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Propensity-matched analysis of association between preoperative anemia and in-hospital mortality in cardiac surgical patients undergoing valvular heart surgeries

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ABSTRACT

Introduction: Anaemia is associated with increased post-operative morbidity and mortality. We retrospectively assess the relationship between preoperative anaemia and in-hospital mortality in valvular cardiac surgical population. **Materials and Methods:** Data from consecutive adult patients who underwent valvular repair/replacement at our institute from January 2010 to April 2014 were collected from hospital records. Anaemia was defined according to WHO criteria (hemoglobin <13g/dl for males and <12g/dl for females). 1:1 matching was done for anemic and non-anemic patients based on propensity for potentially confounding variables. Logistic regression was used to evaluate the relationship between anaemia and in-hospital mortality. MatchIt package for R software was used for propensity matching and SPSS 16.0.0 was used for statistical analysis. **Results:** 2449 patients undergoing valvular surgery with or without coronary artery grafting were included. Anaemia was present in 37.1% (33.91% among males & 40.88% among females). Unadjusted OR for mortality was 1.6 in anemic group (95% Confidence Interval [95% CI] – 1.041-2.570; p=0.033). 1:1 matching was done on the basis of propensity score for anaemia (866 pairs). Balancing was confirmed using standardized differences. Anaemia had an OR of 1.8 for mortality (95% CI- 1.042 to 3.094, P=0.035). Hematocrit of < 20 on bypass was associated with higher mortality. **Conclusion:** Preoperative anaemia is an independent risk factor associated with in-hospital mortality in patients undergoing valvular heart surgery.

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INTRODUCTION

World Health Organization (WHO) defines anemia as hemoglobin (Hb) level under 13 g/dl in men and 12 g/dl in women.[1] Anemia is a well-recognized comorbidity and marker of adverse outcomes in a variety of conditions such as myocardial ischemia,[2] congestive heart failure,[3] acute coronary syndromes,[2] and noncardiac surgery.[4]

Anemia has also been identified as a marker of morbidity and mortality after coronary artery bypass surgery though it is not included as a risk factor in commonly used risk stratification scores EuroSCORE II, STS score or ACEF score.[5,6] Some studies have analyzed the role of anemia as a determinant of outcome in coronary artery bypass grafting (CABG) surgery[7] and elective valve replacements[8-10] and found a significant effect on outcome whereas others failed to demonstrate a significant effect.[11,12]

Prevalence of anemia is high in the Indian population and is mostly nutritional in

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etiology.[13] The prevalence of anemia among the Indian cardiac surgical population or its effect on outcome has not been studied.

We studied the prevalence of anemia and its effect on all-cause in-hospital mortality in patients undergoing valvular heart surgery.

MATERIALS AND METHODS

Patients and data collection

This was a retrospective observational cohort study of consecutive adult (>18 years) patients who underwent valvular heart surgery at our Institute between January 2010 and April 2014. Institutional Ethical Review Board clearance was obtained. Demographic, laboratory, diagnosis, procedure-related and mortality data of 2449 patients were collected from hospital medical records. Latest available laboratory result for Hb before surgery was used to define anemia. Preoperative anemia was defined as per WHO guidelines as Hb <13 g/dl in men and Hb <12 g/dl in women.[1]

Operative technique

All procedures were performed via median sternotomy with standard anesthetic, surgical and perioperative management protocols. All procedures were carried out with cardiopulmonary bypass (CPB) and mild systemic hypothermia (32–34°C). Cardiac arrest was achieved with blood cardioplegia.

Endpoints and definitions

The primary endpoint was in-hospital mortality defined as all-cause mortality in the same admission as that of cardiac surgery.

Statistical analysis

Continuous data were expressed as mean and standard deviation, and categorical data as percentages. Two-tailed $P \leq 0.05$ was considered significant. The anemic and nonanemic groups were compared, and odds ratio (OR) for mortality were calculated from the binary logistic regression.

Cohort was divided on the basis of severity of anemia into mild, moderate, and severe anemia[14] and corresponding mortality was studied [Table 3].

