Preoperative Anemia in Cardiac Operation: Does Hemoglobin Tell the Whole Story?

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Background. Preoperative anemia, defined by hemoglobin level, is associated with elevated risk after cardiac operation. Better understanding of anemia requires characterization beyond this. This investigation focuses on red cell size and its association with patient characteristics and outcomes after cardiac operation.

Methods. From January 2010 to January 2014, 10,589 patients underwent elective cardiac operations at Cleveland Clinic. Anemia was characterized as normocytic, microcytic, or macrocytic based on mean corpuscular volume (MCV). Models for hospital complications were developed using multivariable logistic regression. Other outcomes were postoperative transfusion and intensive care unit (ICU) and postoperative hospital lengths of stay.

Results. A total of 2,715 patients (26%) were anemic. Of these, 2,365 (87%) had normocytic, 219 (8.1%) microcytic, and 131 (4.8%) macrocytic anemia. Non-anemic patients (n = 2,041, 26%) received transfusions compared with 1,553 (66%) normocytic, 148 (68%) microcytic, and 97 (74%) macrocytic anemia patients. Patients with normocytic or macrocytic anemia had more renal failure (normocytic: odds ratio (OR) 1.9, macrocytic: OR 3.5), other complications (normocytic: OR 1.3, macrocytic: OR 2.2) and death (normocytic: OR 2.0, macrocytic: OR 6.2) than non-anemic patients; patients with microcytic anemia had fewer reoperations (OR 0.35) and less postoperative atrial fibrillation (OR 0.50). Anemic patients experienced longer ICU (27 versus 48 hours, $p < 0.001$) and postoperative hospital (6.1 versus 7.4 days, $p < 0.001$) length of stay than non-anemic patients.

Conclusions. Cardiac surgical patients are often anemic. Demographic characteristics, comorbidities, and outcomes are dissimilar according to red cell size. Patients with microcytic anemia had the lowest hemoglobin levels, yet the best clinical outcomes among anemic patients. MCV from the standard complete blood count adds additional information beyond hemoglobin for targeted intervention.

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Anemia, as defined by hemoglobin level, is common among patients presenting for cardiac operation [1]. Although preoperative anemia per se has morbidity implications [2–4], the risk of anemia is compounded by acute hemodilution during operation, perioperative phlebotomy [5], and surgical blood loss. These factors expose patients to the risks of red blood cell (RBC) transfusion [6–9].

Beyond hemoglobin level, anemia can be classified by RBC kinetics (eg, anemia caused by decreased RBC production, increased RBC destruction, or blood loss), pathophysiologic process (eg, hereditary, autoimmune, mechanical), or RBC size (normocytic, microcytic, or macrocytic anemia) [10]. This investigation focuses on RBC size classifications and their associations with patient characteristics and clinical outcomes after elective cardiac operation.

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Patients and Methods

Defining and Classifying Anemia

Anemia was defined as a hemoglobin level less than 13 g/dL for men and less than 12 g/dL for women [11]. Anemia was classified as mild (hemoglobin >11 g/dL and <12 g/dL for women and >11 g/dL and <13 g/dL for men), moderate (hemoglobin >9 g/dL and ≤11 g/dL), and severe (hemoglobin ≤9 g/dL) [11]. Anemia was further classified by mean corpuscular volume (MCV) and the average size of RBCs, available from the standard complete blood count (CBC). Anemia was considered normocytic when MCV was between 80 and 100 femtoliter (fL), microcytic when less than 80 fL, and macrocytic when more than 100 fL (Fig 1) [12].

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Patients and Data Collection

From January 2010 to January 2014, 16,099 adults underwent cardiac operation at Cleveland Clinic. Patients with uncommon procedures (heart transplantation, atrial myxoma removal, pulmonary endarterectomy, pulmonary valve replacement, pulmonary valve repair, and tricuspid valve replacement) were excluded (n = 528), leaving a study group of 15,571 patients. This report focuses on the 10,589 patients from this cohort who underwent elective operations (See Supplemental Tables E1–E4 for characteristics and outcomes of patients operated on urgently and emergently): 8,158 patients (77%) underwent primary operations and 2,431 patients (23%) had reoperations.

