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Hospital discharge hemoglobin values and post-hospitalization clinical outcomes in transfused patients undergoing non-cardiac surgery

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Abstract

Background: Red blood cell (RBC) transfusion is common in surgical patients, yet optimal transfusion targets are incompletely defined in the perioperative period. Hemoglobin levels at the time of hospital discharge may provide insight into transfusion practices, anemia management, and patient outcomes.

Study Design and Methods: This is an observational cohort study of adults receiving RBC transfusion during non-cardiac surgery from 2010-2014. Multivariable regression was used to assess the relationships between hospital discharge hemoglobin concentrations, anemia severity (severe: <8 g/dL; moderate: 8-10 g/dL; mild/none: 10 g/dL), and clinical outcomes, including a primary outcome of 30-day hospital readmission and secondary outcomes of post-hospitalization RBC transfusion, composite stroke or myocardial infarction, and mortality.

Results: 3,129 patients were included: 165 (5%) with severe discharge anemia, 1962 (63%) moderate, and 1002 (32%) with mild/none. 592 (19%) were readmitted, with the highest rates observed with severe anemia (26% versus 19% for mild/none). Readmissions were not

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significantly different after multivariable adjustment (overall $p=0.216$); however, in those receiving postoperative intensive care, severe anemia was associated with increased readmission rates [HR 1.72 (1.09, 2.71), reference mild/none]. Post-hospitalization RBC transfusion rates were highest with severe anemia (25% versus 10% for mild/none; adjusted HR 2.2 (1.5, 3.3); $p<0.001$). There were no significant differences in composite stroke/myocardial infarction or mortality. RBC transfusion volumes did not modify anemia-outcome relationships.

Conclusion: Hospital discharge hemoglobin values for transfused surgical patients were not associated with hospital readmission rates except for those receiving postoperative intensive care. Further evaluation is warranted to understand downstream consequences of post-surgical anemia.

Keywords

transfusion; hemoglobin; red blood cell; non-cardiac surgery; outcomes; readmission

Introduction:

Red blood cell (RBC) transfusion is a common intervention for the treatment of perioperative anemia or acute surgical bleeding, with the intended goal of maintaining tissue oxygen delivery. Despite this, optimal end-points for RBC transfusion remain incompletely defined in surgical patients.¹⁻⁴ Current perioperative transfusion guidelines are based on pre-transfusion hemoglobin “triggers”,⁵ which have been extrapolated from clinical trials showing relative equivalence of restrictive (i.e. hemoglobin 7-8 g/dL) versus liberal (i.e. hemoglobin 9-10 g/dL) transfusion thresholds.⁶⁻¹³ However, there is increasing traction to consider post-transfusion hemoglobin “targets” as markers of resuscitation adequacy in those with acute surgical blood loss.¹⁴⁻¹⁷

Previous investigations of post-transfusion hemoglobin targets obtained early after surgery (i.e. within 24 hours) have been useful in identifying episodes of under- and overtransfusion, with both scenarios associated with negative clinical outcomes.¹⁶⁻¹⁷ However, these early hemoglobin measurements may not provide an accurate reflection of circulating RBC mass given recent bleeding and ongoing fluid resuscitation. Hemoglobin measurements obtained after the resolution of perioperative resuscitation and bleeding (e.g. at the time of hospital discharge) may be more ideally suited for this purpose and may also provide insight into postoperative anemia management and transfusion practices and post-hospitalization clinical outcomes.

In this investigation, we explore the relationships between hospital discharge hemoglobin concentrations, anemia severity, and post-hospitalization clinical outcomes, including a primary outcome of 30-day hospital readmission, for patients that received an intraoperative RBC transfusion during non-cardiac surgery. Specifically, we hypothesized that hospital readmission rates would differ based on discharge hemoglobin levels, with the highest readmission rates in those with severe anemia (i.e. hemoglobin < 8 g/dL).