The differences of patient characteristics between the groups were quantified using the standardized difference (S. diff.). For a continuous covariate, the S. diff. is defined as:

$$\text{S. diff.} = \frac{\bar{X}anemic - \bar{X}nonanemic}{\sqrt{\dfrac{(Sanemic^2 + Snonanemic^2)}{2}}}$$

Where $\bar{X}anemic$ and $\bar{X}nonanemic$ denote the sample mean of the anemic and nonanemic groups, respectively, and *Sanemic* and *Snonanemic* denote sample standard deviation of the covariate in anemic and nonanemic groups, respectively.

For dichotomous variables, S. diff. is defined as:

$$\text{S. diff.} = \frac{(Panemic - Pnonanemic)}{\sqrt{\dfrac{(Panemic\,[1 - Panemic] + Pnonanemic\,(1 - Pnonanemic))}{2}}}$$

where *Panemic* and *Pnonanemic* denote the proportion of dichotomous variable in anemic and nonanemic groups, respectively. The S. diff. compares the difference in means in units of pooled standard deviation and is independent of sample size. A S. diff. of <10% is generally taken to indicate a negligible difference between the groups.

Propensity is the probability of inclusion into anemic or nonanemic groups depending on the respective patient characteristics. The propensity score (PS) is the predicted probability of each patient from a logistic regression model with anemia as the dependent variable and all the patient characteristics as independent variables. Subjects with same PS, in either group would have similar characteristics. Matching selects patients from each group with similar PS and thus similar characteristics. Thus, the matched data would have patients who are similar in all characteristics (balancing) other than anemia and its associated features (ex. Hb_{PREOP}, PCV_{PREOP}, PCV_{LEAST}), which is confirmed by S. diff. of <10%. Relying on significance testing to detect imbalance may be misleading due to diminished sample size after matching.[15,16] Comparing the matched data gives us the direct association of anemia on mortality independent of the effect of other characteristics. Tests to confirm fitting of the model is inconsequential, and thus a nonparsimonious model can be used.

The lowest hematocrit (HCT) on CPB with highest sensitivity and specificity for mortality was estimated in the whole cohort, matched cohort, and anemic and nonanemic groups. Effect of lowest HCT on CPB on mortality was estimated in matched cohort after adjusting for anemia.

To study if mortality due to anemia varied with HCT values on CPB, anemic patients with lowest on CPB HCT of <20 and >20 values were compared for mortality.

Propensity scoring and matching was conducted using MatchIt package (Version: 2.4-21) for R software (R for Windows 3.1.2; The R Foundation for Statistical Computing, Vienna, Austria).[17] We did a 1:1 nearest neighbor matching with caliper distance of 0.2. Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 16.0.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Totally, 2449 patients were studied. Demographic, diagnostic, laboratory, operative, and outcome data in the whole cohort are summarized in Table 1. 37.1% of the whole cohort (33.91% among males and 40.88% among females) was anemic. Prevalence was more among females (40.88% versus 33.91%). Anemia had an unadjusted OR of 1.6 for mortality (95% confidence interval [95% CI]: 1.041, 2.570, $P = 0.033$)

Analysis of covariates between anemic and nonanemic groups showed imbalance - Table 2 (before matching). Matching is shown by balancing of variables with the S. diff. of <10% - Table 2 (after matching). After balancing of 18 confounders, matched anemic patients had higher in-hospital mortality than their nonanemic counterparts with OR of 1.79 (95% CI: 1.042–3.094, $P = 0.035$).

Secondary analysis

The majority of anemic patients were mildly anemic (67.34%). There was no significant difference in mortality between groups with mild and moderate anemia. Only 6 patients were severely anemic.

A cut-off of 20 for lowest HCT on CPB was obtained for predicting mortality across all categories with reasonable sensitivity and specificity [Table 4].

Lowest HCT on CPB was associated to mortality even after adjusting for effect of anemia (OR: 0.885, 95% CI: 0.817–0.958, $P = 0.002$) [Table 5].

In 866 pairs of matched cases, maintaining HCT >20 on CPB reduced mortality in the nonanemic group but not in anemic cases [Table 6].