Preoperative blood samples were processed for hemoglobin, MCV, and red cell distribution width using an automated hematology analyzer. Preoperative data (demographic characteristics, clinical history, and laboratory findings) were prospectively collected and entered into institutional databases. The institutional review board approved use of these data for research, with patient consent waived.

End Points

End points included patient characteristics according to RBC size classification and clinical outcomes, including RBC transfusion, Society of Thoracic Surgeons National Cardiac database hospital complications, hospital death, and intensive care unit (ICU) and postoperative hospital lengths of stay.

Statistical Analysis

All analyses were performed using R software (Vienna, Austria). Categorical variables were summarized as

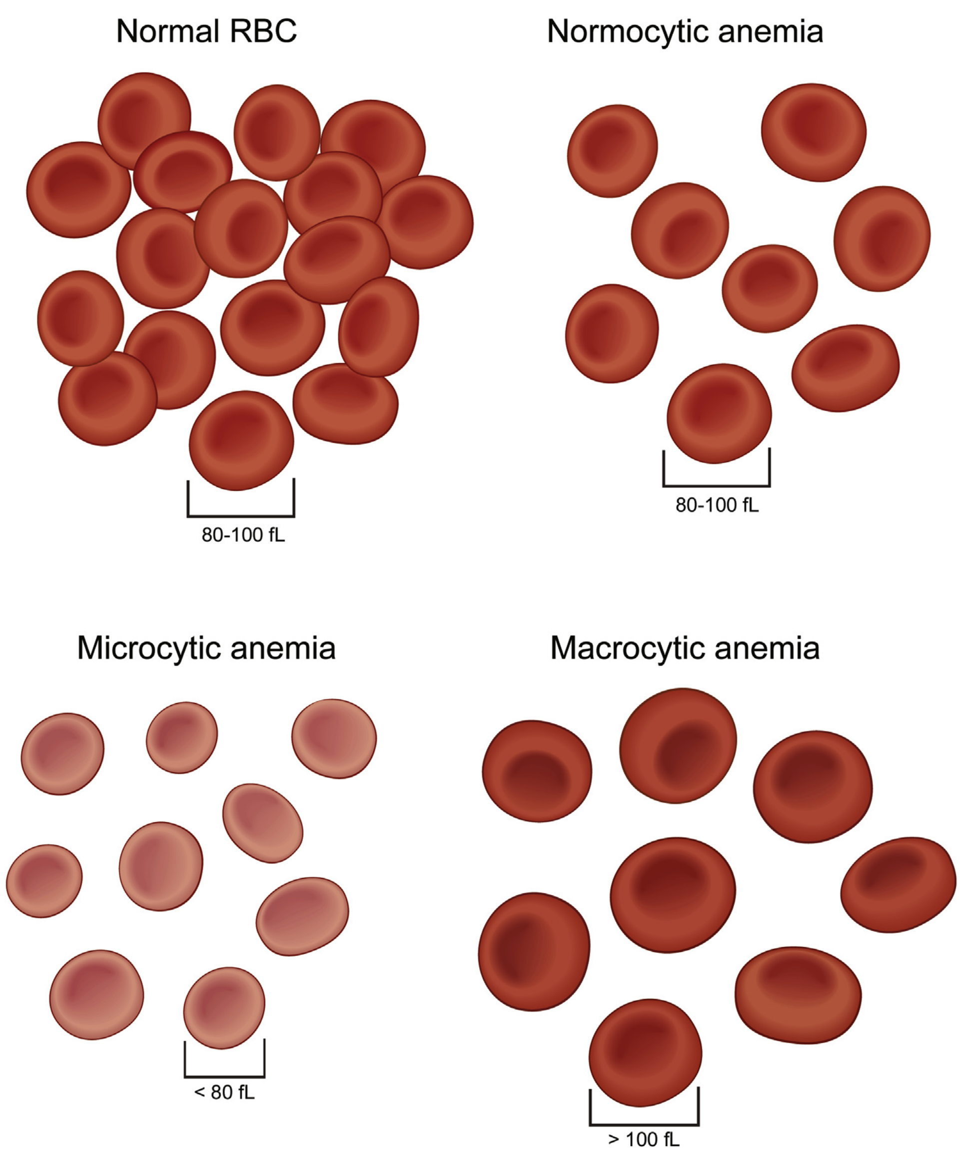

Fig 1. Classification of red blood cells (RBCs) by mean corpuscular volume: normal and normocytic, microcytic, and macrocytic anemia. (fL = femtoliter.)

