Nadir hematocrit during cardiopulmonary bypass: End-organ dysfunction and mortality

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Objective: To discover the effects of the lowest hematocrit during cardiopulmonary bypass on end-organ function and mortality in patients who did not receive red blood cell transfusion and to identify predictors of nadir hematocrit.

Methods: From November 1, 2004, to October 1, 2009, 7957 patients underwent cardiac surgery supported by cardiopulmonary bypass and were not transfused. The relationship between nadir hematocrit and morbidity, markers of end-organ function, and survival was studied using generalized propensity score analysis. Factors associated with nadir hematocrit were identified by linear regression.

Results: Median nadir hematocrit was 30% (25th to 75th percentile, 27%–33%). Lower nadir hematocrit was associated with higher maximum intraoperative lactic acid (intrasubject correlation, -0.44). After risk adjustment, nadir hematocrit was associated with worse renal function (lower estimated glomerular filtration rate; $P = .012$), more myocardial injury (higher troponin level; $P = .004$), longer postoperative ventilator support ($P < .001$), longer hospital stay ($P < .001$), and higher mortality ($P = .042$). Female gender, older age, lower body mass index, higher New York Heart Association class, and combined valve procedure and coronary artery bypass were associated with lower nadir hematocrit; however, the strongest correlate was preoperative hematocrit (correlation coefficient, 0.74).

Conclusions: Although red blood cell transfusion has associated morbidity risk, there must be a tradeoff between adverse effects of low hematocrit during cardiac surgery and those of transfusion. The strong association of nadir hematocrit with preoperative hematocrit suggests the need for investigation and optimization before elective cardiac surgery. (*J Thorac Cardiovasc Surg* 2012;144:654-62)

Supplemental material is available online.

More than one half million patients yearly undergo cardiac surgery with the support of cardiopulmonary bypass (CPB). More than half of these patients receive homologous blood transfusions.¹ Anemia is considered a major risk of these procedures and is primarily related to hemodilution from the CPB priming solutions and intravenous crystalloids, surgical bleeding, and coagulopathy. Blood conservation has become an important institutional initiative to improve

the quality of care, optimize resource usage, lower costs, and achieve better outcomes. Integral to these programs is tolerance of anemia; however, anemia can impair tissue perfusion, particularly in patients with cardiovascular disease, and result in end-organ injury. To date, a safe lower boundary for hematocrit (Hct) has not been determined.

Several studies have associated nadir Hct and red blood cell (RBC) transfusion with adverse clinical outcomes.²⁻¹⁴ However, the ability to discern whether adverse effects are attributable to nadir Hct is confounded by concomitant RBC transfusion, which itself introduces adverse effects. Thus, our objectives were to clarify the relationship between nadir Hct and end-organ function and mortality in cardiac surgical patients who were not transfused and to identify factors associated with nadir Hct.

METHODS

Patients

From November 1, 2004, to October 1, 2009, 15,279 consecutive patients underwent cardiac surgery requiring CPB at the Cleveland Clinic. Of these, 7957 did not receive an RBC transfusion during or after surgery. The baseline demographics and perioperative variables were retrieved from the Cardiovascular Information Registry, a prospective database updated concurrently with patient care (Table 1). The institutional review board approved the use of data from this registry for research, with patient consent waived.

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This study was supported in part by the Kenneth Gee and Paula Shaw, PhD, Chair in Heart Research, held by E. H. Blackstone.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Dec 15, 2011; revisions received Feb 27, 2012; accepted for publication March 20, 2012; available ahead of print April 16, 2012.

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0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2012.03.058

Abbreviations and Acronyms

CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
Hct = hematocrit
RBC = red blood cell

Endpoints

The endpoints were hospital morbidity and mortality, markers of end-organ function, resource usage, and long-term survival. Hospital morbidities (perioperative myocardial infarction, respiratory failure, sepsis, renal failure, and neurologic complications) were recorded prospectively according to definitions from the Society of Thoracic Surgeons National Adult Cardiac Database (available from: http://www.ctsnet.org/file/rptDataSpecifications252_1_ForVendorsPGS.pdf). Intensive care unit and postoperative lengths of stay were used as surrogates for resource use, as was the number of ventilator hours required postoperatively. Serial values of specific markers of end-organ function included troponin, estimated glomerular filtration rate (eGFR), and lactic acid.

Cardiovascular Information Registry follow-up data supplemented with Social Security Death Master File information were used to determine the vital status. The median follow-up was 2.6 years (interquartile range, 1.3–3.9 years). A total of 20,677 patient-years of follow-up were available for analysis; 25% of patients were followed more than 4 years and 10% for more than 4.7 years.

Statistical Analysis

Patient demographics, perioperative risk factors, and postoperative outcomes were summarized using the median and interquartile range (continuous variables) or frequency counts and percentages (categorical variables). Missing values were sporadic, without strong mechanism for informative missingness. They were imputed with the mean of available data (except for the categorical variable, New York Heart Association functional class, for which we created a separate category for its missing value). Of 7957 patients, 6928 (87.1%) had 1 to 5 CPB Hct values. In general, an arterial blood sample was obtained every 30 minutes during CPB for measurement of Hct and lactate. Hct was not measured during CPB in 56 patients (0.7%); we used their lowest intraoperative Hct as a surrogate for nadir Hct during CPB.