Table 1: Summary statistics

Covariate	Mean/*n*	SD/%
All patients (*n*=2449)		
Age (years)	40.58	15.28
Height (cm)	158.69	10.64
Weight (kg)	52.18	12.78
BSA (m^2)	1.16	0.33
BMI (kg/m^2)	20.64	4.5
Gender (*n*)		
Male	1324	54.10
Female	1125	45.90
Stenosis		
Normal	974	39.80
AS	594	24.30
MS	702	28.70
AS+MS	179	7.30
Regurgitation		
Normal	828	33.80
AR	444	18.10
MR	999	40.80
AR+MR	178	7.30
TR		
Absent	1807	73.80
Present	642	26.20
Blood urea (mg/dl)	28.83	12.05
Creatinine clearance (ml/min)	77.3	34.04
Hb preoperative (g/dl)	12.96	1.72
PCV preoperative (%)	38.46	4.81
Surgery		
AVR	693	28.30
MVR	1019	41.60
AVR+MVR	301	12.30
MVRr	248	10.10
OMV	13	0.50
AVR+OMV	28	1.10
AVR+MVRr	27	1.10
Bentall's	20	0.80
AVR+CABG	45	1.80
MVR+CABG	32	1.30
Others	23	0.94
Redo surgery		
No	2420	98.80
Yes	29	1.20
Tricuspid surgery		
No	1817	74.20
TV repair	50	2.00
TV plasty	582	23.80
CPB time (min)	108.56	45.15
AoX time (min)	81.32	36.78
Hb_{LEAST} (g/dl)	7.48	1.32
PCV_{LEAST} (%)	21.74	3.77
Lactate (mmol/L)	2.82	1.21
Mortality		

Contd...

Table 1: Contd...

Covariate	Mean/*n*	SD/%
Alive	2371	96.82
Deaths	78	3.18

SD: Standard deviation, BSA: Body surface area, BMI: Body mass index, AS: Aortic stenosis, MS: Mitral stenosis, AR: Aortic regurgitation, MR: Mitral regurgitation, Hb: Hemoglobin, PCV: Packed cell volume, AVR: Aortic valve replacement, MVR: Mitral valve replacement, MVRr: Mitral valve repair, OMV: Open mitral valvuloplasty, CABG: Coronary artery bypass surgery, CPB: Cardiopulmonary bypass, AoX: Aortic cross-clamp, TR: Tricuspid regurgitation, TV: Tricuspid valve

DISCUSSION

In our cohort, the prevalence of anemia according to WHO criteria was 37.1% (33.91% among males and 40.88% among females). Most of the studies for the prevalence of anemia in the Indian population have been in women and children. In an epidemiological survey of 2559 volunteers from a rural population in 16–70 years of age group from India, the prevalence of anemia was 47.9% (50% among females and 44.3% among males).[13]

