

Risk Associated with Preoperative Anemia in Noncardiac Surgery

A Single-center Cohort Study

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Background: Preoperative anemia is an important risk factor for perioperative red blood cell transfusions and has been shown to be independently associated with adverse outcomes after noncardiac surgery. The objective of this observational study was to measure the prevalence of preoperative anemia and assess the relationship between preoperative anemia and postoperative mortality.

Methods: Data were retrospectively collected on 7,759 consecutive noncardiac surgical patients at the University Health Network between 2003 and 2006. Preoperative anemia was defined as a hemoglobin concentration less than 12.0 g/dl for women and less than 13.0 g/dl for men. The unadjusted and adjusted relationship between preoperative anemia and mortality was assessed using logistic regression and propensity analyses.

Results: Preoperative anemia was common and equal between genders (39.5% for men and 39.9% for women) and was associated with a nearly five-fold increase in the odds of postoperative mortality. After adjustment for major confounders using logistic regression, anemia was still associated with increased mortality (odds ratio, 2.36; 95% confidence interval, 1.57–3.41). This relationship was unchanged after elimination of patients with severe anemia and patients who received transfusions. In a propensity-matched cohort of patients, anemia was associated with increased mortality (odds ratio, 2.29; 95% confidence interval, 1.45–3.63).

Conclusions: Anemia is a common condition in surgical patients and is independently associated with increased mortality. Although anemia increases mortality independent of transfusion, it is associated with increased requirement for transfusion, which is also associated with increased mortality. Treatment of preoperative anemia should be the focus of investigations for the reduction of perioperative risk.

DESPITE improved surgical techniques, the publication of consensus guidelines¹ and the use of improved anesthetic techniques, postoperative mortality has remained unchanged over the past decades.² This report focuses on preoperative anemia, which is emerging as a common and important public health issue.^{3–6} Under the assumption that the results of the Transfusion Requirements in Critical Care trial are transferable to noncardiac surgery,⁷ clinicians have been encouraged to tolerate greater degrees of anemia. However, the Transfusion Requirements in Critical Care trial has been criticized because of treatment misalignment that makes the results difficult to transfer to other settings.⁸ Preoperative anemia is an important issue because it is the strongest predictor of transfusions of blood components,^{9–12} which carry many attendant risks^{7,13} and likely increases morbidity. Second, anemia has been associated with harmful effects over and above the increased risk imparted by the increased need for transfusion. A variety of studies in general and elderly populations, in patients with coronary disease¹⁴ and congestive heart failure,¹⁵ and in cardiac^{16–18} and noncardiac surgery¹⁹ have linked anemia with increased mortality.

Preoperative anemia is a common condition. Although hemoglobin levels are almost universally measured before surgery,²⁰ few studies have explored the implications of reduced hematocrit in noncardiac surgery. The studies that have been reported are limited due to small sample size,^{5,6} failure to examine the entire spectrum of surgeries,³ or failure to account for the major known confounders.¹⁹ The largest and most recent study,¹⁹ although overcoming many of these limitations, suggests that there were possible gender differences, and it failed to show an effect of anemia in women. Second, this study did not adjust for transfusions, which, as we have noted, may have independent deleterious sequelae.²¹

The causes of preoperative anemia include hospital-acquired anemia, iron deficiency anemia, and anemia of chronic illness.²² If preoperative anemia were found to be an important cause of adverse outcomes after noncardiac surgery, it would be an excellent candidate for intervention. With these factors in mind, we undertook a preliminary single-center retrospective cohort study to determine the independent association between preoperative anemia and mortality after noncardiac surgery.

