The least of 3 evils: Exposure to red blood cell transfusion, anemia, or both?

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Background: Anemia and red blood cell (RBC) transfusions are both associated with morbidity and mortality after cardiac surgery. Patients with the lowest hematocrit (HCT) values during cardiopulmonary bypass (CPB) are the most likely to receive a transfusion, which results in a double-negative exposure. We aimed to clarify the effects of anemia, transfusion, and their combination to identify which imposes the greatest risk of end-organ dysfunction and mortality.

Methods: From November 1, 2004, to November 1, 2009, 7942 patients underwent procedures requiring CPB and did not receive intraoperative or postoperative RBC transfusion, and 1202 received intraoperative RBC transfusion alone. They were divided into 4 groups: intraoperative nadir HCT $\geq$25% without RBC transfusion, $\geq$25% with RBC transfusion, <25% without RBC transfusion, and <25% with RBC transfusion. The relationship among HCT, RBC, and outcomes was studied using generalized propensity-score analysis. Outcomes included estimated glomerular filtration rate (eGFR), troponin, ventilatory support time, length of stay, and mortality.

Results: After risk adjustment, comparison of all 4 groups showed that double exposure to anemia (HCT <25%) and RBC transfusion was associated with the highest risk: lowest eGFR ($P = .008$), highest troponin values ($P = .01$), longest ventilator requirement ($P < .001$), longest length of stay ($P < .001$), and highest mortality ($P = .007$). Single exposure to either HCT <25% or RBC transfusion alone was associated with the next risk category, and the lowest morbidity risk was associated with neither exposure.

Conclusions: Although single exposure to anemia or RBC transfusion alone was associated with risk, it was generally lower than that of anemia and RBC exposure in combination. (J Thorac Cardiovasc Surg 2013;146:1480-7)

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Supplemental material is available online.

Cardiac surgical patients face several potentially negative exposures in the perioperative period that pose risk for increased morbidity and mortality. Among these are the threats of developing anemia and receiving red blood cell (RBC) transfusions. Our prior work and other investigations have recognized increased morbidity among cardiac surgical patients who develop perioperative anemia[1-3] and receive RBC transfusions.[1,4-7] Although both of these negative exposures may be avoidable, when physicians must decide whether to circumvent patient exposure to anemia by preemptive treatment with RBC transfusion or to simply tolerate anemia, the trade-off with morbidity risk is unclear.

Our objectives were to evaluate morbidity and survival associated with 3 operative management strategies in patients undergoing cardiac surgery requiring use of cardiopulmonary bypass (CPB): (1) tolerating anemia without RBC transfusion, (2) avoiding anemia with RBC transfusion, and (3) exposing patients to both anemia and its treatment, RBC transfusion.

METHODS

Study Population

From November 1, 2004, to November 1, 2009, 15,282 patients at Cleveland Clinic (Cleveland, OH) underwent cardiac surgical procedures requiring CPB. Patients with missing intraoperative hematocrit (HCT) values or aged younger than 18 years were excluded. Among the remaining 15,115 patients, 7942 (53%) did not receive an intraoperative or postoperative RBC transfusion. Another 7173 (47%) received intraoperative

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
HCT = hematocrit
LOS = length of stay
RBC = red blood cell

or postoperative transfusions, or both. Among the transfused patients, 1202 (17%) had only intraoperative RBC transfusions and were included in the study group. We included only intraoperative RBC transfusions to avoid potential confounding associated with RBC transfusion occurring after the morbidity event.

Our final study cohort comprised 9144 patients: 7942 nontransfused (87%) and 1202 transfused only intraoperatively (13%). For comparison, the study cohort was divided into 4 groups (Figure E1):

1. No negative exposures: nadir HCT ≥25% without RBC transfusion (n = 6937; 76%).
2. Single negative exposure: nadir HCT ≥25% with RBC transfusion (n = 246; 2.7%).
3. Single negative exposure: nadir HCT <25% without RBC transfusion (n = 1005; 11%).
4. Double negative exposure: nadir HCT <25% with RBC transfusion (n = 956; 10%).

Baseline and perioperative variables were retrieved from the Cleveland Clinic Cardiovascular Information Registry and the Cardiothoracic Anesthesia Database, ongoing, prospective, concurrent registries of all cardiac operations maintained concurrently with patient care. They have been approved for use in research by the Institutional Review Board, with patient consent waived.

End Points

End points were markers of end-organ dysfunction (perioperative myocardial infarction, renal and hepatic failure, neurologic complications, and duration of postoperative ventilatory support), hospital mortality, and long-term survival. Serial values of specific markers of end-organ dysfunction included estimated glomerular filtration rate (eGFR) and troponin release level. Intensive care unit and postoperative lengths of stay (LOS) were used as surrogates for resource use, as was duration of postoperative ventilatory support. Hospital morbidities were recorded prospectively, according to definitions from the Society of Thoracic Surgeons National Adult Cardiac Database (http://www.ctsnet.org/file/rptDataSpecifications252_1_ ForVendorsPGS.pdf).

Vital status was determined using Cardiovascular Information Registry follow-up data supplemented with Social Security Death Master File information.[8,9] Median follow-up was 3.7 years, with 25% of patients followed up for more than 5 years and 10% for more than 6 years; 33,775 patient-years of data were available for analysis. *Nadir HCT* was defined as the lowest intraoperative HCT value obtained from intraoperative arterial blood samples.

Data Analysis

Categorical variables are summarized by frequency and percentage, and continuous variables by mean ± SD, or by 15th, 50th (median), and 85th percentiles when values are skewed. Comparisons were made using the χ^2 test for categorical data and the Wilcoxon rank-sum or Kruskal-Wallis nonparametric test (for >2 categories) for continuous data. Multiple imputation using the Markov chain Monte Carlo technique was used to impute missing values. Fivefold multiple imputation was performed with PROC MI (SAS version 9.1; SAS Institute, Inc, Cary, NC). The estimated regression coefficients and their variance-covariance matrix for each of the 5 imputed complete data sets were then combined following Rubin's methodology[10] (PROC MIANALYZE; SAS Institute, Inc).

Adjusted effects of the 4 groups on outcomes were analyzed using propensity-score methods.[11,12] By using polytomous logistic regression (generalized logit link with group 1 as the reference) and variables listed in Appendix E1, we identified variables associated with group membership. Having established a parsimonious model, we added other variables representing groups of patients who may be related to these 4 groups (saturated model). Three propensity scores (probability of being in groups 2, 3, and 4) were then estimated. Similar to traditional 2-group propensity-score strategies, we used the scores in 2 ways: (1) subclassification approach, in which we stratified the study population into 64 strata based on the 3 scores, then adjusted for these strata in the outcome analyses of eGFR, troponin, ventilatory support time, and postoperative LOS; and (2) propensity-score adjustment, in which we forced the 3 scores into the multivariable model of short- and long-term survival.

We used multivariable linear regression (PROC REG; SAS Institute, Inc) and variables listed in Appendix E1 to identify variables associated with continuous outcomes (eGFR, postoperative LOS, troponin, and ventilatory support time) and multivariable binary logistic regression (PROC LOGISTIC; SAS Institute, Inc) for binary outcomes.