The univariate relationship between nadir Hct and outcomes was explored using penalized spline models. The adjusted effect of nadir Hct on outcomes, given confounders, was analyzed using a generalized propensity score analysis.¹⁵ Similar to the traditional 2-group propensity score analysis,¹⁶ generalized propensity score analysis offers a method of stratifying patients such that within each stratum, nadir Hct and confounders appear to be unrelated. Thus, the association between nadir Hct and outcomes is unconfounded within each stratum, and aggregated result across all strata forms an estimator of the independent effect of nadir Hct on outcomes (see Appendix E1).

Intraoperative Hct and lactic acid were measured simultaneously during surgery. We calculated their within-subject correlation and formed an average correlation coefficient. Its confidence interval was calculated using the bootstrap method.

We used a linear regression model with stepwise variable selection to identify preoperative risk factors associated with nadir Hct. Spline terms of continuous predictors were used to check the linearity assumption. The sandwich variance estimator was used to guard against possible heterogeneity or non-normality in the residual distribution.

All *P* values are 2-sided. Statistical analyses were performed with SAS, version 9.1 (SAS Institute, Cary, NC) and R 2.12.2 (R Foundation for Statistical Computing, Vienna, Austria).¹⁷

RESULTS

Unadjusted Nadir Hct and End-Organ Dysfunction

Nadir Hct ranged from 15% to 46% (median, 30%). Most often, the Hct level decreased from baseline shortly after beginning CPB and gradually recovered as the operation proceeded (Figure E1).

The unadjusted association between nadir Hct and selected outcomes is shown in Figure 1. Nadir Hct was associated with lower eGFR and higher troponin levels, suggesting renal and myocardial injury were more likely with a lower nadir Hct. Nadir Hct had no significant association with intensive care unit length of stay. An inverse relationship was seen between nadir Hct and the duration of mechanical ventilation and hospital length of stay. On average, patients with a nadir Hct of 20% were discharged 2.7 days later than patients with a nadir Hct of 35%. Three-year survival decreased from 98% to 85% as nadir Hct decreased from 35% to 20%.

Risk-Adjusted Nadir Hct and End-Organ Dysfunction

The risk-adjusted association of nadir Hct with each outcome is listed in Table 2, and Figure 2 illustrates those relationships. In Table 2, the associations are quantified as the regression coefficients of nadir Hct in the regression of each outcome, stratifying on the generalized propensity score. Nadir Hct was associated with higher mortality, more troponin release, lower eGFR, longer duration of mechanical ventilation, and longer length of hospital stay. Three-year adjusted survival decreased from 97% to 93% as nadir Hct decreased from 35% to 20%.

Pearson's correlation was -0.12 (95% confidence interval, -0.16 to -0.076) between the maximum intraoperative lactic acid level and nadir Hct, as determined from 2156 patients with available lactic acid data. A within-subject correlation analysis of 1893 patients, each with at least 5 pairs of intraoperative Hct and lactic acid measurements, showed that the average within-subject correlation coefficient between intraoperative Hct and lactic acid level was -0.44 (95% confidence interval, -0.45 to -0.42). Both results suggest impaired tissue perfusion at lower Hct values.

Sensitivity analyses using multivariate models were performed to confirm the results of the generalized propensity score analysis. We built regression models for the key outcomes using the variables listed in Table 1. The sensitivity analysis produced consistent results with the generalized propensity score analysis. Nadir Hct was associated with lower eGFR, greater troponin release, longer postoperative ventilation time, longer hospital length of stay, lower survival, and an increase in late mortality (see Appendix E2 and Tables E1 to E7).

Risk Factors for Nadir Hct

The factors associated with lower nadir Hct included lower preoperative Hct, older age, female gender, lower

TABLE 1. Patient characteristics (n = 7957)

Characteristic	Total patients (n)*	Median or count
Demographics		
Age (y)	7957	61 (51–69)
Gender	7957	
Men		5949 (75)
Women		2008 (25)
White race	7727	7219 (93)
Year of surgery	7957	
2004		320 (4)
2005		1669 (21)
2006		1596 (20)
2007		1487 (19)
2008		1587 (20)
2009		1298 (16)
Preoperative clinical and laboratory data		
BMI (kg/m ²)	7820	28.1 (25.1–32.0)
Hct (%)	7957	42 (39–46)
BUN (mg/dL)	7951	17 (14–21)
eGFR (mL/min/1.73 m ²)	7721	75 (64–87)
Bilirubin (mg/dL)	7874	0.6 (0.4–0.8)
Disease severity		
NYHA functional class	6867	
1		2066 (30)
2		3355 (49)
3		1336 (19)
4		110 (1.6)
Emergency operation	7955	
Yes		27 (0.3)
No		7928 (99.7)
IABP	7957	
Yes		26 (0.3)
No		7931 (99.7)
Cardiac comorbidity		
Coronary artery disease	6980	
LMT (>70%)		
Yes		344 (4.9)
No		6636 (95.1)
RCA (>70%)		
Yes	7010	1856 (26)
No		5154 (74)
EF (%)	7722	55 (50–60)
Preoperative AF		
Yes	7713	748 (9.7)
No		6965 (90.3)
History of heart failure		
Yes	7957	1400 (18)
No		6557 (82)
Previous MI		
Yes	7957	1582 (20)
No		6375 (80)
History of cardiogenic shock		
Yes	7957	26 (0.3)
No		7931 (99.7)

