



## Association between Preoperative Anaemia with Post Operative Mortality and Morbidity

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### Abstract

*Preoperative Anaemia is an important risk factor for post-operative morbidity and mortality and has been shown to be independently associated with adverse outcome after non-cardiac surgery. Several large observational studies, including over 600,000 patients, have confirmed the presence of an association between pre-operative anemia and poorer post-operative outcomes. Anaemia is an independent risk factor for the preoperative and post operative patient in all types of surgery. Several studies had been done to assess anemia as independent risk factors in post operative outcome and also in patients with associated comorbidities also. meta analysis of various studies and comparison of result of metanalysis had been done and results interpreted as correction of anemia in all patients is important for better outcome. But specially in surgical patient preoperative correction of anemia should be implemented whenever possible for better surgical and patient outcome.*

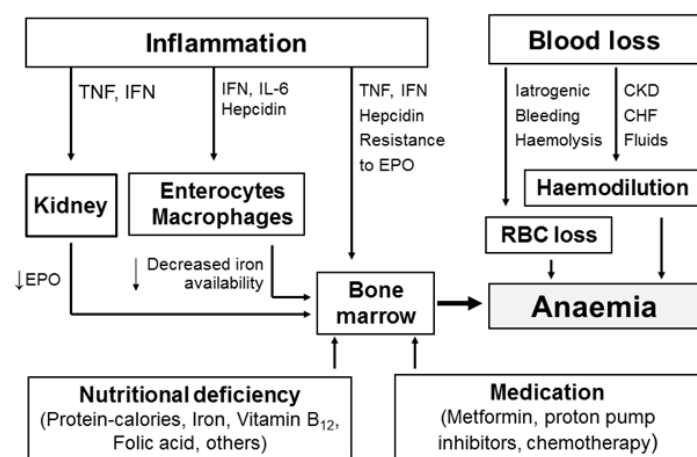
### Introduction

Preoperative Anaemia is an important risk factor for post-operative morbidity and mortality and has been shown to be independently associated with adverse outcome after non-cardiac surgery. Postoperative mortality has remained unchanged over the past decades in anaemic patients. This study focuses on post operative morbidity and mortality. World Health Organization (WHO)

definitions of anaemia, found a significant decrement in the global prevalence of anaemia, which decreased from 40.2% in 1990 to 32.9% in 2010, though the prevalence varied widely across regions. However, a lower prevalence of mild and moderate anemia accounted for most of the reduction, while the prevalence of severe anemia remained largely unchanged.

### Causes of Pre-Operative anemia

Iron deficiency is the commonest cause of anemia worldwide, followed by parasitic infestation (hookworm, schistosomiasis, and malaria), haemoglobinopathies, obstetric and gynecological disorders, and anemia associated with chronic renal failure, though the proportion of cases resulting from specific causes varies widely across regions. The etiology of pre-operative anemia may be multi factorial and complex (Figure 2). Nutritional deficiencies (e.g., iron, folate, vitamin B12, proteins), due to poor nutrition or malabsorption, and some drugs may contribute to reduced red blood cell (RBC) production. Other causes may be activation of the immune system by underlying processes as well as certain immune and inflammatory cytokines, including tumour necrosis factor alpha, interferon gamma and interleukins (IL) 1,6,8 and 10.



### Most common causes and pathophysiological mechanisms of pre-operative anaemia

#### Consequences of pre-operative anaemia

Several large observational studies, including over 600,000 patients, have confirmed the presence of an association between pre-operative anemia and poorer post-operative outcomes. After adjusting for a number of potential confounders, using multivariate logistic regression analysis, preoperative anemia remained an independent risk factor for increased post-operative morbidity and mortality, as well as for prolonged length of hospital stay. Anaemia is an independent risk

factor for the preoperative and post operative patient in all types of surgery. Often, it is a sign of an underlying disease or condition that could affect the surgical outcome. Risk related with preoperative anemia can be measured with different parameters including various medical complications like acute renal injury, stroke, myocardial insult and mortality. Anemia is a common ailment and has been associated with increased mortality<sup>12,13,14</sup> among patients with chronic disease or malignancy. Hemoglobin levels are often robust predictors of long term survival<sup>15,16,17</sup>. The degree of anemia among patients admitted to the hospital for medical and surgical conditions is associated with higher short term mortality<sup>18,19,20</sup>. Anemia at different points during the hospital course may also reflect different problems with varying implications. Anemia on admission may carry a poor prognosis because it is a physiologic indicator of underlying comorbid illness burden, illness severity (anemia of chronic disease), or prehospital bleeding. Many surgical patients who are admitted for urgent or emergent conditions also can have bleeding and fluid shifts before their operation.