Short- and long-term survival were assessed nonparametrically using the Kaplan-Meier estimator and parametrically using a multiphase hazard model.[13] The parametric model was used to resolve several phases of instantaneous risk of the event (hazard function) and to estimate shaping parameters. Multivariable analyses were performed in the hazard function domain. The final model was adjusted further by forcing in the 3 propensity scores.

Bootstrap aggregation (bagging) was used for variable selection.[14] $P = .05$ was set for retention of variables. This was a 4-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 100% the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, results of the variable selection were stored. These 3 steps were repeated 500 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable (aggregation step). All variables with bootstrap reliability of 50% or greater were retained in the final model.[14]

For the troponin release model, patients who underwent atrial fibrillation procedures or septal myectomy were excluded from the study cohort; and for the postoperative LOS model, patients who died in the hospital were excluded. For the troponin release, ventilatory support, and postoperative LOS models, logarithmic transformation was used as the response variable. Any one of the following was used as a neurologic complication: coma (lasting at least 24 hours), permanent stroke, transient ischemic attack, or paraplegia.

All analyses were performed using SAS version 9.1 and R software.[15] The statistical significance level was set at .05. All *P* values are 2 sided.

RESULTS

Intraoperative Nadir HCT and RBC Transfusion

The median intraoperative nadir HCT was 29%. Total intraoperative RBC units transfused ranged from 1 to 30, with 75% of patients receiving either 1 or 2 units. As expected, transfused patients had lower intraoperative nadir HCT values than nontransfused patients (Figure 1). Baseline and perioperative variables, according to exposure group, are presented in Table 1. Compared with patients not having the negative exposures of anemia and transfusion, those exposed to both were more likely to be older, to be

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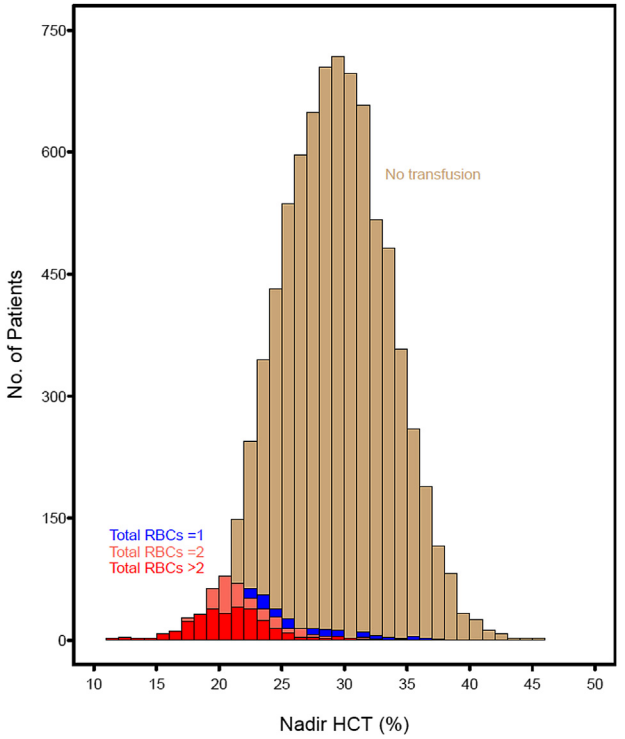

FIGURE 1. Histogram showing relationship between intraoperative nadir hematocrit (*HCT*) and intraoperative red blood cell (*RBC*) transfusion status.

female, and to have a lower body mass index, a lower preoperative hematocrit, and a longer CPB duration. They were also more likely to have an unstable presentation (ie, a higher prevalence of emergency operations, preoperative intra-aortic balloon pump use, and reoperations) (Table 1 and Table E1).

72-Hour Minimum eGFR and Exposure Groups

Unadjusted analysis showed differences in postoperative 72-hour minimum eGFR among the 4 groups, with more negative exposures associated with decreased renal function (Table 2 and Figure 2, *A*). Compared with patients not having negative exposures to anemia or transfusion, patients exposed to anemia (HCT <25%) alone had a lower eGFR (71 ± 27 vs 78 ± 22 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}). The next worst eGFR was noted in patients with a single exposure to transfusion without anemia (68 ± 29 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}). The greatest risk for renal dysfunction was observed in patients with a double exposure to anemia (HCT <25%) and transfusion (60 ± 26 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}), demonstrating that treating anemia with RBC transfusion worsened, rather than helped, renal function.

Risk-adjusted analysis of renal function shows that patients exposed to anemia (HCT <25%) had greater renal dysfunction than those who were not anemic (Table 3, Figure 3, *A*, and Table E2). However, patients with anemia (HCT <25%) who also received an intraoperative transfusion fared worse than those who were anemic but not transfused.

24-Hour Mean Troponin Release and Exposure Groups

Unadjusted analysis revealed that patients with both anemia (HCT <25%) and intraoperative RBC transfusion had greater troponin release than those with anemia (HCT <25%) alone, suggesting increased myocardial injury (Table 2 and Figure 2, *B*).

Risk-adjusted analysis showed that patients with exposure to anemia (HCT <25%) alone did not have a significant increase in troponin release unless they also were transfused (Table 3, Figure 3, *B*, and Table E3). Furthermore, patients without anemia (HCT ≥25%) who received an intraoperative transfusion to avoid it did not have a significantly greater increase in troponin release than those with no negative exposures.

Ventilatory Support Duration and Exposure Groups

Unadjusted analysis showed that patients exposed to intraoperative RBC transfusion with (HCT <25%) or without anemia had the longest postoperative ventilatory support duration (Table 2 and Figure 2, *C*). However, in the risk-adjusted analysis, patients with any negative exposure to anemia (HCT <25%) and RBC transfusion had longer ventilation times than patients without negative exposures (Table 3, Figure 3, *C*, and Table E4).

Postoperative Length of Stay and Exposure Groups

Unadjusted analysis showed that patients who received intraoperative RBC transfusion with (HCT <25%) or without anemia had the longest postoperative LOS, suggesting increased resource use (Table 2 and Figure 2, *D*). This association persisted in the risk-adjusted analysis (Table 3, Figure 3, *D*, and Table E5).

Other Complications and Exposure Groups

Unadjusted analysis revealed that neurologic complications occurred in 2.3% of patients with exposure to both anemia (HCT <25%) and intraoperative RBC transfusion, compared with 1% for those without anemia (HCT ≥25%) and no transfusion ($P = .004$; Table 2). However, there was no statistically significant difference in occurrences among the exposure groups after risk-adjusted analysis ($P > .2$). The prevalence of hepatic dysfunction was similar among the groups (Table 2), and this held after risk adjustment.