(Continued)

TABLE 1. Continued

Characteristic	Total patients (n)*	Median or count
History of peripheral arterial disease		
Yes	7957	1980 (25)
No		5977 (75)
Previous cardiac operation		
Yes	7957	1046 (13)
No		6911 (87)
Previous cardiac operations		
1	7957	6919 (87)
≥2		1038 (13)
History of hypertension		
Yes	7957	5033 (63)
No		2924 (37)
Noncardiac comorbidity		
Previous stroke		
Yes	7957	421 (5.3)
No		7536 (94.7)
History of carotid disease		
Yes	7957	1818 (23)
No		6139 (77)
History of smoking		
Yes	7950	3998 (50)
No		3952 (50)
History of COPD		
Yes	7957	793 (10)
No		7164 (90)
History of NIDDM		
Yes	7893	1047 (13)
No		6846 (87)
History of IDDM		
Yes	7893	429 (5.4)
No		7464 (94.6)
History of renal disease		
Yes	7957	128 (1.6)
No		7829 (98.4)
Operative factors		
Nadir Hct (%)	7957	29.7 (26.7–32.6)
Type of operation	7957	
Isolated CABG		1610 (20)
Isolated valve		2695 (34)
CABG and valve combined		882 (11)
Other		2770 (35)
Internal thoracic artery grafts		
Yes	7957	2358 (30)
No		5599 (70)
CPB time (min)	7957	86 (66–109)
Aortic clamp time (min)	7957	66 (51–85)

Data presented as median (interquartile range [25th–75th percentile]) for continuous variables and counts (percentages) for categorical variables. *BMI*, Body mass index; *Hct*, hematocrit; *BUN*, blood urea nitrogen; *eGFR*, estimated glomerular filtration rate; *NYHA*, New York Heart Association; *IABP*, intra-aortic balloon pump; *LMT*, left main trunk; *RCA*, right coronary artery; *EF*, ejection fraction; *AF*, atrial fibrillation; *MI*, myocardial infarction; *COPD*, chronic obstructive pulmonary disease; *NIDDM*, non–insulin-dependent diabetes mellitus; *IDDM*, insulin-dependent diabetes mellitus; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass.

*Patients with available data.

FIGURE 1. Unadjusted patient outcomes associated with nadir hematocrit (*Hct*). Relationship represented by *black solid line*. *Gray area* indicates 95% point-wise confidence band. *eGFR*, Estimated glomerular filtration rate; *ICU*, intensive care unit.

body mass index, peripheral arterial disease, renal disease, procedure complexity, and longer CPB duration (Table 3). The strongest correlate was preoperative Hct, with a Pearson correlation coefficient of 0.74. With all other variables fixed, older age, lower body mass index, higher New York Heart Association functional classification, and longer duration of CPB were associated with a decrease in predicted nadir Hct (Figure 3).

DISCUSSION

A restrictive RBC transfusion strategy is integral to current blood management programs for cardiac surgery. Part

of this strategy is a tolerance for perioperative anemia, but without the ability to predict whether a given level of anemia is safe. In our study, nadir Hct was associated with more end-organ dysfunction and mortality in a cohort of nontransfused cardiac surgical patients.

Other studies have explored the influence of anemia on surgical outcomes; however, many of these studies did not control for the concomitant influence of RBC transfusion. Moreover, the effects of preoperative anemia are difficult to separate from the effects of anemia occurring during CPB. Approximately 25% to 30% of patients undergoing cardiac surgery are anemic before the procedure, and this

TABLE 2. Risk-adjusted relationship between nadir hematocrit and morbidity outcomes

Outcomes	Effect* (<i>P</i> value)	Lower nadir Hct associated with
24-h mean troponin†	−0.12 (.0042)	Higher postoperative troponin
Lowest eGFR (mL/min/1.73 m ²) within 72 h	2.4 (.012)	Worse renal function
Postoperative ventilator support	−1.2 (<.001)	Greater need for ventilation
Ventilation duration (h), if needed†	−0.1 (.0057)	Longer ventilation time
Postoperative ICU stay (h)†	−0.047 (.062)	Not significant
Postoperative hospital length of stay†	−0.083 (<.001)	Longer postoperative stay
Interval to all-cause death	−0.46 (.042)	Higher risk of death

