (4.4%)	0.56
Previous MI	87(18.3%)	265(19.4%)	0.09
Functional Class III-IV	263 (55.4%)	564 (41.4%)	0.000
Unstable angina	9(1.8%)	22(3.6%)	0.1
Atrial fibrillation	113 (23.8%)	420 (30.9%)	0.003
EF (%)	55.8±13	57.2±12	0.036
EF <40%	74 (15.6%)	161 (11.8%)	0.038
PSHP	53.9±21.4	47.8±17.8	0.000
Creatininemia	10.7±6.7	9.6±3	0.004
Redo cardiac surgery	62 (13%)	132 (9.6%)	0.046
Hemoglobin level	11.2±1.2	14.3±1.2	0.000
Euroscore	3.85±3.3	2.37±2.38	0.000

**Table 2: Perioperative and postoperative data**

Variable	Group with anemia n=475	Group without anemia n=1361	p value
No elective surgery	38(8%)	41 (3%)	0.0001
CPB time	106.8±46.5	97.6±39.6	0.0001
Aortic clamp time	69.9±35.9	65.4±29.9	0.017
Operative time	241±62.7	204±61.5	0.054
Mechanical ventilation	10(6-19.75)	8(6-17)	0.0001
ICU stay (hours)	48(24-72)	44(24-48)	0.0001
Postoperative hospital stay	14.7±19.3	12.5±9.8	0.002
Mechanical ventilation ≥48h	48 (10%)	57(4.2%)	0.0001
Inotropic support	106(22.3%)	123 (9.03%)	0.000
IABP	31 (6.5%)	123 (9.03%)	0.057
LOS	69 (14.5%)	88(6.5%)	0.0001
Postoperative renal failure	52 (10.9%)	48 (3.5%)	0.0001
Brain complication	9 (2%)	11 (8%)	0.05
Sepsis	44(9.3%)	78 (5.7%)	0.01
Redo operation for bleeding	19 (4%)	51 (3.7%)	0.78
MOF	29(6.1%)	26 (1.9%)	0.0001
In-hospital mortality	42 (8.8%)	46 (3.3%)	0.0001
RBC transfusion	204 (42.9%)	457 (33.5%)	0.007
Co morbidities after surgery	133 (28%)	193 (14.2%)	0.0001

Variable	Odds ratio	95% IC	P-value
Surgical time (minutes)	0.98	0.95-1	0.028
Mechanical ventilation (hours)	0.97	0.94-0.99	0.007
ICU Stay (hours)	1.01	1-1.03	0.009
Inotropic drug use	0.13	0.022-0.77	0.025
Postoperative renal failure	0.07	0.02-0.4	0.003

Multivariate analysis : predictors of mortality in anemic patients



**Figure 1:** Study population