Short- and Long-Term Survival and Exposure Groups

The hazard function for death after surgery demonstrated an early decreasing and a late increasing hazard phase. Unadjusted analysis showed differences between groups

TABLE 1. Patient and procedural variables stratified by intraoperative nadir HCT and intraoperative RBC transfusion

	Intraoperative nadir HCT and intraoperative RBC transfusion groups								
	Nadir HCT ≥25 and RBC = 0 (total N = 6937)		Nadir HCT <25 and RBC = 0 (total N = 1005)		Nadir HCT ≥25 and RBC >0 (total N = 246)		Nadir HCT <25 and RBC >0 (total N = 956)		*P*
Variable	No.*	Measure†	No.*	Measure†	No.*	Measure†	No.*	Measure†	value
Demographics									
Age, y	6937	59 ± 13	1005	63 ± 14	246	64 ± 14	956	69 ± 13	<.001
Female sex	6937	1345 (19)	1005	658 (65)	246	80 (33)	956	643 (67)	<.001
Race									
White	6881	6343 (92)	998	864 (87)	244	226 (93)	940	814 (87)	<.001
Other	6881	538 (7.8)	998	134 (13)	244	18 (7.4)	940	126 (13)	<.001
Preoperative BMI, $kg \cdot m^{-2}$	6813	29 ± 5.7	995	28 ± 6.4	242	29 ± 5.7	934	28 ± 6.3	<.001
Cardiac comorbidity									
NYHA functional class	5979		882		207		829		<.001
I		1854 (31)		206 (23)		53 (26)		161 (19)	
II		2944 (49)		411 (47)		79 (38)		373 (45)	
III		1093 (18)		242 (27)		65 (31)		248 (30)	
IV		88 (1.5)		23 (2.6)		10 (4.8)		47 (5.7)	
Emergency operation	6935	24 (0.35)	1005	2 (0.20)	246	8 (3.3)	956	28 (2.9)	<.001
Prior myocardial infarction	6937	1371 (20)	1005	207 (21)	246	90 (37)	956	296 (31)	<.001
Preoperative atrial fibrillation/flutter	6720	654 (9.7)	981	92 (9.4)	240	40 (17)	925	96 (10)	.005
Prior cardiac operation	6937	898 (13)	1005	142 (14)	246	115 (47)	956	328 (34)	<.001
Heart failure	6937	1146 (17)	1005	255 (25)	246	82 (33)	956	358 (37)	<.001
Preoperative IABP use	6937	19 (0.27)	1005	7 (0.70)	246	6 (2.4)	956	7 (0.73)	<.001
Cardiogenic shock	6937	21 (0.30)	1005	5 (0.50)	246	4 (1.6)	956	7 (0.73)	.003
Ejection fraction, %	6728	54 ± 11	981	54 ± 11	234	49 ± 14	910	52 ± 12	<.001
Coronary artery disease (≥50% stenosis)	6811	2311 (34)	981	317 (32)	237	86 (36)	918	397 (43)	<.001
Noncardiac comorbidity									
History of endocarditis	6937	226 (3.3)	1005	55 (5.5)	246	17 (6.9)	956	81 (8.5)	<.001
History of smoking	6933	3526 (51)	1002	470 (47)	246	152 (62)	955	512 (54)	.001
History of peripheral arterial disease	6937	1683 (24)	1005	292 (29)	246	114 (46)	956	439 (46)	<.001
History of carotid disease	6937	1556 (22)	1005	258 (26)	246	102 (41)	956	397 (42)	<.001
History of COPD	6937	659 (9.5)	1005	133 (13)	246	45 (18)	956	178 (19)	<.001
History of hypertension	6937	4370 (63)	1005	660 (66)	246	182 (74)	956	748 (78)	<.001
Diabetes	6888	1254 (18)	1002	229 (23)	243	61 (25)	945	314 (33)	<.001
History of renal disease	6937	91 (1.3)	1005	37 (3.7)	246	18 (7.3)	956	68 (7.1)	<.001
Prior stroke	6937	341 (4.9)	1005	80 (8.0)	246	33 (13)	956	135 (14)	<.001
Preoperative eGFR (MDRD)	6931	81 ± 20	1005	77 ± 25	246	76 ± 31	956	69 ± 27	<.001
Bilirubin, $mg \cdot dL^{-1}$	6865	0.72 ± 0.41	994	0.6 ± 0.43	242	0.73 ± 0.48	944	0.62 ± 0.54	<.001
Preoperative hematocrit, %	6937	43 ± 4.2	1005	36 ± 3.9	246	39 ± 6.2	956	33 ± 4.6	<.001
Procedure									
No. of ITA grafts (>0)	6937	2089 (30)	1005	270 (27)	246	56 (23)	956	291 (30)	<.001
Isolated CABG	6937	1430 (21)	1005	169 (17)	246	33 (13)	956	159 (17)	.001
Isolated valve	6937	2151 (31)	1005	330 (33)	246	46 (19)	956	216 (23)	<.001
Valve + CABG	6937	614 (8.9)	1005	115 (11)	246	27 (11)	956	165 (17)	<.001
Other procedures	6937	2742 (40)	1005	391 (39)	246	140 (57)	956	416 (44)	<.001
No. of components	6937	1.6 ± 0.85	1005	1.7 ± 0.95	246	1.8 ± 0.96	956	2.0 ± 0.99	<.001
Times									
Myocardial ischemia, min	6937	70 ± 28	1005	68 ± 30	246	77 ± 39	956	80 ± 36	<.001
Cardiopulmonary bypass, min	6937	90 ± 34	1005	88 ± 37	246	115 ± 45	956	112 ± 45	<.001
1/1/2004 to index operation, y	6937	3.3 ± 1.4	1005	3.4 ± 1.6	246	2.9 ± 1.3	956	3.4 ± 1.5	<.001

HCT, Hematocrit; *RBC*, red blood cell; *BMI*, body mass index; *NYHA*, New York Heart Association; *IABP*, intra-aortic balloon pump; *COPD*, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *MDRD*, modification of diet in renal disease; *ITA*, internal thoracic artery; *CABG*, coronary artery bypass grafting.
*Patients with data available. †Number (percentage) or mean ± SD.

TABLE 2. Comparison of end-organ dysfunction and hospital complications stratified by intraoperative nadir HCT and intraoperative RBC transfusion

	Intraoperative nadir HCT and intraoperative RBC transfusion groups								
	Nadir HCT ≥25 and RBC = 0 (total N = 6937)		Nadir HCT <25 and RBC = 0 (total N = 1005)		Nadir HCT ≥25 and RBC >0 (total N = 246)		Nadir HCT <25 and RBC >0 (total N = 956)		*P*
Complication	No.*	Measure†	No.*	Measure†	No.*	Measure†	No.*	Measure†	value
72-h Minimum eGFR (MDRD)	6934	78 ± 22	1004	71 ± 27	245	68 ± 29	946	60 ± 26	<.001
24-h Mean troponin	6530	0.23/0.52/1.5	912	0.21/0.53/1.6	228	0.28/0.67/1.9	905	0.31/0.74/1.8	<.001
Ventilatory support, h	6496	3.5/6.0/16	971	3.6/6.4.17	244	4.8/12/36	948	4.8/11/22	<.001
Neurologic complication	6937	72 (1.0)	1005	8 (0.80)	246	4 (1.6)	956	22 (2.3)	.004
GI, MSOF, or bleeding/embolic	6937	93 (1.3)	1005	15 (1.5)	246	7 (2.8)	956	18 (1.9)	.16
Length of stay									
ICU, h	6937	22/26/52	1005	21/27/67	246	24/46/98	956	23/44/99	<.001
Postoperative, d	6937	4.2/6.0/9.0	1005	4.8/6.2/10	246	5.3/7.9/13	956	5.4/8.0/13	<.001