Material and Methods:

This was a retrospective cohort study conducted under the approval of the Institutional Review Board of the Mayo Clinic (Rochester, Minnesota) with waived requirement of written informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were utilized in the design and conduct of this investigation.¹⁸

Study cohort:

Inclusion criteria included adults aged 18 years and older receiving at least one unit of intraoperative allogenic RBCs during non-cardiac surgery performed between January 1st, 2010 and December 31st, 2014 at a single tertiary care academic medical center. Patients not receiving intraoperative transfusion were excluded as the primary goal was to define optimal post-transfusion hemoglobin targets after recovery from acute bleeding and perioperative resuscitation. Patients were limited to those residing within 120 miles of Rochester, Minnesota, as patients falling outside of this radius are inherently at higher risk for hospital re-admission outside of the study institution secondary to a lack of geographic proximity, which would potentially bias the primary outcome of interest (i.e. hospital readmission at the study institution). Additionally, residents of the Twin Cities Metropolitan area (i.e. Minneapolis, St. Paul, and surrounding cities) were explicitly excluded for similar reasons. Further exclusion criteria included those with previous denial of authorization to utilize their medical records for observational research and patients that were American Society of Anesthesiologists Physical Status Classification (ASA) VI. For patients with multiple hospital admissions requiring intraoperative RBC transfusion during the study period of interest, only the first hospital admission was utilized such that no patient was included twice.

The study cohort was identified utilizing the Perioperative DataMart, an institutional datamart containing detailed information regarding patient-specific demographic, clinical, transfusion, laboratory and surgical characteristics for all patients presenting to the operative environment.¹⁹ Any characteristics not available in the Perioperative DataMart were extracted using the Advanced Cohort Explorer, another institutional resource that contains demographic and clinical characteristics for patients outside of the operative environment.²⁰ These databases continually undergo validation with accuracy of extracted data that is superior to that of data extracted through manual efforts alone.²¹ For example, transfusion data derived from the clinical-based Perioperative DataMart is continually validated against blood banking databases to ensure that every ordered unit of blood is accounted for with >99% accuracy.

Exposures:

The primary exposure of interest was the hospital discharge hemoglobin value, defined as the final hemoglobin value obtained after surgery and before hospital discharge, which must have been obtained in the 3 days prior to the discharge date. Covariates included as potential confounding variables included: demographic features (age, sex, body mass index), comorbid disease and severity of illness (ASA physical status, Charlson comorbidity index,

history of coronary artery disease or stroke), perioperative transfusions (intraoperative and postoperative volumes of RBCs, plasma, and platelets), surgical and anesthetic features (surgery type, anesthesia type, estimated blood loss, surgical duration, emergency surgery), laboratory features (preoperative hemoglobin, lowest postoperative hemoglobin), postoperative hospital complications (ICU admission, hospital length of stay, acute kidney injury, acute myocardial infarction, acute stroke, hospital discharge location), and postoperative medication use that may affect surgical hemostasis or bleeding rates (aspirin, warfarin, therapeutic low molecular weight heparin or unfractionated heparin).

Outcomes:

The primary outcome of interest was hospital readmission at the study institution within 30 days of the initial hospital discharge. Secondary outcomes included RBC transfusion requirements, composite stroke and myocardial infarction rates, and all-cause mortality within 90 days of the initial hospital discharge date. Myocardial ischemia was defined as an elevated troponin with at least one of the following: electrocardiographic changes consistent with ischemia, echocardiographic evidence of new regional wall motion abnormalities, or identification of diminished coronary blood flow during coronary angiography. Stroke was diagnosed clinically according to review of all postoperative Neurology consultation notes. All cases of myocardial ischemia and stroke were reviewed and confirmed via manual review by two independent study investigators (MJK, MAW). There were no instances of inter-observer disagreement.

Transfusion decisions:

Decisions for transfusing RBCs intraoperatively during the study period were at the discretion of the attending anesthesiologist. Institutionally-endorsed guidelines for appropriate RBC transfusion practices were in place during the study period, which were available for review on the institution's internal webpage. Indications for RBC transfusion included: hemoglobin < 7 g/dL; hemoglobin < 8 g/dL with hypotension or unexplained tachycardia; hemoglobin < 8 g/dL in those with stable coronary artery disease, chest pain, or heart failure symptoms; hemoglobin < 10 g/dL in the presence of acute coronary syndromes; or at any hemoglobin value for patients with rapid bleeding with marked cardiovascular instability, recognizing that pre-transfusion hemoglobin values are often impractical to obtain and do not provide an accurate assessment of RBC mass or tissue oxygenation needs in this setting. Postoperative RBC transfusion decisions were at the discretion of the primary surgical service, with use of the same institutional transfusion guidelines.