frequencies and percentages and were compared using the χ^2 test. Continuous variables were summarized as median, 25th, and 75th percentiles and were compared using the Wilcoxon rank-sum test. Characteristics of patients in each anemia type were compared with non-anemic patients using standardized differences [13]. We recognized that preoperative anemia and perioperative transfusion were confounded, and both have been associated with adverse clinical outcomes. Therefore, number of RBC units transfused was incorporated into analyses of outcomes in an attempt to at least partially isolate the effect of anemia types on outcome. Results of multivariable logistic regression analyses are reported as odds ratios with 95% confidence intervals for postoperative complications and death. Linear regression was performed to examine the associations between anemia type and ICU and postoperative hospital lengths of stay after logarithmic transformation, adjusted for RBC transfusion.

Results

Prevalence of Anemia

Among patients undergoing elective operation, 2,715 (26%) were anemic. Normocytic anemia was the most common anemia type (n = 2,365, 87%), followed by microcytic (n = 219, 8.1%) and macrocytic (n = 131, 4.8%) anemia, regardless of clinical status (Supplemental Figure E1).

The highest proportions of moderately (n = 110, 50%) and severely (n = 26, 12%) anemic patients were seen in the microcytic anemia group (Fig 2). In contrast, most patients with normocytic anemia had mild anemia (n = 1,551, 66%). Median preoperative hemoglobin level for patients undergoing elective operation was 14 g/dL in the non-anemic group and 12, 11, and 11 g/dL in the normocytic, microcytic, and macrocytic groups, respectively (Fig 3A). Median MCV for the four groups was 90 (non-anemic), 90 (normocytic), 75 (microcytic), and 103 (macrocytic) fL (Fig 3B).

Anemia and Patient Characteristics

Compared with non-anemic patients, patients with normocytic anemia were older, and patients with microcytic anemia were younger, more likely to be women, and had the highest body mass index (BMI) (Supplemental Table E5; Fig 4A). Patients with macrocytic anemia were the oldest, least likely to be women, and had the lowest BMI.

Many comorbidities, including prior myocardial infarction, heart failure, hypertension, chronic obstructive pulmonary disease, diabetes, prior stroke, previous cardiac operation, peripheral arterial disease, atrial fibrillation or flutter, and ventricular arrhythmias, were more common in anemic patients but differed according to type of anemia (Figs 4B, 4C).

Transfusion in Elective Operation

RBC transfusion was more common in anemic than non-anemic patients: 1,553 (66%) with normocytic anemia, 148 (68%) with microcytic anemia, and 97 (74%) with macrocytic anemia. In contrast, 2,041 non-anemic patients (26%) received RBCs (Table 1; Fig 5A). Despite having the lowest hemoglobin level, patients with microcytic anemia who required transfusion received the same median units of RBCs as patients with normocytic and macrocytic anemia who received transfusions (Fig 5B).

Anemic patients received more blood product in general. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets was least common among patients with microcytic anemia and most common

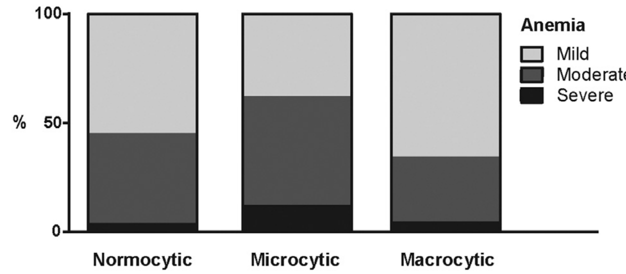

Fig 2. Severity of preoperative anemia in elective cardiac operation. Mild anemia was defined as hemoglobin more than 11 g/dL and less than 12 g/dL for women and more than 11 g/dL and less than 13 g/dL for men; moderate as hemoglobin more than 9 g/dL and 11 g/dL or less; and severe as hemoglobin 9 g/dL or less.