HCT, Hematocrit; *RBC*, red blood cell; *eGFR*, estimated glomerular filtration rate; *MDRD*, modification of diet in renal disease; *GI,* gastrointestinal; *MSOF*, multisystem organ failure; *ICU*, intensive care unit. *Patients with data available. †Number (percentage), mean ± SD, or 15th/50th/85th percentiles.

for both phases, with exposure to anemia (HCT <25%) and intraoperative RBC transfusion associated with the lowest survival (Figure 4). Patients with HCT ≥25% who were not transfused had an overall 6-year survival of 92%. Survival was 82% in patients with HCT <25% who did not receive a transfusion, and patients with HCT ≥25%

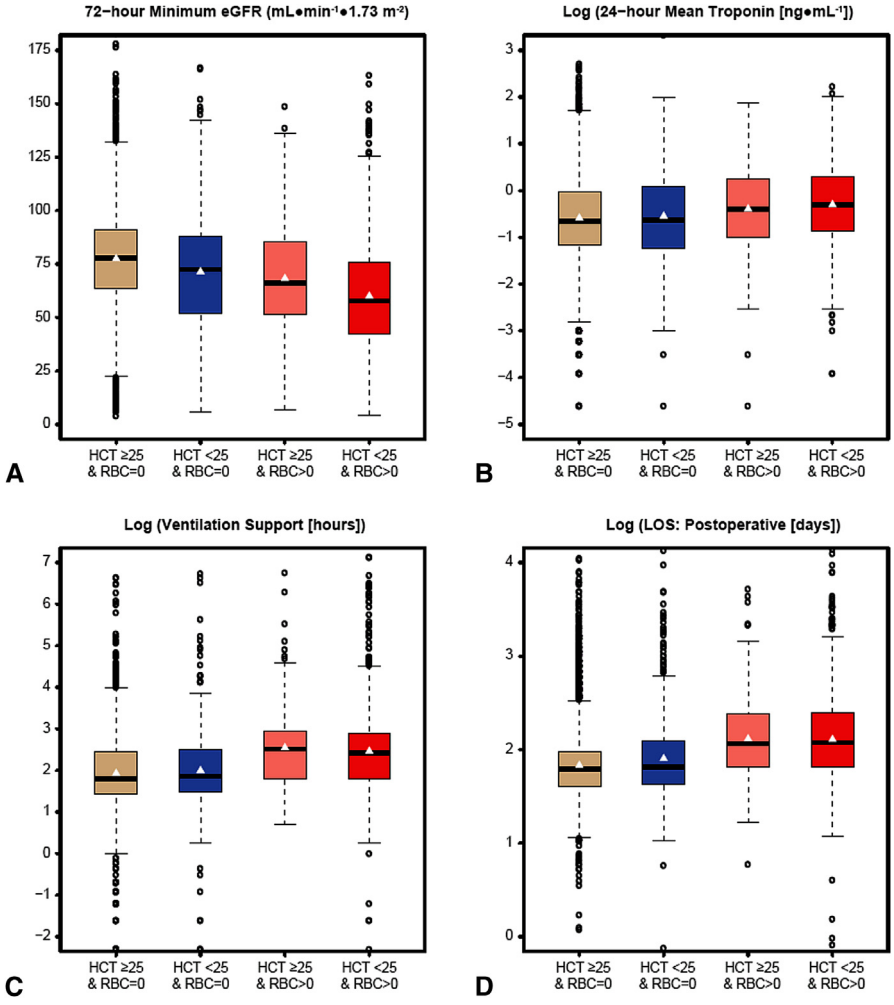

FIGURE 2. A-D, Relationship among anemia and transfusion exposure groups and outcomes. *eGFR*, Estimated glomerular filtration rate; *HCT*, hematocrit; *RBC,* red blood cell; *LOS*, length of stay.

TABLE 3. Risk-adjusted effect stratified by intraoperative nadir HCT and intraoperative RBC transfusion

	Nadir HCT <25 and RBC = 0		Nadir HCT ≥25 and RBC >0		Nadir HCT <25 and RBC >0	
Outcome	Coefficient ± SE	*P* value	Coefficient ± SE	*P* value	Coefficient ± SE	*P* value
eGFR	−1.8 ± 0.61	.004	−1.4 ± 1.00	.15	−2.9 ± 0.73	<.001
Troponin	0.033 ± 0.034	.3	−0.023 ± 0.054	.7	0.087 ± 0.039	.02
Ventilatory support	0.074 ± 0.033	.02	0.304 ± 0.052	<.001	0.305 ± 0.037	<.001
Postoperative length of stay	−0.0029 ± 0.015	.8	0.11 ± 0.025	<.001	0.12 ± 0.017	<.001
Risk of death						
Early	0.49 ± 0.36	.17	0.76 ± 0.45	.09	0.98 ± 0.36	.007
Late	0.026 ± 0.21	.9	0.18 ± 0.25	.4	0.057 ± 0.24	.8

HCT, Hematocrit; *RBC*, red blood cell; *eGFR,* estimated glomerular filtration rate; *SE*, standard error.

who were transfused had a 74% 6-year survival. The lowest survival (67%) was observed in patients exposed to both anemia (HCT <25%) and RBC transfusion.

Risk-adjusted analysis showed that exposure to both anemia (HCT <25%) and RBC transfusion was a risk factor for early death (Table 3). However, early and late survival was similar for the other exposure groups (Table 3 and Table E6).

DISCUSSION

Principal Findings

Our prior work demonstrated increased morbidity risk for both intraoperative RBC transfusion and anemia; what has been unclear is which one, or combination, is weighted most heavily in its contribution to poorer outcomes. Although optimizing preoperative HCT before surgical intervention is the ideal, it is not uncommon for patients to be anemic when they present for surgery. Preoperative anemia is often coupled with procedural blood loss, phlebotomy, and hemodilution from intravenous fluids and CPB priming volume, all of which heighten the risk for developing or worsening anemia.