Pathophysiologically anemia causes decrease in oxygen supply to tissue both by decreasing carrying capacity of hemoglobin and decreasing cardiac output. These mechanism stimulate a vicious cycle affecting tissue healing, central nervous system, cardiovascular, renal system and adversely affecting outcome in surgical patients. Due to its substantial metabolic requirements, neuronal tissue has strict oxygen requirements. Because nearly all the oxygen in blood is carried bound to hemoglobin, the brain is vulnerable to anemia. Changes in both the oxygen extraction ratio<sup>8</sup> and regional alterations in cerebral blood flow due to auto regulation may compensate for poor oxygen delivery secondary to low hemoglobin, although a lower limit of hematocrit that can be tolerated universally has not been fully established.<sup>9</sup> Another study reveals relationship of anemia to acute renal failure and clearly indicate relationship of oliguria and increased creatinine

level to moderate and severe anemia. As these studies clearly indicate anaemia as independent risk factor.

The largest such study was a retrospective cohort study<sup>2</sup> performed on 1958 consecutive surgical patients who refused transfusions based on religious reasons. The overall 30-day risk of mortality increased with decreasing preoperative hemoglobin concentrations, especially in those patients with a hemoglobin level of less than 6 g/dL.<sup>2</sup> Risk of mortality was much greater, however, in patients with underlying cardiovascular disease and preoperative hemoglobin value of 10 g/dl or less. A subsequent study on the same population showed that none of the 99 patients with postoperative hemoglobin concentrations between 7 and 8 g/dl died, whereas there was a sharp rise in mortality in those patients with a hemoglobin concentration less than 5 to 6 g/dL.<sup>2</sup> These two studies indicate direct relationship of preoperative anemia and outcome after surgical procedure<sup>2</sup>.

Another study evaluated eight healthy volunteers during isovolemic reduction and found self-assessed fatigue at a hemoglobin level of 7 g/dL, which then increased further at hemoglobin levels of 6 g/dL and 5 g/dL<sup>33</sup>. Minor and reversible cognitive changes were seen in nine healthy subjects, including decreased reaction times at hemoglobin concentration of less than 6 g/dL and impaired immediate and delayed memory at hemoglobin levels less than 5 g/dL.<sup>11</sup> These studies show that even healthy subjects can exhibit clinical changes at hemoglobin concentrations between 5 and 7 g/dL.

Results are consistent with a series of studies in which healthy subjects underwent acute isovolemic reduction to a hemoglobin level of 5 g/dL.<sup>3,4,5</sup> Two of these studies found evidence of asymptomatic and reversible ST-segment changes suggestive of myocardial ischemia in 5 of the 87 combined patients at hemoglobin concentrations between 5 to 7 g/dL<sup>3,4</sup>. Myocardial ischemia as mentioned in study indicate relationship with preoperative anemia.

One important aspect of effect of anemia on post operative morbidity and mortality is age. Several factors relate aging and anemia as a risk factor for operative mortality. First, cardiac reserve is diminished in elderly persons,<sup>8</sup> which may restrict regular physiologic compensation for anemia<sup>24</sup>. Second, the high prevalence of subclinical coronary disease in elderly persons potentially decreases tolerance of anemia,<sup>25,26</sup> as coronary vasodilation is not possible in the presence of significant stenosis and the cardiac oxygen extraction ratio may be limited.<sup>27,28</sup> Elderly patients however, may respond to preoperative anemia differently than younger patients. In one study of twenty patients over the age of 65 and free from known cardiac disease, isovolemic anaemia to a mean haemoglobin concentration of 8.8 g/dL was well tolerated<sup>35</sup>. Another study examined patients with known coronary artery disease and found that isovolemic anaemia was well tolerated to haemoglobin value of 9.9 g/dL. In addition, the increase in cardiac index and oxygen extraction during hemodilution was found to be independent of age. A more recent study analyzed preoperative hematocrit levels in over 310,000 elderly veterans undergoing non cardiac surgery. In contrast to the previous studies, even mild anemia was associated with an increased risk of thirty-day morbidity and mortality. There was a monotonically rise in mortality and cardiac events when the hematocrit level was less than 39%. These results, however, may not be able to be generalized to elderly females. Moreover, it is unclear whether the anemia is causal or associated with the increased morbidity and mortality, and whether this risk may be corrected with transfusion.<sup>54</sup>

Breast reconstructive surgery with preoperative anemia significantly associated with increased 30-day morbidity with no mortality.

Another study involving hepatectomy in elective patients shows out of 12,987 patients, of whom 4260 (32.8%) had preoperative anemia. Patients with preoperative anemia experienced higher morbidity and mortality<sup>5</sup>.