Hct, Hematocrit; eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

*Only in these analyses, Hct is expressed as change/10-unit increase in percentage of Hct; for troponin, eGFR, ventilation duration, and ICU and hospital length of stay, linear regression analysis was used, and the effect is the mean change; for ventilation support, logistic regression analysis was used, and the effect is the log odds ratio; for survival, the Cox model was used, and the effect is the log hazard ratio. †Natural logarithmic transformation.

is a recognized risk factor for increased morbidity and mortality.¹⁸⁻²⁰

Lower nadir Hct during CPB has been associated with increased in-hospital and long-term mortality.^{6,7} A recent study investigated the influence of nadir Hct on mortality in a group of nontransfused patients undergoing isolated coronary artery bypass grafting.³ The investigators found an increase in major morbidity related to nadir Hct, but no effect on survival. Two small randomized trials failed to demonstrate a difference in operative, in-hospital, or 1-year survival for patients with low Hct during CPB.^{21,22}

To investigate the relationship between anemia and poor outcomes, we examined laboratory markers for end-organ function with varying Hct levels. Swaminathan and colleagues² showed that nadir Hct during CPB was associated with a higher peak fractional change in creatinine and that RBC transfusion further exacerbated the effects of low nadir Hct on renal function. Others have reported the susceptibility of renal function to low nadir Hct, as reflected by increased creatinine values and renal failure.⁵ We discovered a significant interaction between nadir Hct and eGFR. Patients progressed along a spectrum of mild renal dysfunction as nadir Hct decreased from 30% to 20%. This is a subtle, but important, finding. Previous studies have shown that even mild degrees of renal dysfunction can influence adverse outcomes among patients undergoing cardiac surgery.²³⁻²⁵

Patients with a low nadir Hct have a greater prevalence of postoperative myocardial infarction, cardiac arrest,⁶ intra-aortic balloon pump use, and return to CPB.^{6,7} We did not find an association between nadir Hct and Society of Thoracic Surgeons–defined postoperative myocardial

infarction. However, we did note a relationship between nadir Hct and the release of troponin. This subclinical myocardial injury can be explained by a low nadir Hct in the cardioplegia solution, which derives its Hct from systemic circulation. The nadir Hct is often reached shortly after the initiation of CPB and before the period of protected ischemic arrest, which might explain this increase in troponin. Although the implications of this troponin release are unclear, it has been shown to be a sensitive marker for perioperative myocardial infarction and postoperative heart failure.^{26,27}

The increased hospital length of stay associated with lower nadir Hct might be related to fatigue-induced lack of mobility in the immediate postoperative period. A recent study reported that postoperative cardiac surgery patients admitted to rehabilitation with hemoglobin values less than 10 g/dL had significantly worse performance on the 6-minute walk test than patients with higher hemoglobin values.²⁸

Study Limitations

This was a prospective cohort investigation in which unmeasured variables could have biased the results from the generalized propensity score analysis and regression models. However, we improved on previous studies by incorporating a larger number of confounders into our model, including preoperative anemia. Patients in the present investigation were lower risk than patients who received blood transfusions, as previously demonstrated by our group.^{10,11} Nadir Hct was analyzed as a continuous variable, and we found no threshold below which the morbidity sharply increased to suggest a sharp cutoff. Furthermore, our analysis showed that the effect of nadir Hct was different for individual organ systems and was affected by the patients' unique comorbidities. Thus, we cannot recommend a subject- or morbidity-specific transfusion trigger.

Clinical Implications

We identified several risk factors for low nadir Hct on CPB that could guide patient selection and preoperative management. Preoperative anemia should be investigated for potentially reversible causes, and, if possible, surgery should be delayed until Hct improves. The observation that women had a lower preoperative Hct was consistent with previous work from our group.²⁹ Iron supplements and short-term therapy with erythropoietin are possible interventions. A number of intraoperative strategies can ameliorate reductions in Hct associated with surgery requiring CPB. Retrograde autologous priming and smaller bypass circuits are encouraged in patients with a low body mass index and low preoperative Hct. Many of these blood conservation strategies have been implemented at our institution during the past decade. These strategies did not confound

FIGURE 2. Adjusted relationship between nadir hematocrit (*Hct*) and outcomes from generalized propensity score analysis. *Gray lines* indicate the relationship within each patient strata defined by the generalized propensity score. Fifty strata were used, representing a spectrum of risk levels (except for all-cause death, for which we combined 50 strata into 5 to estimate the baseline survival probability accurately). *Solid line* indicates average across all strata. For comparison purposes, the *dashed lines* represent the same model between outcomes and nadir Hct without stratification. *eGFR*, Estimated glomerular filtration rate; *ICU*, intensive care unit.

our ability to examine the effect of nadir Hct on outcomes; rather, they reduced the overall level of anemia experienced by patient population. The relationship between New York Heart Association functional class and nadir Hct was most likely due to the patients' excess free water coupled with the CPB priming solution. These patients should undergo diuresis before surgery to help avoid lower nadir Hct.