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Materials and Methods

Study Setting, Patient Sample, and Data Collection

The Toronto General Hospital is one of three sites of University Health Network, a tertiary referral center in Toronto, Ontario, Canada, affiliated with the University of Toronto. Noncardiac surgical services at this institution include vascular and oncology surgery in head and neck, urology, and thoracic, hepatobiliary, general, and gynecologic procedures. After obtaining institutional research ethics board approval from the University Health Network Research Ethics Board, Toronto, Ontario, Canada, data were retrospectively collected on 7760 consecutive adult patients (age > 18 yr) who underwent noncardiac surgery. Patients were identified from the Acute Pain Service database (APS Manager; Adjuvant Informatics Hamilton, Ontario, Canada) from March 2003 to June 2006. All patients receiving patient-controlled analgesia, patient-controlled epidural anesthesia, epidural, and intravenous pain management were included, comprising virtually all patients having major surgery. The notable exceptions are patients having emergent surgery. For patients who underwent more than one relevant procedure during the study period, only their initial surgery was included for analysis. Transplantation and cardiac surgery cases were excluded.

The details and validity of the data collection have been previously published.²³ Details of perioperative data and outcomes were collected from existing clinical databases and the patient chart, including demographics; laboratory tests were retrieved from the electronic data warehouse; nature of surgery and preoperative comorbidities were downloaded from the hospital enterprise system (MISYS Computerized Patient Record; Allscripts, Chicago, IL); laboratory tests were retrieved from the laboratory data warehouse; details of all medications signed out for use in individual patients from the time of admission to discharge were retrieved from the Pharmacy database (Centricity; GE Medical Systems, Chalfont St. Giles, United Kingdom). A blinded and trained technician manually retrieved the details of blood products used within the first 7 days of the hospital stay from the blood bank database (Hemocare; Mediware Information Systems, Alton, IL). Mortality was assessed and retrieved from the hospital enterprise system, death certificates were retrieved, and the cause of death was recorded. Data were merged and collated for analysis in a separate electronic database using the patient's unique hospital identifiers and the date of admission.

Dependent Variable

The primary dependent variable was mortality within 90 days of the index surgery.

Statistical Analyses

SAS version 9.1 (SAS Institute, Inc., Cary, NC) was used for the statistical analyses. Categorical variables are summarized as frequencies and percentages, and continuous variables are reported as means and standard deviations.

The prevalence of preoperative anemia was measured, defined as a hemoglobin concentration threshold of the World Health Organization's gender-based definition of 12.0 g/dl in women and 13.0 g/dl in men. Multivariable logistic regression modeling was carried out to assess the adjusted association between preoperative hemoglobin and mortality. Bivariate analysis (using the chi-square statistic for categorical variables and the *t* test or Wilcoxon rank sum test for continuous variables) was first carried out to identify which preoperative and intraoperative variables were associated ($P < 0.3$) with preoperative anemia, as defined above, and the primary outcome for inclusion in the modeling. Modeling was by backward stepwise selection, with $P < 0.1$ as the criteria for variable retention in the models. In the logistic regression model, the variables assessed included height, weight, age, sex, history of coronary disease, congestive heart failure, cerebrovascular disease, diabetes, renal disease, chronic obstructive pulmonary disease, preoperative platelet count, time in hospital before surgery, type of surgery, perioperative transfusion, and medications, including β -blockers, lipid-lowering agents, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Specifically, transfusions were categorized as 0, 1–2 units, 3–4 units, 4–9 units, and 10 or more units. The mathematical relationships between the continuous independent variables and the probability of the primary outcome were assessed using restricted cubic spline functions. Variables that were not linearly related were either mathematically transformed or categorized along appropriate cut-points for the logistic regression analyses. A Pearson correlation matrix of variables was used to identify collinear predictive variables.²⁵ The models' fit was assessed by the Hosmer-Lemeshow test (larger P value means better fit or calibration), and predictive accuracy was assessed by the c-index (equivalent to the area under the receiver operating characteristic curve).²⁵ Two additional models were constructed for a sensitivity analysis that excluded patients on the basis of whether they had severe preoperative anemia (hemoglobin < 9.5 g/dl) or had received intraoperative or postoperative red blood cell (RBC) transfusions.

Propensity Score-based Matching

Patient matching based on propensity scores was employed to obtain an adjusted estimate of the effects of anemia on mortality by balancing the measured covariates in anemic and nonanemic patients.²⁶ The propen-

|| World Health Organization: Iron deficiency anemia: Assessment, prevention and control. Available at: http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf. Accessed December 1, 2008.