Our findings illustrate that it is preferable to allow patients to have a single negative exposure to avoid a double negative exposure (HCT <25% and RBC transfusion),

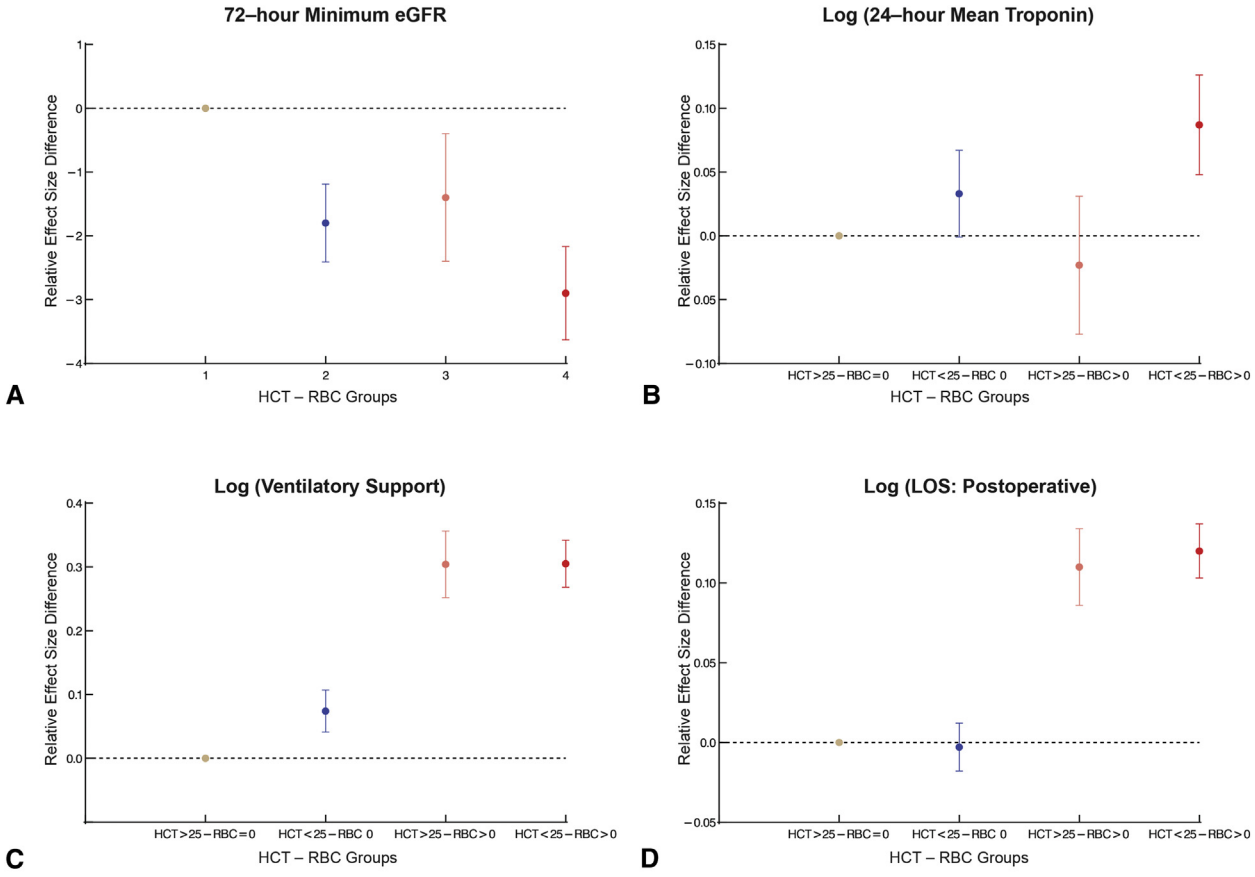

FIGURE 3. A-D, Relative effect size stratified by intraoperative red blood cell (*RBC*) transfusion and intraoperative nadir hematocrit (*HCT*). *eGFR,* Estimated glomerular filtration rate; *LOS,* length of stay.

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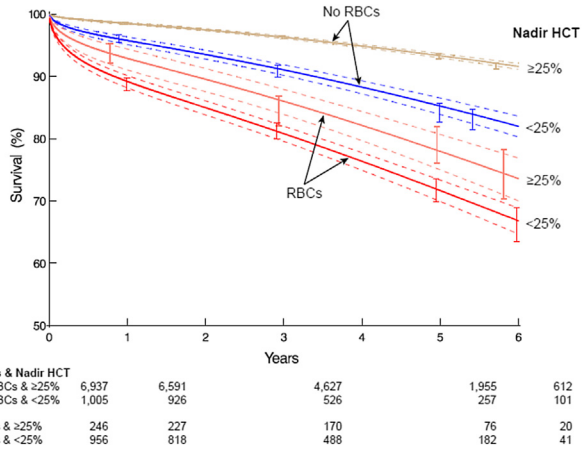

FIGURE 4. Survival after cardiac surgery stratified by intraoperative nadir hematocrit (*HCT*) and intraoperative red blood cell (*RBC*) transfusion exposure groups. *Vertical bars*, confidence limits equivalent to ±1 SE; *solid lines enclosed within dashed 68% confidence bands*, parametric estimates. Numbers of patients remaining at risk appear below the horizontal axis.

albeit no negative exposure is preferable. Patients exposed to the combination of intraoperative anemia and transfusion had the greatest risk for renal, cardiac, and pulmonary morbidities, as well as increased resource use and earlier death. The trade-off in morbidity risk with a single exposure varied depending on the exposure.

Single Exposure: Anemia

At a certain value, nadir HCT contributes to complications as a result of a critical decrease in oxygen supply; however, the lower cutoff value is unclear. We found that patients exposed to intraoperative anemia (HCT <25%) alone had more renal dysfunction, more myocardial injury, and longer ventilatory support times, yet mortality was not higher. Other investigations have demonstrated increased morbidity, increased mortality, and longer postoperative LOS in cardiac surgical patients with low nadir HCT.[3,16-19] Recently, our group reported more end-organ dysfunction and mortality associated with lower nadir HCT during CPB.[2]

Our prior investigation was unable to provide a clear cutoff value for lower nadir HCT because the effect of lower HCT and morbidity was closely tied to patient-specific risk factors and the specific morbidity measured. This investigation is consistent with our earlier work on anemia exposure in demonstrating the kidney's sensitivity to anemia and increased resource use, reflective of longer ventilation times. The Society of Thoracic Surgeons guidelines recommend tolerance of anemia down to a hemoglobin level of 6 $g \cdot dL^{-1}$ on CPB. Although the exact cutoff value is not widely agreed on, the general message is that anemia should be tolerated.[20]

Single Exposure: Transfusion

Intraoperative RBC transfusion without anemia exposure was associated with longer ventilatory support duration and postoperative LOS, with mortality trending higher than that for anemia alone. Several investigations in cardiac surgical patients have linked RBC transfusion with higher morbidity and mortality.[5-7] A recent randomized trial by Hajjar and colleagues[21] found that more RBC units transfused was an independent risk factor for poor outcomes. Other studies have implicated RBC transfusion in greater cardiac and renal dysfunction, delirium, poor quality of life, impaired respiratory tract function, and more infectious complications.[7,22,23]

Least of 3 Evils

This investigation uniquely examined the interplay of negative exposures in a single at-risk population. Ideally, patients with preoperative anemia should have their RBC mass optimized before surgery. Use of perioperative blood conservation measures, such as antifibrinolytics, cell salvage, miniaturized bypass circuits, and retrograde autologous priming, should be implemented whenever possible.[24-27] Methods are available to predict nadir HCT on CPB, which is often the trigger for RBC transfusion (Box E1).[28]

When one is faced with a projection of an intraoperative nadir HCT at lower thresholds of anemia, these practice scenarios may be followed: (1) place a unit of RBCs in the CPB pump before commencing bypass to avoid patient exposure to anemia; (2) commence CPB and tolerate lower levels of HCT without RBC transfusion; or (3) commence CPB, tolerate anemia for a period of bypass time, use methods to ameliorate anemia, such as ultrafiltration, and transfuse RBCs after a period of exposure to anemia when ameliorating methods are unsuccessful. Patients who are predicted to have a nadir HCT lower than 25% despite these conservative measures, or who cannot tolerate blood conservation measures, such as retrograde autologous priming, may benefit from a unit of RBCs in the CPB circuit before bypass is commenced, to prevent the HCT from decreasing lower than 25% and causing 2 negative exposures.