Future studies should address factors that can help define subgroups of patients with severe intraoperative anemia who would benefit from RBC transfusions. The risks of tolerating a lower Hct must be weighed against the risks of interventions used to increase it, such as RBC transfusion. To date, evidence has suggested that patients do worse when given RBC products during cardiac surgery. Specifically, for reasons that are not entirely understood, patients who

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TABLE 3. Factors associated with lower nadir hematocrit

Factor	Regression Coefficient*	95% CI	P value
Demographics			
Older age (per 5-y increase)	-0.16	-0.18, -0.13	<.001
Lower BMI (per 5-kg/m ² decrease)	0.51	0.46, 0.56	<.001
Gender			
Men	2.6	2.4, 2.7	<.001
Women	0	—	—
Race (white)	0.56	0.33, 0.78	<.001
Year of surgery			
2004	0	—	—
2005	0.25	-0.063, 0.56	.1
2006	0.48	0.16, 0.80	.003
2007	0.63	0.31, 0.94	<.001
2008	0.35	0.033, 0.67	.03
2009	-0.069	-0.39, 0.25	.7
Preoperative clinical and laboratory data			
Lower Hct (%)	0.55	0.54, 0.57	<.001
Lower bilirubin (mg/dL; log scale)	0.37	0.25, 0.49	<.001
Disease severity			
NYHA functional class			
1	0	—	—
2	-0.18	-0.32, -0.04	.01
3	-0.24	-0.42, -0.06	.009
4	-0.11	-0.63, 0.42	.7
IABP	-1.2	-2.3, -0.13	.03
Cardiac comorbidity			
Coronary artery disease			
LMT (>70%)	-0.48	-0.76, -0.19	.001
RCA (>70%)	-0.31	-0.48, -0.13	<.001
Preoperative AF	0.54	0.32, 0.75	<.001
Previous cardiac operation	-0.26	-0.4, -0.12	<.001
History of peripheral artery disease	-0.48	-0.83, -0.12	.009
Higher ejection fraction (per 10% increase)	-0.058	-0.12, 0.0011	.054
Noncardiac comorbidity			
History of carotid disease	0.44	0.064, 0.81	.02
History of renal disease	-0.47	-0.9, -0.045	.03
Operative factors			
Operation type			
Isolated CABG	-0.14	-0.38, 0.11	.3
Isolated valve	0.29	0.15, 0.44	<.001
CABG and valve combined	-0.5	-0.72, -0.27	<.001
Other	0	—	—

(Continued)

receive an RBC transfusion during cardiac surgery have an incremental decrease in long-term survival proportionate to the number of units received.¹¹ Several large-scale observational studies have demonstrated an association between RBC transfusion and increased morbidity after cardiac surgery.^{9-11,13,14,30,31}

TABLE 3. Continued

Factor	Regression Coefficient*	95% CI	P value
Internal thoracic artery graft	-0.33	-0.53, -0.12	.002
Longer CPB time (h)	-0.27	-0.46, -0.082	.005
Longer aortic clamp time (h)	-0.22	-0.45, 0.0094	.06

The intercept of this model is 4.1 (95% CI, 3.2, 5.0). *CI*, Confidence interval; *BMI*, body mass index; *Hct*, hematocrit; *NYHA*, New York Heart Association; *IABP*, intra-aortic balloon pump; *LMT*, left main trunk; *RCA*, right coronary artery; *AF*, atrial fibrillation; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass. *The regression coefficient quantifies the increase in nadir Hct (%) for each unit increase of the corresponding covariate (or the presence of the condition).

CONCLUSIONS

Nadir Hct is associated with more end-organ dysfunction and increased resource usage and mortality. Preoperative anemia is the most significant risk factor for low nadir Hct. Identification and treatment of preoperative anemia might eliminate the risk associated with both anemia and RBC transfusion. Once perioperative anemia has occurred, it is unclear whether tolerating the anemia would be riskier than treating it with an RBC transfusion.

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FIGURE 3. Predicted mean nadir hematocrit (Hct) based on regression model presented in Table 3. First 3 plots are predicted nadir Hct vs age, body mass index, and duration in minutes of cardiopulmonary bypass (CPB), stratified by gender (male, solid line; female, dashed line) and with all other predictors fixed at values corresponding to a middle-risk patient. The last plot is a box plot comparing nadir Hct and New York Heart Association (NYHA) functional class.

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APPENDIX E1. TECHNICAL DETAILS ON GENERALIZED PROPENSITY SCORE ANALYSIS