Preoperative anemia is usually regarded as a risk factor because of its association with increased perioperative transfusions of blood components<sup>29,30,31,32</sup>. Perioperative transfusion is associated with increased morbidity and mortality, even when as little as one unit of packed red blood cells is administered<sup>33,34,35</sup>. Several studies have tried to assess whether anemia is independently associated with harmful effects in addition to the risks caused by an increased need for transfusion. However, such studies have had small sample sizes,<sup>36,37</sup> been undertaken only in specific subgroups such as elderly patients or individual surgery types,<sup>36,37,38</sup> included patients undergoing emergency surgery without stratification of outcomes<sup>37</sup> or failed to adjust for the major known confounders, especially the use of perioperative transfusions<sup>35</sup>. Furthermore, most of these studies assessed only the outcomes of mortality or cardiac morbidity, leaving other serious complications unexplored. With these limitations in mind, this study<sup>39</sup> established that patients with preoperative anemia undergoing major non-cardiac surgery were less likely to survive or more likely to have major morbidities than were patients without anemia. Study<sup>39</sup> has large sample size 69229 having preoperative anemia and included all major and minor co morbidities.

An important aspect of management of preoperative anemia has been allogenic blood transfusion. Blood transfusion is itself associate with poor outcome hence at present findings emphasize importance of PBM [Patients Blood management]<sup>49</sup> which has been promoted by WHO with initiative underway in many countries. PBM Guidelines are elaborative guidelines regarding management of Anemia and various aspect of anemia in different subgroups of patients. Total guidelines divided into Module1 to Module 6.

### Study search strategy

All data extracted from studies and tabled were put as dichotomous data on free version of

software Comprehensive meta analysis v3 and various results obtained from software analysis are discussed in statistical analysis as calculated by software.

### Results

After thorough analysis by manual and software results a total of 932834 patients were screened in all seven studies. After carefully selection by concerned study author 825874 patients are eligible for final analysis. Out of 825874 total patients 294261[35.63%] patients are anaemic [as per WHO definition of anaemia] and rest were non anaemic. In our study we have not classified anaemia as mild, moderate or severe rather only anaemia and no anaemia and if a included study have shown these classification we have added all figures for anemia and taken as one cohort.

### Primary outcome

#### In-hospital or 30days post surgery mortality

Post operative 30 days Mortality is reported in all included studies except one Karim A. et.al. Out of total 825874 patients included 40180[4.86%] patients died within 30days of surgery in hospital or follow up. Of these 40180death28949 were anemic out of 294262 total anaemic patients [9.83%] this figure is more than average of total no of patients. Among total of 531613 non anemic patients 11159 died which is 2.09%.

As per statistical analysis patient with pre operative anemia dies more frequently as compared to patient with no preoperative anemia Odds Ratio [OR]-Fixed model-3.878 Random-2.230 with p value-0.000[Fixed Model] and p=0.060[with Random model]. Z value in Fixed model is 108.115 and in Random model is 1.877.

#### Analysis of study conducted in our institute

Out of total 256 patients screened for study 102 patient lost follow-up in 30 days period of in hospital or follow up. 4 patients were excluded due to not fulfilling age criteria for inclusion. Total 150 patients were finally selectedfor analysis. Out of 150 patients 56 patients have preoperative anemia and 94 patients do not have anemia preoperatively. In total anemic patients of

56 ,12 died in mentioned time period while 4 died out of total 94 non anemic cohort. 15 out of 56 anemic patients have one or combinations of morbidities and 10 out of 94 non-anemic patients have one or combined morbidities.

**Calculation of various other Statistical Outcome of our study**

**Mortality and Combined morbidity Indicators**

S.No.	Outcome Indicators	Patients with Anemia [n=56]	Patients without Anemia [n=94]	Remark
1	30 days in hospital or post surgery mortality	12[21.42%]	4[4.25%]	
2	30 day in hospital or post surgery combined morbidities	15[26.78%]	10[10.63%]	

**[Statistical analysis for 30 day mortality Indicators]**

S.No	Statistical Parameters	Results
1	Odds Ratio[OR]	8.2727
2	95% Confidence Interval[CI]	2.2202 to 30.8252
3	Z Statistics	3.148
4	Significance Level [p Value]	0.0016

P value<.05 taken as significant with 95% Confidence Interval

**Statistical parameters for Combined morbidity Indicators**

S.No	Statistical Parameters	Results
1	Odds Ratio[OR]	3.2308
2	95% Confidence Interval[CI]	1.3324 to 7.8338
3	Z Statistics	2.959
4	Significance Level [p Value]	P = 0.0095