Harrell FE: SAS macros and data step programs useful in survival analysis and logistic regression. Available at: <http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/SasMacros>. Accessed December 1, 2008.

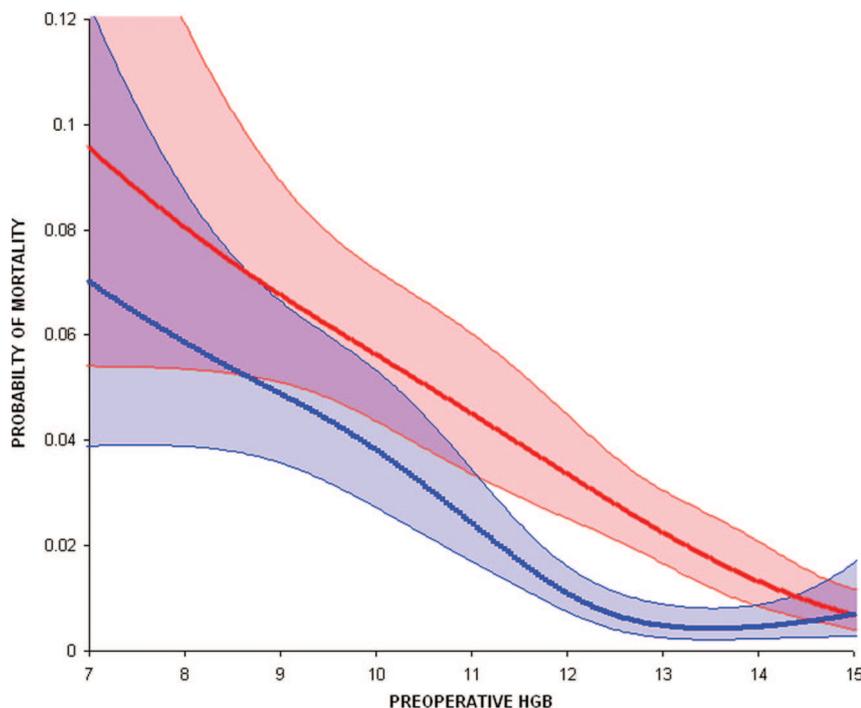


Fig. 1. Unadjusted cubic spline relationship for men and women (95% confidence intervals are indicated by the shaded areas) showing the relationship between preoperative anemia and 90-day mortality. The x axis represents the preoperative hemoglobin level in g/dl, and the y axis represents the probability of death.

sity score for preoperative anemia was estimated using multiple logistic regression. This regression included all measured predictor variables that could be related to preoperative anemia.

Individual patients with preoperative anemia were then matched 1:1 to patients without preoperative anemia on the basis of similar propensity scores. A 5→1 computerized greedy matching technique was used for this matching process; cases were first matched to controls that had a propensity score (logit transform) that was identical in all 5 digits. Those that did not match were then matched to controls on 4 digits of the propensity score. This continued down to a 1-digit match on propensity score for those remaining unmatched.²⁷ Measured covariates and adverse postoperative events in these matched pairs were compared using paired *t* test or Wilcoxon signed-rank test for continuous variables and conditional matched-pair logistic regression for categorical variables.²⁸

Results

Of the 7,679 patients included in the study, 3,047 (39.7%) fulfilled the World Health Organization definition of anemia in the preoperative period. The prevalence of anemia was 39.8% (1,622) in men and 39.5% (1,425) in women ($P = 0.74$). The mean (\pm SD) preoperative hemoglobin concentration was 12.7 ± 2.1 g/dl, with values ranging from 3.4 to 21.3 g/dl. Transfusions were administered in 1,430 patients (18.6% of all patients), with 68% of the transfusions occurring in patients who had preoperative anemia. The transfusion rate was 3 times higher in

anemic patients (30.4% vs. 10.6%) than in nonanemic patients. Figure 1 shows the unadjusted relationship between preoperative hemoglobin concentration and postoperative mortality in men and women, respectively. Of note, the slopes for men and women are virtually identical, and the threshold for increased mortality falls within the 95% confidence interval (CI) for the World Health Organization definition of anemia.