The analysis was started by developing a generalized propensity function for nadir hematocrit (Hct). In theory, this is defined for each subject as the cumulative distribution function of the conditional distribution of nadir Hct, given all the confounders in Table 1. In the present investigation, we found that a linear regression model with homogeneous residual variance approximated the data well. In such situations, the generalized propensity function can be simplified as a generalized propensity score, which is the predicted mean of nadir Hct from that linear regression. The theory reported by Imai and van Dyk^{E1} shows that, conditional on the generalized propensity score, nadir Hct and all confounders were independent. Therefore, we can use an approach similar to that of Rosenbaum and Rubin^{E2} and stratify the subjects into a number of strata such that subjects within each stratum have similar generalized propensity scores. For the present report, we used 50 strata. The validity of the generalized propensity score analysis can be checked by balance diagnosis. If the generalized propensity score is calculated correctly, and the stratification is adequate, we would expect that nadir Hct and confounders would be approximately independent within each stratum. We used a balance-check procedure similar to that reported by Rosenbaum and Rubin^{E2} for 2-group propensity score analysis. First, perform a 1-way analysis of variance with a confounder (eg, age) as the dependent variable and nadir Hct as the covariate. Second, perform a 2-way analysis of variance with the strata indicator as the second covariate. Finally, compare the F-statistic of nadir Hct before and after adding the strata indicator. If the generalized propensity score is calculated correctly and the stratification is good, the F-statistic should be reduced to near 0 after stratification. We can define a threshold by the upper tail (0.05 quartile) of the F-distribution with the same degrees of freedom as the F-statistic, and the F-statistic should be within the threshold with 95% probability after stratification. The analysis of the association between nadir Hct and outcomes proceeded by a stratified regression model of each outcome on nadir Hct, with no need to adjust for the large number of confounders in the model. Linear regression was used for continuous outcomes, logistic regression for binary outcomes, and stratified Cox regression for time-to-event outcomes.

APPENDIX E2. SENSITIVITY ANALYSIS

Multivariate regression models were used to study the adjusted relationship between nadir Hct and end-organ function and postoperative morbidity and mortality (sensitivity analyses). The main objective of this ancillary analysis was to further corroborate the results obtained using the generalized propensity score method. We considered the following 5 endpoints for the sensitivity analyses: eGFR (first 3-day minimum), troponin (24-hour mean), ventilation, hospital length of stay, and death. The risk factors associated with continuous variables (ie, eGFR, troponin, duration of ventilation, and hospital length of stay) were identified using multivariate linear regression (PROC REG, SAS; SAS Institute, Cary, NC). The risk factors associated with the binary variable (receiving ventilation) were identified using multivariate logistic regression (PROC LOGIT, SAS; SAS Institute). Survival was assessed nonparametrically using the Kaplan-Meier estimator and parametrically using a multiphase hazard model.^{E3} The parametric model was used to resolve a number of phases of instantaneous risk of the event (hazard function) and to estimate the shaping parameters (details can be found at <http://my.clevelandclinic.org/professionals/software/hazard/default.aspx>). Variable selection, with a *P* value criterion for the retention of variables in the model of .05, used bootstrap bagging (bootstrap aggregation).^{E4,E5} 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% of the size of the original. Second, risk factors were identified using automated forward stepwise selection. Third, the results of the variable selection were stored. These 3 steps were repeated 500 times. Finally, the frequency of the 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 guided analysis (Tables E1 to E6).

E-References

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FIGURE E1. Operative trends in hematocrit (*Hct*) values for the patient population. *CPB*, Cardiopulmonary bypass.

TABLE E2. Factors associated with higher troponin release

Factor	Coefficient $\pm$ SD	<i>P</i> value	Reliability* (%)
Lower nadir Hct	-0.0082 ± 0.0022	.0002	91
Atrial fibrillation	0.63 ± 0.032	<.0001	100
Race other than white	0.19 ± 0.035	<.0001	99
Heart failure	0.13 ± 0.024	<.0001	99
Preoperative IABP	0.79 ± 0.15	<.0001	98
Lower preoperative eGFR†	-0.44 ± 0.031	<.0001	100
Absence of NIDDM	-0.056 ± 0.027	.04	68
Smaller BMI‡	0.18 ± 0.035	<.0001	100
Longer CPB duration§	0.69 ± 0.029	<.0001	100
Higher bilirubin¶	0.076 ± 0.019	<.0001	92
Fewer previous surgeries	-0.12 ± 0.021	<.0001	65
Longer aortic clamp time	0.14 ± 0.0202	<.0001	100
Other procedures			100
Isolated CABG	-0.52 ± 0.026	<.0001	
Isolated valve	-0.42 ± 0.022	<.0001	
Isolated CABG + valve	-0.37 ± 0.031	<.0001	

SD, Standard deviation; *Hct*, hematocrit; *IABP*, intra-aortic balloon pump; *eGFR*, estimated glomerular filtration rate; *NIDDM*, non-insulin-dependent diabetes mellitus; *BMI*, body mass index; *CPB*, cardiopulmonary bypass; *CABG*, coronary artery bypass grafting. *Percentage of times the variable appeared in 500 bootstrap models. †Log (preoperative eGFR), logarithmic transformation. ‡(40/BMI), inverse transformation. §Log (time on pump + 1), logarithmic transformation. ¶Log (bilirubin), logarithmic transformation. ||Log (aortic clamp time + 1), logarithmic transformation.