Statistical Analyses:

For the primary analysis, discharge hemoglobin values were divided *a priori* into three categories based upon the severity of anemia, in accordance with published definitions:²² severe (<8.0 g/dL), moderate (8.0 – 9.9 g/dL), and mild/none (≥ 10.0 g/dL). Cox proportional hazards analyses adjusting for potentially confounding variables were used to assess the relationships between discharge anemia category (reference: mild/none) and clinical outcomes. Models were fully adjusted utilizing the previously mentioned variables for the primary outcome of hospital readmission and the secondary outcome of post-hospitalization RBC transfusions. Due to a lower number of events for mortality, fewer

adjustment variables were utilized to prevent overfitting. These included age, Charlson comorbidity score, procedure type, preoperative hemoglobin, lowest postoperative hemoglobin, total units of RBCs transfused intraoperatively and postoperatively, postoperative acute kidney injury, postoperative ICU admission, and hospital length of stay. For the composite outcome of myocardial infarction or stroke, adjustment variables chosen a priori based upon clinical reasoning included age, preoperative hemoglobin, history of stroke or known diagnosis of coronary artery disease, and total perioperative RBC transfusion volume (i.e. intraoperative and postoperative). Additionally, analysis for this outcome was performed by comparing those with hemoglobin ≥ 10 g/dL to those with lower hemoglobin values, rather than by the 3 groups of anemia severity, given the limited number of observations (i.e. 41 unique events). Multiple imputations using 25 independently imputed datasets using fully conditional specification were utilized for missing variables, which included: ASA physical status ($<1\%$), BMI (10%), and pre-operative hemoglobin ($<2\%$). Data were assumed to be missing at random. In a pre-defined secondary approach, hospital discharge hemoglobin values were assessed as continuous predictors of post-hospitalization outcomes.

Recognizing that intraoperative and postoperative RBC transfusion volumes may also be important predictors of post-hospitalization outcomes independent of the discharge hemoglobin, multivariable Cox proportional hazards analyses were performed adjusting for potentially confounding variables as previously described in order to assess the relationships between RBC transfusion volumes (per 1 unit increase) and clinical outcomes. Additionally, interaction analyses were performed to assess potential effect modification on the relationship between anemia severity and the primary outcome of hospital readmission. Interaction terms included: postoperative RBC transfusion (any versus none) and postoperative ICU admission (any versus none). As a pre-defined sensitivity analysis, we further limited the study cohort to those residents residing in Olmsted County and the immediate surrounding 9 counties in southeastern Minnesota (rather than a 120 mile radius, recognizing that this radius may include patients residing across state lines and those in closer proximity to the Twin Cities Metropolitan area, and hence at greater risk of seeking post-hospitalization care at another facility). All tests were 2-sided, and p-values less than 0.05 were determined statistically significant. All analyses were performed in SAS 9.4 M3 (SAS Institute Inc., Cary, NC).

Results:

373,376 unique patients underwent non-cardiac surgery during the study period of interest, with 8,320 (2%) receiving intraoperative RBC transfusion. From these, 3,129 unique patients met all study inclusion criteria (Figure 1). The distribution of hemoglobin concentrations at the time of hospital discharge is displayed in Figure 2, with most patients discharged with hemoglobin concentrations between 9.0 and 9.9 g/dL (35%). Baseline demographic, clinical, and surgical characteristics of the study cohort are provided in Table 1. Moderate anemia was the most common hospital discharge anemia category (63%, $n=1962$), followed by mild/no anemia (32%, $n=1002$) and severe anemia (5%, $n=165$). Patients with severe anemia at discharge were generally younger with less severe comorbid disease, had lower preoperative hemoglobin concentrations, received less intraoperative

RBCs, and experienced shorter hospital lengths of stay. The most common surgical type was general surgery (22%), followed by trauma surgery (15%), and orthopedic surgery (14%; Supplemental Table 1).