In a recent pilot investigation, Karkouti and colleagues[29] suggested treating preoperative anemia with prophylactic RBC transfusions as a protective measure against postoperative acute kidney injury. The authors hypothesized that transfusing patients days before surgery potentially decreased its negative effects by allowing time for functional properties of RBCs to recover and by clearing senescent RBCs. The authors did not address whether these patients had iron-deficient anemia and could have been treated with iron therapy rather than a transfusion. Certainly, in patients who are not candidates for iron or erythropoietin therapy, early transfusion might be a consideration. However, others cautioned against using RBC transfusion as a prophylactic strategy, noting the availability of myriad perioperative blood conservation measures that are preferable to RBC transfusion.[30]

Limitations

This is a prospective cohort investigation, and unmeasured variables have the potential to bias study results. In addition, this is a single-center investigation, which limits the generalizability of our findings. Treating HCT as a categorical, rather than a continuous, variable could influence results, depending on what cutoff is used. We chose 25% because lower than this number there were still enough patients who did and did not get transfused to allow comparative analysis. Below an HCT of 20%, few patients at our institution escape RBC transfusions.

CONCLUSIONS

Ideally, all cardiac surgical patients would have preoperative HCT optimized before surgical intervention; however, the reality is that patients are prone to being exposed to both anemia and RBC transfusion perioperatively. Our findings have practical implications for clinical practice. Clearly, a double negative exposure to RBCs and anemia (HCT <25%) carries the highest morbidity risk; however, single exposures carry increased morbidity risk as well. Managing preoperative anemia more aggressively and implementing measures to avoid development of operative anemia may circumvent negative exposures and improve patient outcomes.

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APPENDIX E1. Variables included in multivariable analyses

Patient variables	
Demographic:	Age (y),* sex,* race,* height (cm), weight (kg), body surface area (m^2), body mass index ($kg \cdot m^{-2}$)*
Symptoms:	New York Heart Association functional class (I-IV),* emergency operation*
Ventricular function:	Ejection fraction (%),* prior myocardial infarction*
Coronary anatomic features:	Left main trunk disease, right coronary artery system disease, left circumflex coronary artery disease, left anterior descending coronary artery disease (all, any, $\geq$50% stenosis,* $\geq$70% stenosis)
Cardiac comorbidity:	Atrial fibrillation or flutter,* hypertension,* heart failure,* cardiogenic shock,* intra-aortic balloon pump use,* ventricular arrhythmia,* prior cardiac operation,* complete heart block/pacer*
Noncardiac comorbidity:	History of chronic obstructive pulmonary disease,* non–insulin-treated diabetes,* insulin-treated diabetes,* pharmacologically treated diabetes,* history of peripheral artery disease,* history of smoking,* carotid disease,* blood urea nitrogen ($mg \cdot dL^{-1}$),* bilirubin ($mg \cdot dL^{-1}$),* hematocrit (%),* creatinine ($mg \cdot dL^{-1}$), creatinine clearance ($mL \cdot min^{-1}$), glomerular filtration rate ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$),* prior stroke,* total cholesterol ($mg \cdot dL^{-1}$)*
Experience:	Date of operation*
Procedure variables	
Support:	Cardiopulmonary bypass time (min),* myocardial ischemia (min)
Procedures:	Isolated coronary artery bypass grafting (CABG),* isolated valve,* isolated valve + CABG,* internal thoracic artery graft,* other procedures, number of surgical components

*Variables included in the balancing-score model.

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BOX E1. Algorithm for calculating patient-machine hematocrit

The need for and amount of additional red blood cells to achieve a desired hemoglobin concentration early after commencing cardiopulmonary bypass is determined by the patient's blood volume (VpB) and hemoglobin concentration before bypass (expressed as hematocrit, HCTp), and the volume of pump-oxygenator prime (VmB) and its hemoglobin concentration (expressed as hematocrit, HCTm). Patient blood volume is estimated as follows:

$$VpB = 1000f - wt,$$

where f is the proportion of body weight attributable to blood volume; $f = 0.08$ for infants and children up to 12 years of age, $f = 0.065$ for older patients, and wt is weight in kilograms. (These are average values for the proportion of body weight that is blood volume. More complex regression equations are available for more accurate estimates.[28])

Patient (VpRBC) and machine (VmRBC) red blood cell (RBC) volumes are as follows:

$$VpRBC = VpB \cdot HCTp$$

$$VmRBC = VmB \cdot HCTm$$

Then, mixed patient-machine hematocrit (HCTpm) is as follows:

$$HCTpm = (VpRBC + VmRBC)/(VpB + VmB).$$

If no blood is in the prime:

$$HCTpm = VpRBC/(VpB + VmB).$$

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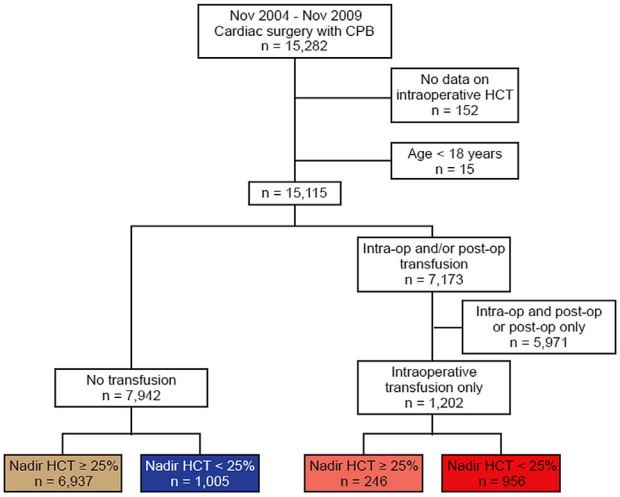

FIGURE E1. CONSORT-style diagram of patient population. The 4 groups analyzed are color coded as in manuscript Figures 1 through 4. *CPB*, Cardiopulmonary bypass; *HCT*, hematocrit; *Intra-op*, intraoperative; *post-op*, postoperative.