Table 2: Distribution of covariates-before and after matching

Covariate	Before matching						After matching					
	Nonanemic (*n*=1540, 62.9%)		Anemic (*n*=909, 37.1%)		*P*	S. diff.	Nonanemic (*n*=866, 50%)		Anemic (*n*=866, 50%)		*P*	S. diff.
	Mean/*n*	SD/%	Mean/*n*	SD/%			Mean/*n*	SD/%	*n*	Percentage	*P*	
Age (years)	41.74	14.11	38.63	16.9	0	19.98	40.77	14.91	39.58	16.37	0.11	7.6
Height (cm)	159.84	9.49	156.73	12.1	0.000	28.6	157.86	9.56	157.64	10.59	0.65	2.18
Weight (kg)	54.24	12.31	48.69	12.8	0	44.2	50.42	11.5	49.65	12	0.17	6.55
BSA (m^2)	1.21	0.32	1.08	0.32	0	44.44	1.12	0.3	1.1	0.3	0.17	6.67
BMI (kg/m^2)	21.18	4.32	19.72	4.66	0	32.53	20.2	4.16	19.93	4.42	0.19	6.29
Gender (*n*)												
Male	875	56.80	449	49.40	0	−14.87	425	49.10	427	49.30	0.9	0.4
Female	665	43.20	460	50.60		14.87	441	50.90	439	50.70		−0.4
Stenosis												
Normal	553	35.90	421	46.30	0	−21.26	370	42.70	386	44.60	0.7	−3.83
AS	393	25.50	201	22.10		7.99	197	22.70	194	22.40		0.72
MS	473	30.70	229	25.20		12.28	231	26.70	229	26.40		0.68
AS+MS	121	7.90	58	6.40		5.82	68	7.90	57	6.60		5.01
Regurgitation												
Normal	571	37.10	257	28.30	0	18.84	259	29.90	254	29.30	0.9	1.31
AR	304	19.70	140	15.40		11.32	140	16.20	138	15.90		0.82
MR	579	37.60	420	46.20		−17.5	392	45.30	393	45.40		−0.2
AR+MR	86	5.60	92	10.10		−16.79	75	8.70	81	9.40		−2.44
TR												
Absent	1152	74.80	655	72.10	0.14	6.12	634	73.20	630	72.70	0.8	1.13
Present	388	25.20	254	27.90		−6.12	232	26.80	236	27.30		−1.13
Blood urea (mg/dl)	28.36	10.54	29.62	14.21	0.01	−12.37	29.18	11.91	28.91	11.83	0.6	2.27
Creatinine clearance (ml/min)	78.45	34.9	75.36	32.45	0.03	9.2	75.16	41.5	76.06	32.78	0.6	−2.41
Hb preoperative (g/dl)	13.93	1.24	11.32	1.05	0	227.17	13.74	1.17	11.35	1.05	0	215
PCV preoperative (%)	40.92	3.78	34.31	3.26	0	187.27	40.45	3.66	34.35	3.25	0	176.25
Surgery												
AVR	472	30.60	221	24.30	0.04	14.15	215	24.80	219	25.30	1	−1.15
MVR	644	41.80	375	41.30		1.01	362	41.80	369	42.60		−1.62
AVR+MVR	180	11.70	121	13.30		−4.84	113	13.00	113	13.00		0
MVRr	129	8.40	119	13.10		−15.22	104	12.00	100	11.50		1.55
OMV	9	0.60	4	0.40		2.84	6	0.70	4	0.50		2.59
AVR+OMV	20	1.30	8	0.90		3.84	13	1.50	8	0.90		5.51
AVR+MVRr	12	0.80	15	1.70		−8.11	11	1.30	13	1.50		−1.7
Bentall's	15	1.00	5	0.60		4.49	5	0.60	5	0.60		0
AVR+CABG	25	1.60	20	2.20		−4.4	19	2.20	18	2.10		0.69

Contd...

Table 2: Contd...

Covariate	Before matching						After matching					
	Nonanemic (*n*=1540, 62.9%)		Anemic (*n*=909, 37.1%)		*P*	S. diff.	Nonanemic (*n*=866, 50%)		Anemic (*n*=866, 50%)	*P*		S. diff.
	Mean/*n*	SD/%	Mean/*n*	SD/%			Mean/*n*	SD/%	*n*	Percentage	*P*	
MVR+CABG	21	1.40	11	1.20		1.77	12	1.40	11	1.30		0.87
Others	13	0.84	10	1.10		−2.58	6	0.70	6	0.70		0
Redo												
No	1527	99.20	893	98.20	0.04	8.84	855	98.70	854	98.60	0.83	0.87
Yes	13	0.80	16	1.80		−8.84	11	1.30	12	1.40		−0.87
TR surgery												
TV plasty	351	22.80	231	25.40		−6.08	210	24.20	213	24.60		−0.93
CPB time (min)	107.62	45.2	110.16	45.04	0.18	−5.63	108.78	44.94	109.15	44.91	0.87	−0.82
AoX time (min)	81.35	38.22	81.28	34.22	0.05	0.19	80.69	33.97	80.91	34.01	0.89	−0.65
Hb least (g/dl)	7.74	1.33	7.04	1.19	0	55.47	7.57	1.34	7.06	1.18	0	40.39
PCV least (%)	22.49	3.82	20.47	3.31	0	56.52	21.96	3.79	20.52	3.3	0	40.52
Lactate (mmol/L)	2.81	1.12	2.83	1.34	0.73	−2.43	2.82	1.19	2.8	1.33	0.68	1.58