**Discussion**

As seen in results and statistical analysis of our study the core findings of most studies- Preoperative anemia is associated with increased short term-[30days] mortality. Though Samer et. al study shows no significant relationship between preoperative anemia and postoperative mortality but rest of studies and combined effect after Meta analysis also shows identical findings.. In spite of using Regression models to eliminate confounding factors various factors like Age and type of surgery may affect outcome after surgery and hence can give erroneous results. Almost all the data of patients in all studies is collected from ACS-NSQIP but most of studies have varied time

period. some of the studies period may coincide but these studies are variable in terms of type of surgeries. Period of studies selected also emphasize on an important aspect that expertise[surgeon/anesthesia/Infrastructure] involved with studies of recent time period [eg- Samer et al] is better than studies with comparatively older period [Mussalam et.al] and this aspect of surgery has not been addressed in meta analysis of studies ,although Random Effect Model used for meta analysis of studies addresses variance between studies but this analysis cannot surely tell about this aspect. As recent surgeries are associated with more expertise and hence less intraoperative bleeding and less anesthesia related complications and hence less post operative complications and mortality.

One of the important limitation of these selected studies and meta analysis is that measurement of Hb or Hematocrit values are taken not immediately before surgery [eg- In Musallam et al 7% of patients hematocrit value taken 4 weeks prior to surgery, Karim et al study - 3% of patients >7weeks before surgery , Prateek et al .21% patient >4weeks before surgery]. However this can be justified as variation of hematocrit over a short duration of time is not significant in absence of major bleeding or Coagulation disorder which has already been covered preoperatively during confounding factors in Regression models. Other important findings seen in all studies invariably that we cannot conclude that postoperative outcome [mortality and morbidity] was result of pre operative hematocrit value or as a result of intraoperative and postoperative Hb. Other important drawback of ACS-NSQIP data is that it does not take into account if <3 blood transfusion has taken place in patients preoperatively or Pre/Intra/Postoperatively combined hence in some patient these transfusion have improved and in some patients worsen the results. Samer et al found a interesting relationship preoperative anemia and perioperative transfusion i.e. many studies in different surgical specialties have shown that there may be negative effect of transfusion

including increased length of stay surgical complications and mortality. This finding also suggest that correction of anemia by blood intraoperatively to maintain end organ perfusion in emergency surgeries but in planned elective surgeries it is better to correct haemoglobin by other methods like IV Iron therapy or Erythropoetin rather than by blood transfusion. Various studies though orthopedic and cardiac surgery compelling evidence supports use of preoperative treatment of anemia for reduction of blood transfusion and improved outcome. For emergency surgeries many studies shows that perioperative haemoglobin level of 5-7 are well tolerated by patients without major cardiac morbidities with regards to cardiac performance, tissue oxygenation systemic oxygen delivery and overall postoperative morbidity. other important limitation of in NSQIP data is that some confounder were either not recorded or non known at time of data collection and matched only those factors which were recorded hence we cannot say that disease process marked by anemia have causal relationship with outcome only an association independent of those factors that were available in NSQIP . One of the main criticisms of meta-analysis is that studies that are quite different can have their results combined inappropriately, and the result is not an accurate reflection of the “true” value. To overcome this we have used Random effect model for meta analysis which catches not only variance in a study but variance among various studies. One important statistical limitation of our study is that we didn't used sensitivity analysis and didn't plotted Funnel graph to rule our publication bias and no published scale was used for screening and selection of studies. We searched these data over internet and evaluated it carefully, no of studies taken are also less hence chanced of publication bias and need for sensitivity analysis is not significant. Limitation of our study as compared with previous study is that we can specifically tell about chances of one particular morbidity. An important finding in results of our meta analysis is

that mortality indicators are more uniformly distributed among studies and these indices are also higher in numbers but morbidity indicators are not uniformly distributed in studies. One of reason for this gap may be mortality has been taken as one single outcome and in morbidity indicators various studies has taken one or combination of more than one morbidity as outcome. Some studies eg Wu et al which has largest number of participants has taken into consideration only cardiac morbidity as indicators leaving behind all other morbidity like stroke renal failure infections etc decreasing the no of total morbidity figure. But this has not affected our overall analysis as we have given weight age to different studies based on random effect model and hence absolute no. of participant cannot affect our results though heterogeneity may be affected. Discussion over small study conducted in our institution is helpful in drawing conclusion for studies with small no of patients as we have seen results obtained with meta analysis and our study is comparable in almost all parameters. Despite the fact that sample size of our study was very small as compared to other studies included, all Preoperative variables have not taken into account and there is more chances of interviewer's bias as compared to studies. After carefully examining results we can see that except type of surgery [Routine Vs Emergency] all preoperative variables are statistically not significant. This may be due to poor preoperative optimization of patients or surgical expertise quality in emergency hours. We cannot comment over statistical significant relationship of this as no analysis has been done in this regard.

### **Conclusion**

To conclude we can say that correction of anemia in all patients is important for better outcome. But specially in surgical patient preoperative correction of anemia should be implemented whenever possible for better surgical and patient outcome.

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