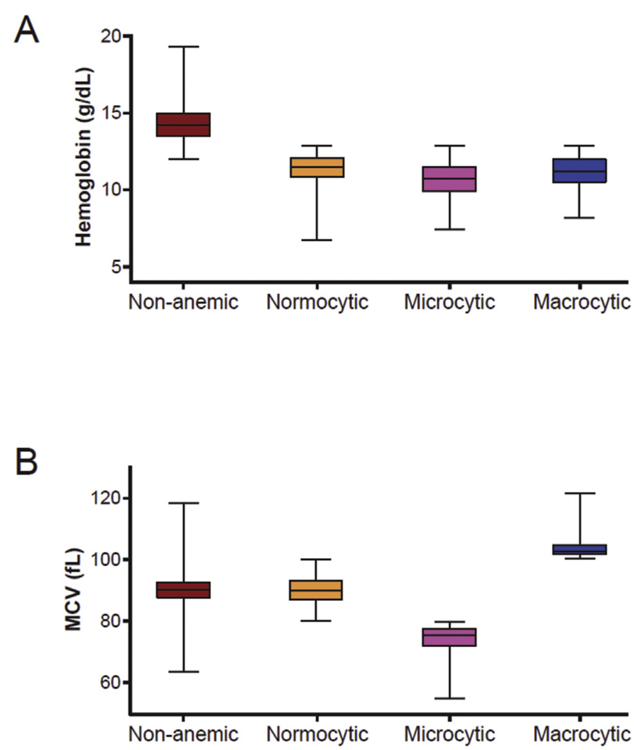

Fig 3. (A) Hemoglobin and (B) mean corpuscular volume (MCV) for non-anemic patients and patients with various types of anemia. Box encompasses 25th and 75th percentiles, horizontal line within box is median, and whiskers indicate minimum and maximum values.

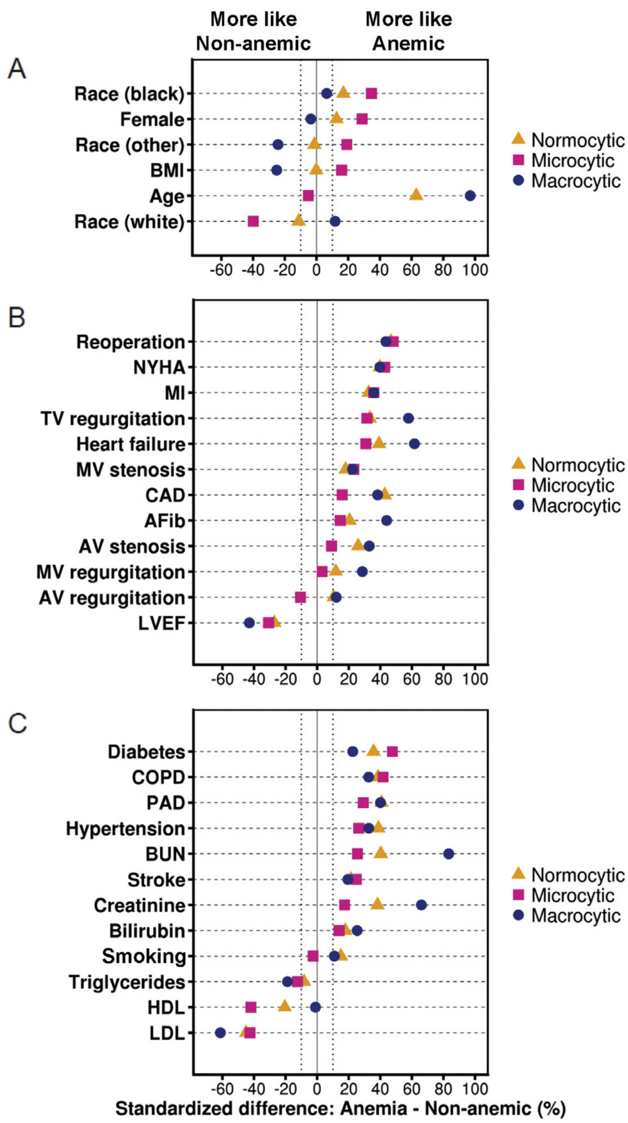

Fig 4. Standardized differences between patients with each type of anemia and non-anemic patients. (A) Demographic characteristics. (B) Cardiac comorbidities. (C) Noncardiac comorbidities and laboratory values. (AFib = atrial fibrillation; AV = aortic valve; BMI = body mass index; BUN = blood urea nitrogen; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MV = mitral valve; NYHA = New York Heart Association; PAD = peripheral arterial disease; TV = tricuspid valve.)

among patients with macrocytic anemia (Supplemental Table E6).