S. diff.: Standardised difference, SD: Standard deviation, BSA: Body surface area, BMI: Body mass index, AS: Aortic stenosis, MS: Mitral stenosis, AR: Aortic regurgitation, MR: Mitral regurgitation, TR: Tricuspid regurgitation, Hb: Hemoglobin, PCV: Packed cell volume, AVR: Aortic valve replacement, MVR: Mitral valve replacement, MVRr: Mitral valve repair, OMV: Open mitral valvuloplasty, CABG: Coronary artery bypass surgery, TV: Tricuspid valve, CPB: Cardiopulmonary bypass, AoX: Aortic cross-clamp

Table 3: Distribution of mortality according to severity of anemia

	Total (*n*, % of 2449)	Mortality (*n*, % in each category)
No anemia	1564 (63.86)	41 (2.6)
Mild anemia		
Men - 11-12.9 g/dL	596 (24.34)	24 (4)
Women - 11-11.9 g/dL		
Moderate anemia		
8-10.9 g/dL	283 (11.56)	13 (4.6)
Severe anemia		
<8 g/dL	6 (0.25)	0

Table 4: Optimum cut-off values for least HCT on CPB for prediction of mortality

Cohort	Least HCT on CPB	Sensitivity	Specificity
Whole cohort	20.41	62.8	59.5
Matched cohort	20.12	60.3	62.3
Anemic group	20.41	67.6	46.9
Nonanemic group	20.12	66.7	68.4

HCT: Hematocrit, CPB: Cardiopulmonary bypass

Low dietary intake, bioavailability, and chronic blood loss contribute to the anemic burden in India.

Previously published studied have looked at the prevalence of anemia according to WHO criteria in diverse populations. In the Multicenter Study of Perioperative Ischemia that included 5065 patients from 70 institutions worldwide, undergoing coronary surgery with CPB, Kulier *et al*. found that anemia was present in 28.1% of the male and 35.9% of the female patients.[7] In a study by Muñoz *et al*., of 576 patients undergoing elective cardiac surgery, the prevalence of preoperative anemia was 37%.[18] Elmistekawy *et al*. retrospectively analyzed 2698 patients undergoing nonemergent aortic valve surgery with or without concomitant procedures. Prevalence of anemia in their population was 32.2% and was similar between genders.[9]

Table 5: Effect of lowest HCT on CPB on mortality after adjusting for anemia

	OR	95% CI	*P*
Anemia	1.546	0.891-2.693	0.121
Lowest HCT on CPB	0.885	0.817-0.958	0.002

HCT: Hematocrit, CPB: Cardiopulmonary bypass, OR: Odds ratio, CI: Confidence interval

Table 6: Effect of HCT on mortality in anemic and nonanemic patients

	Least PCV on CPB			
	Nonanemic (*n*=866)		Anemic (*n*=866)	
	<20 count	>20 count	<20 count	>20 count
Alive	265	580	361	468
Dead (%)	13 (4.7)	8 (1.4)	21 (5.5)	16 (3.3)
P	0.0071		0.1554	

HCT: Hematocrit, PCV: Packed cell volume, CPB: Cardiopulmonary bypass

We observed that anemia was a predictor of in-hospital mortality (4.2% in anemic group vs. 2.6% in the nonanemic group) with unadjusted OR of 1.6 and an OR of 1.8 after propensity matching.

Cladellas *et al*. retrospectively studied the effect of anemia (Hb <12 g/dl – 42 [18.02%] patients) as a risk marker for in-hospital mortality in 201 consecutive patients who underwent valve surgery and concluded that it was associated with greater than three-fold increase in the unadjusted odds of death (OR: 3.2; 95% CI: 1.09–9.55; $P = 0.03$). In-hospital mortality in their study was 23.8% in the anemic group, significantly higher than 5.7% in the nonanemic group. Their cohort had significant differences between anemic and nonanemic groups in age, gender, comorbidities, NYHA status, and EuroSCORE. But anemia remained a significant predictor even after adjustment for EuroSCORE (OR: 3.64; 95% CI: 1.32–10.06; $P = 0.01$).[8] Compared to their cohort, ours was younger (40.5 ± 15.2 vs. 65 ± 10.6 years), had lesser aortic valve diseases (45.4% vs. 50.7%) and lesser associated CABGs (3.1% vs. 19.1%), and might have contributed to lower mortality in our cohort.