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TABLE E1. Patient and procedure factors associated with different exposures to anemia, transfusions, or both

Factor	Coefficient ± SE	*P* value
Nadir HCT <25 and RBC = 0 vs nadir HCT ≥25 and RBC = 0		
Older age	0.019 ± 0.0031	<.001
Female sex	1.7 ± 0.092	<.001
Lower body mass index	−0.065 ± 0.0069	<.001
Prior cardiac operation	0.33 ± 0.12	.007
No atrial fibrillation or flutter	−0.57 ± 0.15	.002
Lower preoperative hematocrit	−0.36 ± 0.011	<.001
Right coronary artery disease (≥50% stenosis)	0.39 ± 0.14	.004
Lower bilirubin*	0.091 ± 0.041	.02
Longer cardiopulmonary bypass time	0.0053 ± 0.00013	<.001
More recent date of operation	0.063 ± 0.0017	.03
Nadir HCT ≥25 and RBC > 0 vs nadir HCT ≥25 and RBC = 0		
Older age	0.025 ± 0.0056	<.001
Female sex	0.55 ± 0.16	.005
Lower body mass index	−0.042 ± 0.012	.006
Prior cardiac operation	1.6 ± 0.12	<.001
Lower preoperative hematocrit	−0.23 ± 0.017	<.001
Emergency operation	1.7 ± 0.50	.009
Preoperative intra-aortic balloon pump use	2.4 ± 0.58	<.001
Lower bilirubin*	0.15 ± 0.069	.03
Prior stroke	0.56 ± 0.22	.009
Procedure other than isolated CABG or valve	0.79 ± 0.15	<.001
Longer cardiopulmonary bypass time	0.015 ± 0.0017	<.001
Earlier date of operation	−0.17 ± 0.048	.004
Nadir HCT <25 and RBC > 0 vs nadir HCT ≥25 and RBC = 0		
Older age	0.065 ± 0.0043	<.001
Female sex	2.2 ± 0.12	<.001
Lower body mass index	−0.081 ± 0.0088	<.001
Prior cardiac operation	1.4 ± 0.13	<.001
No atrial fibrillation or flutter	−1.1 ± 0.15	<.001
Lower preoperative hematocrit	−0.53 ± 0.015	<.001
Right coronary artery disease (≥50% stenosis)	0.400 ± 0.16	.01
Emergency operation	2.1 ± 0.49	<.009
Lower bilirubin*	0.21 ± 0.047	<.001
Prior stroke	0.43 ± 0.18	.02
Procedure other than isolated CABG or valve	0.50 ± 0.12	<.001
Internal thoracic artery graft used	0.57 ± 0.15	.002
Longer cardiopulmonary bypass time	0.019 ± 0.0014	<.001
More recent date of operation	0.089 ± 0.035	.01

HCT, Hematocrit; *RBC*, red blood cell; *CABG*, coronary artery bypass grafting; *SE*, standard error. *(1/Bilirubin), inverse transformation.

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TABLE E2. Patient variables associated with lower 72-hour minimum estimated glomerular filtration rate

Variable	Coefficient ± SE	*P* value	Reliability, %*
Compared with nadir HCT ≥25 and RBC = 0			99
Nadir HCT <25 and RBC = 0	−1.8 ± 0.61	.004	
Nadir HCT ≥25 and RBC > 0	−1.4 ± 1.00	.15	
Nadir HCT <25 and RBC > 0	−2.9 ± 0.73	<.001	
Older age	−0.19 ± 0.015	<.001	100
Lower preoperative eGFR	−0.75 ± 0.0078	<.001	100
African American	−3.5 ± 0.78	<.001	84
Male sex	−1.6 ± 0.55	.005	67
Cardiogenic shock	−12 ± 2.5	<.001	92
Diabetes (insulin dependent)	−3.06 ± 0.67	<.001	92
Hypertension	−1.9 ± 0.36	<.001	95
Heart failure	−1.2 ± 0.43	.006	77
Lower preoperative hematocrit†	−14 ± 2.6	<.001	99
Atrial fibrillation or flutter	−1.5 ± 0.59	.01	86
Higher body mass index	−0.38 ± 0.031	<.001	100
Longer time undergoing cardiopulmonary bypass	−0.044 ± 0.0052	<.001	100
History of COPD	−1.3 ± 0.51	.01	63
Lower ejection fraction‡	1.5 ± 0.44	.001	96
Peripheral arterial disease	−0.92 ± 0.40	.02	45

HCT, Hematocrit; *RBC*, red blood cell; *eGFR*, estimated glomerular filtration rate; *COPD*, chronic obstructive pulmonary disease; *SE*, standard error. *Percentage of times variable appeared in 500 bootstrap models. †(40/Preoperative hematocrit), inverse transformation. ‡(Ejection fraction/50)^2, squared transformation.

TABLE E3. Variables associated with higher troponin (24-hour mean)*

Variable	Coefficient ± SE	*P* value	Reliability, %†
Compared with nadir HCT ≥ 25 and RBC = 0			76
Nadir HCT < 25 and RBC = 0	0.033 ± 0.034	.3	
Nadir HCT ≥ 25 and RBC > 0	−0.023 ± 0.054	.7	
Nadir HCT < 25 and RBC > 0	0.087 ± 0.039	.02	
Atrial fibrillation or flutter	0.13 ± 0.053	.01	54
Male sex	0.13 ± 0.028	<.001	56
No prior cardiac operation	−0.085 ± 0.033	.01	97
Preoperative intra-aortic balloon pump use	0.70 ± 0.12	<.001	97
Lower preoperative eGFR‡	−0.35 ± 0.034	<.001	100
Diabetes (non–insulin dependent)	0.075 ± 0.036	.04	91
Lower weight§	0.32 ± 0.048	<.001	100
Longer time undergoing cardiopulmonary bypass‖	0.84 ± 0.027	<.001	100
Higher total cholesterol¶	0.012 ± 0.0056	.04	84
Higher blood urea nitrogen	0.0038 ± 0.0014	.009	74
LCx disease (≥70% stenosis)	0.12 ± 0.027	<.001	97
Nonemergency operation	0.29 ± 0.0104	.005	80
Procedure other than isolated CABG	0.21 ± 0.028	<.001	100
Earlier date of operation	−0.073 ± 0.0068	<.001	85

HCT, Hematocrit; *RBC*, red blood cell; *eGFR*, estimated glomerular filtration rate; *LCx*, left circumflex coronary artery; *CABG*, coronary artery bypass grafting; *SE*, standard error. *Log(troponin – 24-hour mean); logarithmic transformation was used as the response variable. †Percentage of times variable appeared in 500 bootstrap models. ‡Log(preoperative eGFR), logarithmic transformation. §(80/Weight), inverse transformation. ‖Log(time on pump + 1), logarithmic transformation. ¶(Total cholesterol/120)^2, squared transformation.