TABLE E1. Factors associated with lower eGFR (worse renal function)

Factor	Coefficient $\pm$ SD	<i>P</i> value	Reliability* (%)
Lower nadir Hct	0.26 ± 0.043	<.0001	93
Older age [(age/50) ² , squared transformation]	-3.6 ± 0.28	<.0001	100
Lower preoperative eGFR (eGFR/75) ² , squared transformation	1.1 ± 0.034	<.0001	100
Male gender	-1.8 ± 0.41	<.0001	92
Cardiogenic shock	-12 ± 2.8	<.0001	91
IDDM	-2.4 ± 0.69	.0006	88
Hypertension	-1.2 ± 0.34	.0005	87
Heart failure	-1.4 ± 0.43	.002	85
Stroke	-2.1 ± 0.68	.003	81
COPD	-1.4 ± 0.52	.006	74
Larger BMI [(40/BMI), inverse transformation]	10 ± 0.63	<.0001	100
Longer CPB duration	-0.031 ± 0.0044	<.0001	99
Lower EF [(50/EF), inverse transformation]	-1.1 ± 0.37	.002	70

eGFR, Estimated glomerular filtration rate; *SD*, standard deviation; *Hct*, hematocrit; *IDDM*, insulin-dependent diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *BMI*, body mass index; *CPB*, cardiopulmonary bypass; *EF*, ejection fraction. *Percentage of times the variable appeared in 500 bootstrap models.

TABLE E3. Factors associated with higher likelihood of postoperative ventilator support

Factor	Coefficient $\pm$ SD	<i>P</i> value	Reliability* (%)
Lower nadir Hct	-0.12 ± 0.019	<.0001	98
Older age†	0.51 ± 0.091	<.0001	100
Lower EF‡	-0.602 ± 0.16	.0001	100
Larger BMI	0.071 ± 0.011	<.0001	100
COPD	0.58 ± 0.24	.02	55
Previous cardiac surgery	1.3 ± 0.27	<.0001	71
Longer CPB duration§	1.2 ± 0.13	<.0001	100
Higher preoperative Hct¶	1.6 ± 0.33	<.0001	98
Recent date of surgery			100
Surgery year 2007 vs 2004–2006	0.83 ± 0.14	<.0001	
Surgery year 2008 vs 2004–2006	3.3 ± 0.36	<.0001	
Surgery year 2009 vs 2004–2006	2.5 ± 0.29	<.0001	
Isolated CABG vs other procedures	0.88 ± 0.23	.0001	75
Isolated valve vs other procedures	-0.69 ± 0.11	<.0001	100

SD, Standard deviation; *Hct*, hematocrit; *EF*, ejection fraction; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CPB*, cardiopulmonary bypass; *CABG*, coronary artery bypass grafting. *Percentage of times the variable appeared in 500 bootstrap models. †(Age/50)², squared transformation. ‡(EF/50)², squared transformation. §Log (time on pump + 1), logarithmic transformation. ¶(Preoperative Hct/40)², squared transformation.

TABLE E4. Factors associated with increased duration of ventilator support

Factor	Coefficient ± SD	P value	Reliability* (%)
Lower nadir Hct	−0.013 ± 0.0031	<.0001	95
Older age†	0.17 ± 0.016	<.0001	100
Race other than white	−0.102 ± 0.035	.004	77
Lower EF‡	−0.18 ± 0.036	.0001	99
Larger BMI	0.024 ± 0.0016	<.0001	100
COPD	0.14 ± 0.228	<.0001	99
Previous cardiac surgery	0.13 ± 0.26	<.0001	87
Longer CPB duration	0.0037 ± 0.00025	<.0001	100
Higher preoperative Hct§	0.23 ± 0.053	<.0001	98
Preoperative IABP	1.1 ± 0.15	<.0001	100
Emergency surgery	0.75 ± 0.14	<.0001	96
Heart failure	0.095 ± 0.025	.0001	96
Internal thoracic artery grafting	0.084 ± 0.023	.0003	88
IDDM	0.14 ± 0.038	.0004	75
History of myocardial infarction	0.070 ± 0.024	.004	84
Higher NYHA functional class	0.044 ± 0.012	.0005	82
Cardiogenic shock	0.49 ± 0.15	.001	80
Higher bilirubin¶	0.030 ± 0.0076	.0001	84
Peripheral arterial disease	0.042 ± 0.022	.05	67
Absence of LMT disease (≥70% stenosis)	−0.094 ± 0.042	.03	62
Stroke	0.088 ± 0.038	.02	60
Atrial fibrillation	0.063 ± 0.032	.05	57
Isolated valve vs other procedures	−0.13 ± 0.022	<.0001	100
Isolated CABG + valve vs other procedures	−0.068 ± 0.029	.02	61

SD, Standard deviation; Hct, hematocrit; EF, ejection fraction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; IDDM, insulin-dependent diabetes mellitus; NYHA, New York Heart Association; LMT, left main trunk; CABG, coronary artery bypass grafting. *Percentage of times the variable appeared in 500 bootstrap models. †(Age/50)², squared transformation. ‡Log (EF), logarithmic transformation. §(Preoperative Hct/40)², squared transformation. ¶(Bilirubin)², squared transformation.