The unadjusted relationships with preoperative anemia and important perioperative variables and measured outcomes are seen table 1. The unadjusted odds of a perioperative death is higher in anemic than nonanemic patients (odds ratio [OR], 4.74; 95% CI, 3.3–6.7; $P < 0.0001$) (table 2).

Adjustment for Confounders of Postoperative Death Using Multivariable Logistic Regression

Using logistic regression to control for known confounding factors, preoperative anemia was associated with increased mortality (OR, 2.36; 95% CI, 1.57–3.41; $P < 0.0001$) (table 2). The model had good calibration (Hosmer-Lemeshow test, $P = 0.39$) and good discrimination (C index = 0.826). In addition to preoperative anemia, we also found that a history of congestive heart failure, transfusion of RBCs (in a dose-dependant manner) (table 3), small size (as denoted by a height under 155 cm), an inpatient status of more than 5 days before surgery, age over 70 yr, and a preoperative creatinine of over 176 mm were associated with increased odds of death. The perioperative use of β -blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and nonsteroidal antiinflammatory drugs also influenced outcome. Notably, statins were not retained in the model. The introduction of

Table 1. Patients Demographics and Perioperative Variables

Variables	Entire Sample		P Value	Propensity-matched Sample		P Value
	Nonanemic (4,129)	Anemic (3,047)		Nonanemic (2,090)	Anemic (2,090)	
Demographics						
Female gender, n (%)	2,182 (47.1)	1,425 (46.8)	0.06	998 (47.7)	975 (46.7)	0.476
Age > 70 yr, n (%)	992 (21.4)	816 (26.8)	0.0001	552 (26.4)	537 (25.7)	0.597
Weight < 55 kg, n (%)	316 (6.8)	347 (11.4)	0.0001	201 (9.6)	192 (9.2)	0.633
Height, cm, mean 95% CI	168	167	0.0001	167	167	
Height < 155 cm, n (%)	421 (9.1)	349 (11.5)	0.0001	208 (10.0)	210 (10.1)	0.919
Inpatient > 5 days, n (%)	67 (1.6)	264 (8.7)	0.0001	59 (2.8)	68 (3.3)	0.417
Comorbidities						
High-risk surgery*	1,574 (34.0)	1,113 (36.5)	0.022	820 (39.2)	794 (38.0)	0.409
Coronary artery disease	308 (6.7)	397 (13.0)	0.0001	221 (10.6)	217 (10.4)	0.840
Congestive heart failure	41 (.9)	82 (2.7)	0.0001	32 (1.5)	37 (1.8)	0.544
Cerebrovascular disease	24 (.5)	28 (.9)	0.036	13 (0.6)	18 (.9)	0.868
Diabetes mellitus type I or II	362 (7.8)	470 (15.3)	0.0001	254 (12.2)	242 (11.6)	0.566
Renal dysfunction†	74 (1.6)	274 (9.0)	0.0001	70 (3.3)	56 (2.7)	0.205
Revised Cardiac Risk Index						
0	2,695 (58.2)	1,316 (43.2)	0.0001	1,002 (47.9)	1,026 (49.1)	0.968
1	1,563 (33.7)	1,244 (40.8)	0.0001	826 (39.5)	819 (39.2)	0.968
2	312 (6.7)	369 (12.1)	0.0001	212 (10.1)	199 (9.5)	0.968
3	54 (1.2)	93 (3.1)	0.0001	42 (2.0)	39 (1.9)	0.968
4+	8 (0.2)	25 (0.8)	0.0001	8 (0.4)	7 (0.3)	0.968
Platelet count	232	251	0.0001	228	226	0.203
Proportion with plt > 150	484	492	0.04	342 (16.4)	318 (15.4)	0.309
Medications						
β-blockers	904 (19.5)	972 (32.0)	0.0001	545 (26.1)	543 (25.9)	0.985
Metoprolol	542 (11.7)	635 (20.9)	0.0001	340 (16.3)	335 (16.0)	0.970
Atenolol or bisoprolol	362 (7.8)	337 (11.1)	0.0001	205 (9.8)	208 (9.9)	0.970
ACE inhibitors	479 (10.3)	416 (13.6)	0.0001	258 (12.3)	254 (12.2)	0.850
CCBs	405 (8.7)	471 (15.5)	0.0001	241 (11.5)	245 (11.7)	0.281
Statins	653 (14.1)	503 (16.5)	0.004	321 (15.3)	319 (15.3)	0.931
NSAIDs	2,245 (48.5)	846 (27.7)	0.0001	662 (31.7)	668 (33.4)	0.235
Epidural analgesia‡	1,200 (25.9)	828 (27.2)	0.214	647 (31.0)	597 (28.5)	0.09
RBC transfusions (total in visit)§						
1–2 units	314 (6.8)	571 (18.7)	0.0001	276 (13.2)	286 (13.7)	0.753
3–4 units	128 (2.8)	209 (6.9)		108 (5.2)	110 (5.3)	
5–9 units	38 (0.8)	102 (3.4)		35 (1.7)	35 (1.7)	
10 or more units	23 (0.5)	45 (1.5)		21 (1.0)	29 (1.4)	
Outcomes						
Mortality (30 days)	24 (0.6)	76 (2.4)	0.001	19 (0.9)	40 (1.9)	0.006
Mortality (90 days)	42 (0.9)	118 (3.9)	0.0001	27 (1.3)	61 (2.9)	0.0002
Length of stay (days)	8 (11)	13 (18)	0.0001	9 (12)	11 (14)	0.0001