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TABLE E4. Variables associated with longer duration of postoperative ventilatory support*

Variable	Coefficient ± SE	*P* value	Reliability, %†
Compared with nadir HCT ≥ 25 and RBC = 0			100
Nadir HCT < 25 and RBC = 0	0.074 ± 0.033	.02	
Nadir HCT ≥ 25 and RBC > 0	0.304 ± 0.052	<.001	
Nadir HCT < 25 and RBC > 0	0.305 ± 0.037	<.001	
Older age	0.0083 ± 0.00074	<.001	100
Higher NYHA functional class	0.043 ± 0.014	.004	97
History of smoking	0.062 ± 0.017	.004	85
Higher body mass index	0.020 ± 0.0015	<.001	100
History of COPD	0.19 ± 0.027	<.001	100
Prior cardiac operation	0.15 ± 0.033	<.001	94
Longer time undergoing cardiopulmonary bypass	0.0045 ± 0.00029	<.001	100
Preoperative intra-aortic balloon pump use	1.2 ± 0.12	<.001	100
Emergency operation	0.90 ± 0.11	<.001	99
Heart failure	0.062 ± 0.023	.008	84
Prior stroke	0.15 ± 0.034	<.001	96
Prior myocardial infarction	0.12 ± 0.022	<.001	83
Lower ejection fraction‡	−0.26 ± 0.034	<.001	100
Peripheral arterial disease	0.089 ± 0.022	<.001	68
Higher bilirubin§	0.023 ± 0.0056	<.001	91
Hypertension	0.094 ± 0.019	<.001	83
Procedure other than isolated CABG or valve	0.17 ± 0.021	.001	100

HCT, Hematocrit; *RBC*, red blood cell; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass grafting; *SE*, standard error. *Log(ventilatory support duration); logarithmic transformation was used as the response variable. †Percentage of times variable appeared in 500 bootstrap models. ‡Log(ejection fraction), logarithmic transformation. §$(\text{Bilirubin})^2$, squared transformation.

TABLE E5. Patient and procedural variables associated with longer postoperative length of stay*

Variable	Coefficient ± SE	*P* value	Reliability, %†
Compared with nadir HCT ≥ 25 and RBC = 0			100
Nadir HCT < 25 and RBC = 0	−0.0029 ± 0.015	.8	
Nadir HCT ≥ 25 and RBC > 0	0.11 ± 0.024	<.001	
Nadir HCT < 25 and RBC > 0	0.12 ± 0.017	<.001	
Older age‡	0.058 ± 0.0053	<.001	100
Atrial fibrillation or flutter	0.061 ± 0.015	<.001	97
Higher NYHA functional class	0.040 ± 0.0056	<.001	100
Heart failure	0.041 ± 0.011	<.001	92
Prior stroke	0.10 ± 0.016	<.001	100
History of COPD	0.10 ± 0.012	<.001	100
Cardiogenic shock	0.40 ± 0.063	<.001	94
Female sex	0.050 ± 0.012	<.001	52
Lower ejection fraction§	−0.16 ± 0.016	<.001	100
Higher blood urea nitrogen	0.0027 ± 0.00053	<.001	62
Higher body mass index‖	0.15 ± 0.017	<.001	100
Diabetes (insulin dependent)	0.053 ± 0.017	.001	95
Emergency operation	0.17 ± 0.051	.006	58
Higher bilirubin	0.059 ± 0.0096	<.001	99
Peripheral arterial disease	0.034 ± 0.011	.007	62
Prior cardiac operation	0.042 ± 0.016	.007	53
Procedure other than isolated CABG or valve	0.081 ± 0.097	<.001	100
Endocarditis	0.086 ± 0.020	<.001	97
Longer time undergoing cardiopulmonary bypass	0.041 ± 0.0045	.004	99
Earlier date of operation¶	−0.0025 ± 0.00045	<.001	58

HCT, Hematocrit; *RBC*, red blood cell; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass grafting; *SE*, standard error. *Log(postoperative length of stay); logarithmic transformation was used as the response variable. †Percentage of times variable appeared in 500 bootstrap models. ‡Exp(age/50), exponential transformation. §Log(ejection fraction), logarithmic transformation. ‖$(\text{Body mass index}/40)^2$, squared transformation. ¶(Years from 1/1/2004 to date of operation)^2, squared transformation.

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TABLE E6. Incremental risk factors for mortality

Factor	Coefficient ± SE	*P* value	Reliability, %*
Early decreasing phase			
Compared with nadir HCT ≥ 25 and RBC = 0			92
Nadir HCT < 25 and RBC = 0	0.49 ± 0.36	.17	
Nadir HCT ≥ 25 and RBC > 0	0.76 ± 0.45	.09	
Nadir HCT < 25 and RBC > 0	0.98 ± 0.36	.007	
Heart failure	0.79 ± 0.18	<.001	84
Prior stroke	0.66 ± 0.21	.002	78
Higher bilirubin†	0.052 ± 0.013	.001	49
Lower preoperative eGFR‡	−0.605 ± 0.16	.001	66
Lower total cholesterol§	1.1 ± 0.46	.02	77
Procedure other than isolated CABG or valve	0.35 ± 0.18	<.001	68
Propensity of nadir HCT < 25 and RBC = 0	0.57 ± 0.73	.4	
Propensity of nadir HCT ≥ 25 and RBC > 0	2.2 ± 1.1	.05	
Propensity of nadir HCT < 25 and RBC > 0	1.4 ± 0.44	.002	
Late increasing phase			
Compared with nadir HCT ≥ 25 and RBC = 0			42
Nadir HCT < 25 and RBC = 0	0.026 ± 0.21	.9	
Nadir HCT ≥ 25 and RBC > 0	0.18 ± 0.25	.4	
Nadir HCT < 25 and RBC > 0	0.057 ± 0.24	.8	
Older age‖	0.66 ± 0.066	<.001	100
Emergency operation	1.00 ± 0.42	.02	50
Complete heart block/pacer	0.41 ± 0.17	.02	51
Lower ejection fraction¶	−0.56 ± 0.11	<.001	96
History of COPD	0.67 ± 0.11	<.001	100
History of smoking	0.43 ± 0.11	<.001	98
Peripheral arterial disease	0.53 ± 0.11	<.001	97
Lower preoperative eGFR#	0.22 ± 0.028	<.001	95
Lower preoperative HCT**	1.5 ± 0.51	.003	98
Diabetes (pharmacologically treated)	0.49 ± 0.102	<.001	50
Propensity of nadir HCT < 25 and RBC = 0	0.72 ± 0.47	.12	
Propensity of nadir HCT ≥ 25 and RBC > 0	0.503 ± 0.76	.5	
Propensity of nadir HCT < 25 and RBC > 0	−0.13 ± 0.41	.8	

HCT, Hematocrit; *RBC*, red blood cell; *eGFR*, estimated glomerular filtration rate; *CABG*, coronary artery bypass grafting; *COPD*, chronic obstructive pulmonary disease; *SE*, standard error. *Percentage of times variable appeared in 500 bootstrap models. †(Bilirubin)^2, squared transformation. ‡Log(preoperative eGFR), logarithmic transformation. §(100/Total cholesterol), inverse transformation. ‖Exp(age/50), exponential transformation. ¶(Ejection fraction/50)^2, squared transformation. #(75/Preoperative eGFR), inverse transformation. **(40/Preoperative HCT), inverse transformation.

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