Postoperative Complications

Among non-anemic patients, 284 (3.6%) underwent reoperation, compared with 168 (7.1%), 6 (2.7%), and 12 (9.2%) with normocytic, microcytic, and macrocytic anemia, respectively (Table 1). Prolonged ventilation (6.1% non-anemic versus 13% normocytic, 13% microcytic, 19% macrocytic; $p < 0.001$), renal failure (1.7% non-anemic versus 5.2% normocytic, 3.2% microcytic, 11% macrocytic; $p < 0.001$), and other complications (4.2% non-anemic versus 8.8% normocytic, 6.8% microcytic, 16% macrocytic; $p < 0.001$) were more common in anemic than non-anemic patients (Table 1). Atrial fibrillation (26% non-anemic versus 26% normocytic, 16% microcytic, 28% macrocytic; $p < 0.001$) and hospital death (0.4% non-anemic versus 1.5% normocytic, 0% microcytic, 4.6% macrocytic; $p < 0.001$) were more common in patients with normocytic and macrocytic anemia than in non-anemic patients.

Adjusted for RBC transfusions, normocytic and macrocytic anemias were associated with higher risk of renal failure, other complications, and death (Fig 6). In addition to these events, macrocytic anemia was also associated with a higher risk of other arrhythmias (cardiac arrest, heart block). Patients with microcytic anemia had a lower risk of reoperation and atrial fibrillation than non-anemic patients.

ICU and Postoperative Hospital Lengths of Stay

Anemic patients experienced longer ICU and postoperative hospital lengths of stay than non-anemic patients (Table 1). After adjusting for RBC transfusions, this remained true for all but microcytic anemia (Table 2).

Comment

Principal Findings

Anemia is common in patients presenting for elective cardiac operation (even more so in patients undergoing urgent or emergency operation). RBC size classification adds information beyond hemoglobin level from a standard CBC in terms of better understanding demographic, comorbidity, and clinical outcome profiles and treatment options associated with each anemia classification. In addition, anemic patients have increased hospital resource utilization in terms of requiring more RBC transfusions and increased ICU and postoperative hospital lengths of stay. After adjusting for transfusions, normocytic, and particularly macrocytic, anemias are associated with increased risk of adverse outcomes.

Prevalence and Anemia Classification

Our finding that preoperative anemia is common is consistent with other studies [1, 14–16]. Normocytic anemia can be caused by blood loss, hemolysis, RBC membrane or enzyme defects, and bone marrow suppression. Microcytic anemia is commonly seen in iron deficiency and may also reflect anemia of chronic disease/inflammation or underlying thalassemia [17]. Macrocytic anemia can be caused by vitamin B_{12} or folate deficiencies, alcohol use, myelodysplasia, liver disease, or certain medications [18]. Anemia caused by many causes often presents as normocytic in the early stages. This is consistent with our finding that most anemias were normocytic.

Table 1. Clinical Outcomes of Elective Operation by Anemia Type

Outcomes	Non-Anemic (n = 7,874)	Normocytic (n = 2,365)	Microcytic (n = 219)	Macrocytic (n = 131)	*p* Value
RBC transfusion, units					<0.001
0	5,833 (74)	812 (34)	71 (32)	34 (26)	
1	851 (11)	396 (17)	32 (15)	21 (16)	
2	548 (7.0)	356 (15)	37 (17)	21 (16)	
3	212 (2.7)	256 (11)	25 (11)	12 (9.2)	
4	140 (1.8)	184 (7.8)	22 (10)	12 (9.2)	
≥5	290 (3.7)	361 (15)	32 (15)	31 (24)	
Reoperation	284 (3.6)	168 (7.1)	6 (2.7)	12 (9.2)	<0.001
Atrial fibrillation	2,065 (26)	613 (26)	35 (16)	37 (28)	0.007
Other arrhythmias[a]	113 (1.4)	59 (2.5)	2 (0.9)	12 (9.2)	<0.001
Prolonged ventilation	477 (6.1)	306 (13)	29 (13)	25 (19)	<0.001
Renal failure	134 (1.7)	124 (5.2)	7 (3.2)	14 (11)	<0.001
Other complications[b]	334 (4.2)	209 (8.8)	15 (6.8)	21 (16)	<0.001
Hospital death	32 (0.4)	35 (1.5)	0 (0.0)	6 (4.6)	<0.001
ICU length of stay, hours	27 [23, 51]	48 [25, 93]	42 [24, 74]	66 [28, 128]	<0.001
Postoperative hospital length of stay, days	6.1 [5.0, 8.1]	7.4 [6.0, 10.0]	7.1 [5.2, 9.9]	8.2 [6.2, 12.0]	<0.001