Unadjusted and propensity-matched values for variables that are potential confounders in the relationship between anemia and postoperative mortality. Chi-squared tests and *t* tests were used to determine the significance of differences between categorical and continuous variables respectively.

* High-risk surgery refers to thoracic, vascular, or major upper abdominal procedures. † Renal dysfunction is defined as a preoperative creatinine of at least 175 mmol/l. ‡ Epidural analgesia refers to patients with thoracic or lumbar epidural analgesia used for more than 24 hours. § Transfusions refers to the number of units of packed red cells that were transfused during the entire postoperative period. || Length of stay is reported as mean and standard deviation.

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; NSAIDs = nonsteroidal antiinflammatory drugs; RBC = red blood cells.

interaction terms did not significantly change the model. In separate sensitivity analyses (table 4), the model was not significantly altered after exclusion of all patients with severe anemia (a preoperative hemoglobin of less than 9.5 g/dl) or after all patients who had received any transfusion of red cells had been excluded. Finally, the model was not changed when the genders were analyzed separately (not shown).

Adjustment of Confounders Using Propensity Score-Matching

The propensity score was based on a nonparsimonious logistic regression model with 27 variables. Before

matching, all 27 variables (table 1) were statistically significantly different, with a 5.7% mean difference between the anemic and nonanemic populations. The process of matching balanced the confounding variables, with no statistically significantly different difference seen for any variable and a mean difference between groups of 0.6%. In the course of the propensity score-matching, we were able to successfully match 2090 anemic patients with nonanemic patients (69% of all the anemic patients). The only difference between the anemic and nonanemic groups was preoperative and discharge hemoglobin levels. Importantly, the matched pairs had similar red cell transfusions rates. The matched

Table 2. Regression Analysis of Anemia Model Predicting Mortality

Parameter	OR (95% CI)	P Value
Amenia (WHO gender defined)	2.43 (1.65–3.60)	< 0.0001
Comorbidities		
Age > 70 yr	2.31 (1.64–3.26)	< 0.0001
In-hospital status*	3.51 (2.26–5.44)	< 0.0001
History of CHF	7.99 (4.73–13.5)	< 0.0001
Preoperative renal dysfunction†	2.08 (1.22–3.53)	0.0067
Perioperative medications		
β-Blockers		
No β-blockers	Reference	
Metoprolol	1.67 (1.05–2.68)	0.020
Atenolol or bisoprolol	0.97 (0.63–1.52)	0.198
ACE inhibitors	0.56 (0.33–0.95)	0.033
CCBs	0.57 (0.34–0.96)	0.036
Any postoperative NSAID‡	0.58 (0.38–0.88)	0.011
Transfusion		
No blood products	Reference	
1–2 units	1.83 (1.20–2.80)	0.032
3–4 units	2.99 (1.77–5.07)	0.013
5–10 units	3.19 (1.62–6.32)	0.021
More than 10 units	3.43 (1.12–10.5)	0.040

The receiver operating characteristic of the model describing factors associated with postoperative death is 0.826.