TABLE E5. Factors associated with increased length of hospital stay

Factor	Coefficient ± SD	P value	Reliability* (%)
Lower nadir Hct	−0.0036 ± 0.0017	.03	96
Older age†	0.053 ± 0.0060	<.0001	100
AF	0.065 ± 0.017	.0001	97
Higher NYHA functional class	0.059 ± 0.0066	<.0001	100
Heart failure	0.13 ± 0.013	<.0001	100
Stroke	0.15 ± 0.0202	<.0001	100
COPD	0.13 ± 0.013	<.0001	100
Race other than white	0.092 ± 0.018	<.0001	100
Cardiogenic shock	0.85 ± 0.0801	<.0001	100
Larger BMI‡	0.16 ± 0.019	<.0001	100
Female gender	0.040 ± 0.012	.002	90
Lower EF§	−0.28 ± 0.019	<.0001	100
Lower BUN¶	0.027 ± 0.012	.02	92
Lower preoperative Hct	0.24 ± 0.057	<.0001	82
History of myocardial infarction	0.043 ± 0.012	.0005	83
IDDM	0.072 ± 0.021	.0005	80
Previous cardiac surgery	0.057 ± 0.014	<.0001	78
Higher bilirubin	0.048 ± 0.012	<.0001	94
Peripheral arterial disease	0.099 ± 0.012	<.0001	63
Isolated valve vs other procedures	−0.12 ± 0.0104	<.0001	100
Isolated valve + CABG vs other procedures	−0.091 ± 0.016	<.0001	100
Longer CPB duration	0.0013 ± 0.00013	<.0001	99

SD, Standard deviation; Hct, hematocrit; AF, atrial fibrillation; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; BMI, body mass index; EF, ejection fraction; BUN, blood urea nitrogen; IDDM, insulin-dependent diabetes mellitus; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass. *Percentage of times the variable appeared in 500 bootstrap models. †Exp (age/50), exponential transformation. ‡(BMI/40)², squared transformation. §Log (EF), logarithmic transformation. ¶(20/BUN), inverse transformation. ||(40/Preoperative Hct), inverse transformation.

TABLE E6. Factors associated with increased likelihood of death

Factor	Coefficient $\pm$ SD	P value	Reliability* (%)
Early decreasing phase			
Lower nadir Hct	-0.054 ± 0.038	.15	39
Older age†	0.51 ± 0.14	.0002	94
Higher NYHA functional class	0.41 ± 0.16	.01	62
AF	0.63 ± 0.25	.01	75
Heart failure	1.3 ± 0.24	<.0001	99
IDDM	0.74 ± 0.30	.01	53
Stroke	0.71 ± 0.30	.02	61
Lower preoperative Hct‡	1.9 ± 0.86	.03	63
Lower BUN§	0.51 ± 0.13	.0001	71
Lower preoperative eGFR¶	0.16 ± 0.079	.04	59
Longer aortic clamp time	0.21 ± 0.079	.008	66
Late increasing phase			
Lower nadir Hct	-0.048 ± 0.017	.005	67
Older age#	0.56 ± 0.089	<.0001	100
Stroke	0.45 ± 0.20	.02	100
History of MI	0.38 ± 0.15	.01	70
Lower EF**	-0.51 ± 0.166	.002	76
COPD	0.59 ± 0.16	.0002	78
Smoking	0.36 ± 0.15	.02	76
Peripheral arterial disease	0.64 ± 0.16	<.0001	70
Higher BUN	0.044 ± 0.0059	<.0001	93
Higher bilirubin††	0.077 ± 0.030	.01	60

SD, Standard deviation; Hct, hematocrit; NYHA, New York Heart Association; AF, atrial fibrillation; IDDM, insulin-dependent diabetes mellitus; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; EF, ejection fraction; COPD, chronic obstructive pulmonary disease. *Percentage of times the variable appeared in 500 bootstrap models. †Exp (age/50), exponential transformation. ‡(40/preoperative Hct), inverse transformation. §(40/BUN), inverse transformation. ¶(75/preoperative eGFR), inverse transformation. ||(aortic clamp time/70)², squared transformation. #Exp (age/50), exponential transformation. ** (EF/50)², squared transformation. ††(Bilirubin)², squared transformation.

TABLE E7. Summary of risk-adjusted association of nadir hematocrit and end-organ dysfunction: composite for Tables E1–E6

Outcome	Effect (P value)	Interpretation (lower nadir Hct associated with)
eGFR (first 3-d minimum)	0.26 (<.0001)	Lower eGFR
Troponin (24-h mean)*	-0.0082 (.0002)	Higher troponin
Ventilation		
Postoperative ventilation	-0.12 (<.0001)	Higher likelihood
Ventilation duration*	-0.013 (<.0001)	Longer duration
Hospital length of stay*	-0.0036 (.03)	Longer duration
Death		
Early	-0.054 (.15)	Increased risk
Late	-0.048 (.005)	Increased risk

Hct, Hematocrit; eGFR, estimated glomerular filtration rate. *Logarithmic transformation was used as the response variable.