[a] Composite of heart block and cardiac arrest. [b] Composite of infection, vascular complications, stroke, coma, paralysis, pulmonary embolism, renal dialysis, and gastrointestinal complications.

Values are n (%) or median [25th, 75th percentiles].

ICU = intensive care unit; RBC = red blood cell.

Demographic Characteristics and Comorbidity

Although the average hemoglobin level is lower in older patients [19], patients with microcytic anemia were younger than non-anemic patients in our study. This group also had the highest proportion of women. It is likely that most of these women presented with iron deficiency from obligate iron loss through menses [17].

Preoperative anemia has been associated with increased rates of morbidity and mortality after major surgical procedures, mainly because of the presence of other cardiovascular risk factors in this population [1–3, 15, 20]. Pathophysiologic process of these conditions is often interconnected. For example, heart failure is associated with iron deficiency, renal dysfunction, impaired erythropoietin production, and a blunted erythropoietin response [21, 22], all contributing to development of anemia. Anemia in turn causes peripheral vasodilatation and activates the renin-angiotensin-aldosterone system. This leads to volume expansion and worsening of heart failure [23].

Clinical Outcomes

The higher prevalence of RBC transfusion seen in our anemic group is intuitively understandable and consistent with previous reports [1, 15, 24]. Although blood products are given in an effort to improve oxygen delivery, there is mounting evidence demonstrating an association between transfusion and a multitude of complications [6–9, 25]. Ex vivo storage of RBCs can impair the cells' metabolic activities, reduce their ability to deliver oxygen, and impair their antioxidant defenses. Prolonged storage also leads to changes in cell shape, thereby increasing aggregability and adhesion to endothelial cells [26, 27]. Furthermore, accumulation of potentially toxic microparticles in the plasma may cause vascular dysfunction, inflammation, and thrombosis [28].

Clinical Implications

Our data suggest a relationship between MCV and clinical outcome in cardiac operation. Patients with microcytic anemia had the lowest hemoglobin levels (ie, were the most anemic), yet their risks of postoperative complications were similar to those of non-anemic patients. In contrast, patients with macrocytic anemia had higher median hemoglobin levels (ie, were less anemic) than patients with microcytic anemia, yet they were the most likely to receive RBC transfusion, had the highest risk of adverse outcome, and the longest ICU and postoperative hospital lengths of stay. The finding of a potential association between MCV and clinical outcome in cardiac operation may represent a first step toward understanding how different types of anemia affect surgical outcome.

How might the cardiac surgeon use this information available from the standard preoperative CBC, along with hemoglobin level? Imagine a 42-year-old woman undergoing preoperative evaluation for a mitral valve repair. Her CBC reveals microcytic anemia: hemoglobin of 10.5 g/dL and MCV of 75 fL. It is likely that her anemia is caused by iron deficiency, the most common cause of microcytic anemia [29]. Intravenous iron provides a mechanism for more rapid repletion of iron stores compared with oral supplementation. It increases reticulocyte counts and hemoglobin levels and may reduce RBC transfusion [30–32].