* In-hospital status was defined as any patient who was in the hospital for more than 5 days before the surgical intervention. † Preoperative renal dysfunction was defined as a preoperative creatinine of at least 176 mmol/l. ‡ Any NSAID includes any type of nonsteroidal antiinflammatory given for analgesia (this is predominantly ketorolac 15 mg · g⁻¹ · 8 h⁻¹).

ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; CHF = congestive heart failure; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; WHO = World Health Organization.

anemic patients had higher death rates than nonanemic patients (OR, 2.29; 95% CI, 1.45 to 3.63; $P < 0.0001$) (table 1), which is similar to the OR derived using the full logistic regression model. The unmatched population had higher preoperative risk predictors and a two-fold greater incidence in postoperative mortality than the matched population (see table, Supplemental Digital Content 1, which compares the characteristics of patients who were matched by the propensity score with those who were unmatched, <http://links.lww.com/A732>). Using the propensity-matched cohort, we then performed a time to death analysis comparing the anemic and nonanemic patients (fig. 2). This analysis once again showed the higher mortality rate, which is seen very early after surgery and continues to diverge. We retrieved the causes of death using the provincial death certificates (table 5). Deaths

were grouped as cardiac (myocardial infarction, congestive heart failure, cardiac arrest), respiratory (respiratory arrest, hypoxia) septic, multi-organ failure, hemorrhagic, or cancer-related. Anemic patients were more likely to die in each category, and the increase was similar in all causes of death.

Discussion

In this single-center cohort study of consecutive patients who underwent noncardiac surgery in 3 yr between March 2003 and June 2006, we found that preoperative anemia was a highly prevalent condition that was strongly and independently associated with postoperative mortality. Fully one-third of patients who presented for nonemergent surgery had a hemoglobin concentration that the World Health Organization would define as anemia. After adjusting for important preoperative and perioperative confounders, including RBC transfusions, patients with preoperative anemia had more than two-fold greater odds of dying within 90 days of surgery. This difference was significant within 14 days of surgery, and the survival curves continued to diverge for 90 days.

The prognostic value of anemia in surgery has been studied in many populations, including cardiac surgery and noncardiac surgery. These studies have shown that anemia is an important risk factor for short- and long-term outcomes in the general population, as well as in patients with coronary artery disease and congestive heart failure.^{15,29} Our study indicates that preoperative anemia is similarly associated in patients undergoing a wide variety of noncardiac surgical procedures. There are well known risks of RBC transfusion^{7,13,21}; therefore, the fact that anemic patients required RBC transfusions twice as often as nonanemic patients indicates that preoperative anemia exposes them to additional harm, the “second hit” theory.

The relationship between preoperative anemia and adverse outcomes in noncardiac surgery has been examined by previous studies.^{3,3,4,6,19} In the largest and most recent of these observational studies,¹⁹ in-hospital mortality rates increased linearly as red cell mass decreased; the threshold for this response was found at a hematocrit of 0.39. After adjusting for preoperative comorbidities in this multicentered Veterans Administration population,

Table 3. Effect of Transfusions

	No Transfusions*	1–2 Units	3–4 Units	5–9 Units	10+ Units
Total population (percent mortality)	88/6,161 (1.41)	35/885 (3.95)	21/337 (6.23)	12/153 (7.84)	4/55 (7.27)
No anemia (percent mortality)	25/4,129 (0.61)	11/314 (3.50)	2/128 (1.56)	4/61 (6.6)	
Anemic (percent mortality)	63/2,102 (2.97)	24/571 (4.20)	19/209 (9.09)	12/147 (8.2)	
Relative risk (95% CI) of transfusion (anemia vs. no anemia)		1.94 (1.84–2.05)	1.77 (1.65–1.89)	1.86 (1.67–2.03)	

The risk-adjusted odds ratio (95% CI) for 90-day mortality in the population with no transfusions is 3.04 (1.54–4.12). Comparison of anemia vs. no anemia merged 5–9 and > 9 due to the sample size.