Kulier *et al*. studied the relationship between preoperative anemia and cardiac and noncardiac adverse events in 4804 patients who underwent cardiac surgery at 72 institutions during 1990s and found a strong independent association between preoperative anemia and noncardiac complications (which included cerebral, renal, gastrointestinal, and "other" adverse events) but not cardiac complications. In-hospital mortality occurred in 3.3%. There was no increase in adjusted OR for the cardiac outcome (myocardial infarction, congestive heart failure or death form cardiac causes) with lower Hb levels.[7]

Karkouti *et al*. in a multicenter cohort study of 3500 patients showed overall prevalence of anemia (defined by Hb <12.5 g/dl, the average threshold of the WHO's gender-based definition of 12.0 g/dL in women and 13.0 g/dL in men) was 26%. Mortality was observed in 6.6% of anemic patients compared to 1.4% in nonanemic patients ($P < 0.0001$), though after propensity matching, among 515 pairs of patients there was no significant difference in mortality among anemic and nonanemic groups (4.7% and 3.1%, respectively, $P = 0.2$). They noted a significant difference in acute kidney injury and the composite outcome of death, stroke or acute kidney injury. Preoperative anemia was associated with an unadjusted OR of 3.6 (95% CI: 2.7–4.7, $P < 0.0001$) in the entire sample and OR of 1.8 (95% CI: 1.2–2.7; $P = 0.005$) in the propensity-matched sample.[19]

Zindrou *et al*. and Bell *et al*. studied CABG patients and described an OR of 3.2 and 2.3, respectively, for mortality.[12,20]

There are a number of potential mechanisms that may explain the negative association between anemia and outcome. The reduced oxygen-carrying capacity with low Hb can result in tissue malperfusion that can increase susceptibility to postoperative adverse outcomes.[21]

Several recent clinical studies have found that severe anemia and low oxygen delivery during CPB are associated with increased risk of renal failure, stroke, and death.[22-24] Transfusions might also adversely affect outcome via immunomodulation or other ways not yet understood.

Chronic disease can cause activation of hepcidin causing a state of functional iron deficiency leading to anemia.[25]

Strengths of our study

This is the first reported study in the Indian population which assesses the prevalence of anemia and studies its effect on mortality after cardiac surgery. This study includes the entire spectrum of adult valvular procedures and balances the effect of 18 covariates in the anemic and nonanemic groups to obtain the effect of anemia *per* se on mortality. We also looked into the effect of lowest HCT on CPB on mortality.

Limitations

We are unable to determine the exact relationship between anemia and mortality. It is possible that preoperative anemia was associated with adverse outcomes simply because it is a marker for severity of illness.

The effects of unknown or unmeasured confounders on the observed association cannot be ruled out. The critical assumption underlying PS analysis is that of "no unmeasured confounders."[16] Left ventricle ejection fraction (LVEF, available in 22.78%) was not included as a variable. There was no significant difference in LVEF between anemic and nonanemic groups (57.18 ± 7.5 and 55.73 ± 8.65, respectively, $P = 0.17$). It is our assumption that after balancing of the other variables included in PS matching the results of other confounders are likely to be insignificant.

The cause, duration or corrections of preoperative anemia, all of which have prognostic implications, were not studied.

The duration of follow-up was limited to the period of hospitalization. Thus, postdischarge complications could not be accounted for in our analysis.

Our results are not adjusted for perioperative blood transfusions. But since the indication for transfusion is anemia in itself, we believe that they are interdependent, and, therefore, their respective effects should not be separated.

CONCLUSION

This study demonstrates the independent association of preoperative anemia with increased odds of in-hospital mortality after cardiac surgery. HCT of less than 20 on CPB is associated with postoperative mortality.

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