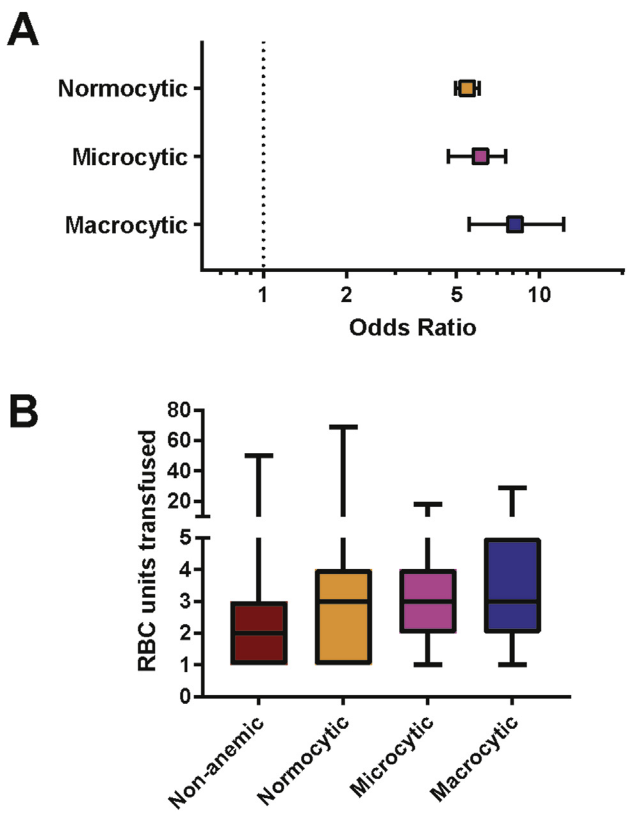

Fig 5. (A) Odds ratios of anemic patients compared with non-anemic patients for receiving red blood cell (RBC) transfusion. Squares represent odds ratios and whiskers 95% confidence intervals. (B) Units of RBCs transfused among patients who received blood. Box encompasses 25th and 75th percentiles, horizontal line within box is median, and whiskers indicate minimum and maximum values.

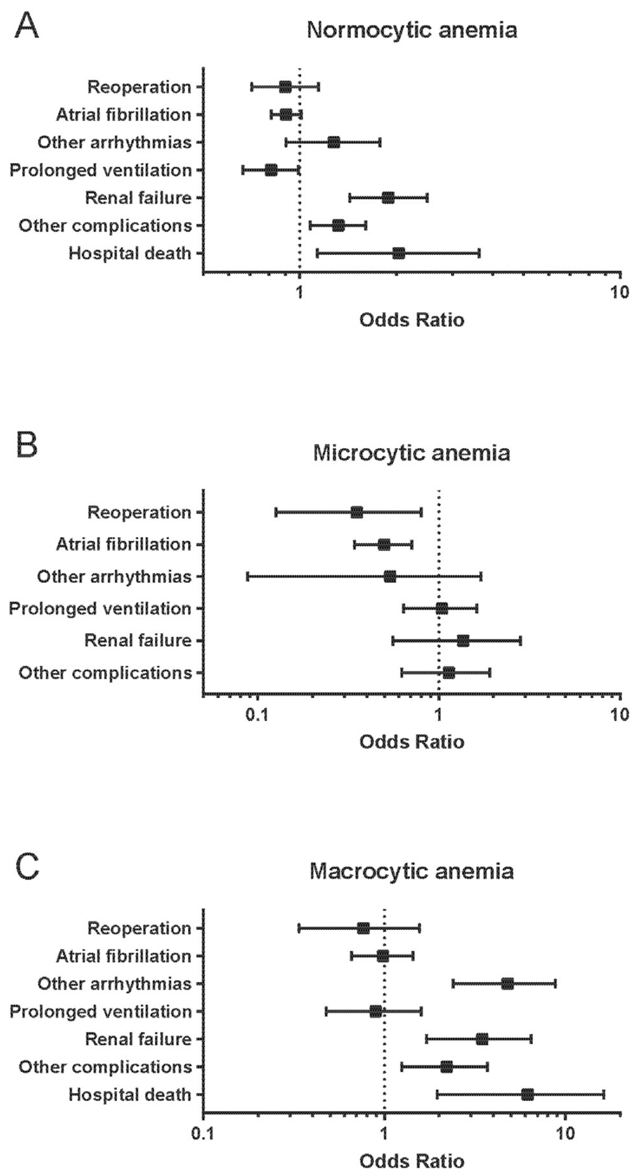

Fig 6. Odds ratios, adjusted for transfusion, for adverse outcomes in patients with (A) normocytic, (B) microcytic, and (C) macrocytic anemia, compared with non-anemic patients. Squares represent odds ratios and whiskers 95% confidence intervals.