Table 4. Sensitivity Analysis

Analysis	Anemia/Total	Deaths	Relationship between Preoperative Anemia and Postoperative Death		
			OR (95% CI)	P Value	C Index
Unadjusted relationship	2,929/7,659	160	4.74 (3.32–6.76)	0.0001	NA
Logistic regression (full model)	2,929/7,659	160	2.36 (1.57–3.41)	0.0001	0.826
Logistic regression severe anemia excluded*	2,317/6,907	113	1.79 (1.17–2.70)	0.003	0.826
Logistic regression transfusions excluded	2,057/6,249	88	3.04 (1.80–5.00)	0.0001	0.804
Propensity matched sample	2,090/4,180	88	2.29 (1.45–3.63)	0.0001	0.716

* Severe anemia is defined as a preoperative hemoglobin less than 9.5 g/dl. Odds ratios (OR) for the relationship between preoperative anemia and 90-day mortality. Logistic regression was used to adjust for potentially confounding variables, and subgroups were analyzed by eliminating patients with severe anemia and patients receiving transfusions. Two groups were also created by using propensity-matching to balance the measured covariates between the anemic and nonanemic groups. Robustness of the findings was assessed with this sensitivity analysis. The effects of severe anemia, of transfusions, and of a different statistical methodology (a propensity score-matched cohort) on relationship between anemia and mortality were assessed.

anemia was associated with approximately a three-fold increase in the odds of in-hospital death (OR, 3.2; 95% CI, 1.2–8.1). The study, however, failed to show the relationship between anemia and mortality in their female population and importantly, could not adjust for perioperative transfusions. The results of our analysis add to these findings, reconfirming the relative intolerance of anemia in men and extending the findings to women. Our analysis also adds strength to the assertion that the morbid effects of anemia exist independently of the effects of transfusion. Our analysis adjusted for transfusion in 2 ways, using logistic regression and propensity-matching. The other reports of the independent morbid effects of anemia in noncardiac surgery are less clear. In the study by Carson *et al.*,⁴ preoperative anemia was not the primary focus. In situations where the nadir hemoglobin fell below a threshold (hemoglobin < 12.0 g/dl) there was a stepwise increase in mortality. Transfusion did not statistically significantly change mortality; however, the highest mortality occurred in patients with a nadir hemoglobin below 8.0 g/dl. Moreover, 90% of these patients were transfused, making it difficult to determine the independent effects of anemia and transfusion. The studies by Nelson *et al.*⁵ and Hogue *et al.*⁶ are single-center studies with

small sample sizes and therefore possessed limited power to assess anything more than surrogate outcomes.

Compared with these previous studies, our study had several strengths. Our study has a relatively large sample size, and shows that anemia is associated with mortality in both men and women. Our study sample included a wide variety of operative procedures in subjects with myriad comorbidities. The analysis used both logistic regression and propensity score analyses to adjust for important comorbidities, and importantly, for RBC transfusions. This adjustment for RBC transfusions allows a relatively unbiased comparison between patients who had preoperative anemia with those without preoperative anemia but receiving similar amounts of blood products. Similar to our findings in cardiac patients,¹⁷ nonanemic patients in this cohort likely lost more blood than the cohort of anemic patients; since the nonanemic group had superior outcomes, having lost more blood while receiving the same amount of blood, affirms the robustness of our results and secondarily attests to the importance of anemia as a risk factor for adverse outcomes.