Imagine another patient with a history of rheumatoid arthritis. The CBC shows hemoglobin of 11 g/dL and MCV of 79 fL. Anemia of chronic disease, which can present as microcytic anemia, should be considered in this case. It occurs as a result of functional iron deficiency, whereby patients may have adequate iron stores, but there is insufficient mobilization in the presence of increased demand. In this setting, iron supplementation, which treats iron deficiency anemia, may expose patients to iron overload. Recombinant erythropoietin (rEPO) can be used to reduce transfusions [33]. However, no large-scale safety study for use of rEPO in cardiac surgical patients has been conducted, and a black box warning has been added to its label after several studies have shown that rEPO is associated with increased risk of thrombosis and cardiovascular events [34–36]. Thus, at the present time, this strategy needs to be used cautiously.

For patients with macrocytic anemia, serum vitamin B_{12} and folate levels should be obtained, and any deficiency corrected. Alcohol toxicity can independently cause macrocytosis, which corrects itself with abstinence. Drug therapies for human immunodeficiency virus, cancer, and other disorders may also cause macrocytic anemia. rEPO may correct the anemia in some of these patients but must be used with caution. Treating macrocytic anemia caused by liver disease, myelodysplasia, and myeloproliferative disorders involves addressing the underlying disease [37, 38]. Referral to a hematologist and consideration of bone marrow examination should be considered in patients with macrocytic anemia of uncertain cause.

Treatment of normocytic anemia depends on the underlying cause. Anemias due to nutritional deficiencies are corrected by supplementation. Hemolytic anemias are diverse, and their therapy depends on the reasons for hemolysis and may necessitate corticosteroid or other

Table 2. *Risk-Adjusted Intensive Care Unit and Postoperative Hospital Lengths of Stay by Anemia Type*

	Non-Anemic	Normocytic		Microcytic		Macrocytic	
Length of Stay	Median [25th, 75th percentiles]	Median [25th, 75th percentiles]	p Value	Median [25th, 75th percentiles]	p Value	Median [25th, 75th percentiles]	p Value
Intensive care unit, hours			<0.001		0.4		<0.001
No RBC transfusion	34 [33, 34]	38 [37, 39]		32 [29, 36]		44 [38, 50]	
1 unit of RBC transfusion	38 [37, 39]	43 [42, 45]		36 [33, 40]		49 [43, 56]	
Postoperative hospital, days			<0.001		<0.001		<0.001
No RBC transfusion	6.6 [6.5, 6.6]	7.8 [7.6, 8.0]		7.3 [6.9, 7.8]		8.0 [7.4, 8.6]	
1 unit of RBC transfusion	7.1 [7.0, 7.2]	8.4 [8.2, 8.6]		7.9 [7.4, 8.4]		8.6 [8.0, 9.3]	

RBC = red blood cell.

immunosuppression regimen [39]. Hypersplenism may again have diverse underlying causes, but it is usually managed supportively; splenectomy may be used but is associated with considerable morbidity in some conditions [39]. Anemia of chronic renal disease may be managed with rEPO, with close monitoring [40].

Limitations

Several limitations should be considered when interpreting these data. We classified anemia using conventional cut points of a continuous variable, MCV. Anemia type was not further stratified by severity in our analyses because of limited sample size in the microcytic and macrocytic groups. This study is based on retrospective analysis of a single institution's observational, prospectively collected data. It was conducted at a large quaternary referral center, and results may not be applicable to other medical settings. It reports only preliminary results for clinical outcome without control for comorbidities. Finally, it would be valuable for future studies to examine the correlation between anemia severity and transfusion requirement or surgical outcomes in each type of anemia.

Conclusion

Preoperative anemia in the cardiac surgical setting is common, even in elective cases. In addition to hemoglobin levels, the type of anemia, as defined by RBC size (MCV) available from the standard CBC, should also be considered when evaluating anemic patients because patients with normocytic, microcytic, or macrocytic anemia have different demographic characteristics, cardiac and non-cardiac comorbidities, surgical outcomes, and therapeutic options. Better understanding of different types of anemia, beyond simple hemoglobin level, may allow physicians to optimize patient management before operation to circumvent downstream events and to allow for more accurate preoperative risk estimation.

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