There are several limitations to be considered when interpreting our study. First, this was a retrospective

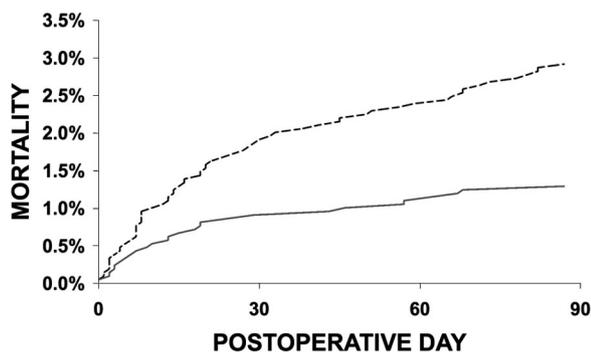


Fig. 2. The risk adjusted effect of anemia on postoperative mortality. This figure represents the time to event comparing anemic to nonanemic patients in the propensity-matched cohorts. x axis = postoperative day; y axis = percent mortality; broken line = patients with preoperative anemia; solid line = nonanemic patients.

Table 5. Causes of Death*

	Anemia, n (%)	No Anemia, n (%)	Total %
Cardiac†	29 (32.5)	10 (30.3)	(31.9)
Cerebrovascular	1 (1.1)	1 (3.0)	(1.6)
Respiratory‡	6 (6.7)	4 (12.0)	(8.2)
Pulmonary embolism	1 (1.1)	0	(0.8)
Septic	22 (24.7)	6 (18.1)	(22.9)
Hemorrhagic	8 (8.9)	0	(6.6)
Multorgan failure	15 (16.8)	6 (18.1)	(17.1)
Cancer-related	6 (6.7)	6 (18.1)	(9.8)

Cause of death was ascertained in 122 of the 160 deaths; 38 death certificates could not be obtained (n = 28) or were not legible (n = 10).

* Cause of death was obtained from the death certificate. † Cardiac death was a combination of myocardial infarction, congestive failure, or cardiac arrest. ‡ Respiratory was either a respiratory arrest or hypoxic death. || Included septic shock, pneumonia, and abdominal anastomotic leak.

observational study; therefore, causality could not be determined. It is possible that preoperative anemia was associated with adverse outcomes simply because it is a marker for severity of illness. Second, the effects of unknown or unmeasured confounders on the observed association cannot be ruled out. However, owing to the breadth of the variables and the robustness of our results, the impact of any such unknown or unmeasured confounders is likely to be small. Third, neither the cause nor the duration of preoperative anemia, both of which have prognostic implications, was known. Another limitation of our study is that we did not attempt to delineate the mechanisms by which preoperative anemia may lead to adverse outcomes. Thus, patients with preoperative anemia may be at increased risk due to an unrecognized comorbidity, or the effect may be secondary to inadequate tissue oxygen delivery during the perioperative period, resulting in impaired tissue oxygenation and organ dysfunction. Consistent with this hypothesis, there is experimental evidence that oxygen supply to critical organs is compromised during the early stages of anemia.³⁰ Finally our mortality data are in-hospital data only. The relationship between total mortality and anemia may have been altered if out-of-hospital deaths were included, but privacy considerations prevent access to this information.

The overriding clinical implications of this study's findings are that if the observed association between preoperative anemia and mortality in noncardiac surgery is causal, correcting the anemia will likely improve outcomes. We, however, advocate a cautious approach to correcting preoperative anemia. There are currently at least three available therapeutic options. Therapies such as iron and erythropoietin are not risk-free. The Federal Drug Administration has recently issued an advisory on erythropoietin,** and it is relatively contraindicated in patients with malignancy. The use of iron, although relatively safe, would necessitate delays in surgery. Surgical delays are not risk-free. In the Coronary Artery Revascularization before Major Vascular Surgery Trials, delaying surgery by a median of 36 days longer than in the control population resulted in an excess of 10 deaths, whereas there was only 1 death in patients who proceeded without intervention.³¹ Alternatively, preoperative transfusions may be indicated as a means of increasing preoperative hemoglobin levels in a timely manner, but this practice also carries attendant risk.³² All of these options may be viable alternatives in selected populations and will need to be tested prospectively in randomized controlled trials.

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