Adjusted and unadjusted outcomes are displayed in Table 2. In unadjusted analyses, patients with severe anemia had the highest rates of hospital readmission (26% versus 19% for mild/no anemia), post-hospitalization RBC transfusion (25% versus 10%), and mortality (8% versus 5%). Notably, 80% of post-hospitalization RBC transfusions occurred during hospital readmissions, with 20% occurring during outpatient encounters. In adjusted analyses, anemia severity at the time of hospital discharge was not associated with the primary outcome of 30 day hospital readmission [HR (95% CI) for severe anemia, 1.16 (0.81, 1.68), reference mild anemia; overall $p=0.216$]. Severe anemia was associated with higher 90-day RBC transfusion requirements [2.17 (1.45, 3.25); reference mild/no anemia; overall $p<.001$]. Anemia severity at hospital discharge was not associated with the 90-day mortality or the composite outcome of post-hospitalization stroke or myocardial infarction. Associations between discharge hemoglobin values (per 1 g/dL increase) and outcomes were similar to the primary analysis (Table 3), with the notable addition of increased risk for myocardial infarction or stroke with higher discharge hemoglobin concentrations (adjusted HR 1.33 (1.03, 1.70); $p = 0.027$).

RBC transfusion volumes intraoperatively and postoperatively were not significantly associated with clinical outcomes after multivariable adjustment (Table 4). A total of 1,347 patients (43%) received a postoperative RBC transfusion prior to hospital discharge. There was insufficient evidence to suggest that the relationship between anemia and readmission rates differed based upon the presence or absence of postoperative transfusion ($p=0.630$).

A total of 1,787 patients (57%) had a postoperative ICU admission after the index surgical procedure, and the relationship between discharge anemia and hospital readmission was modified by the presence of postoperative ICU admission ($p=0.020$), such that severe anemia at the time of hospital discharge was associated with increased hospital readmission rates for those that had received postoperative ICU care [HR 1.72 (1.09, 2.71), reference mild/no anemia] but not for those that did not [HR 0.91 (0.52, 1.62)]. Critically ill patients discharged with severe anemia were generally younger (median 62 vs. 68 years for mild/no anemia), had less coronary disease (18% vs. 26%), and were more likely to suffer postoperative AKI (36% vs. 19%) and receive postoperative RBCs (73% vs. 54%) than those with higher hemoglobin values (Supplemental Table 2). In a sensitivity analysis with a more restricted study population, the study results remained unchanged (Supplemental table 3).

Discussion:

In this cohort of over 3,000 patients undergoing non cardiac-surgery who received intraoperative allogeneic RBC transfusion, there was no significant relationship between the severity of anemia at hospital discharge anemia and 30-day hospital readmission. Similarly, there were no significant differences in mortality or post-hospitalization myocardial infarction or stroke rates based upon anemia severity. However, one quarter of patients discharged with severe anemia received an RBC transfusion within 3 months of

hospitalization, indicating increased exposure to the health care system for those with greater anemia severity. Further, there was no suggestion that RBCs transfusion during the hospital encounter modified anemia-outcome relationships.

This study suggests that the severity of anemia at the time of hospital discharge for surgical patients experiencing anemia and/or bleeding severe enough to warrant intraoperative transfusion is not associated with hospital readmissions. These findings are largely consistent with previous literature from cardiac surgery. In approximately 2,000 patients undergoing coronary artery bypass grafting (CABG), there were no significant difference in hospital readmission rates between those discharged with hemoglobin values between 8-10 g/dL and those discharged between 10-12 g/dL.¹⁴ Similarly, in a multi-center study of nearly 5,000 patients undergoing CABG, discharge hemoglobin levels were not associated with readmission.²³ A more recent study of over 1,500 patients undergoing isolated CABG, however, noted that those discharged with hemoglobin <8 g/dL experienced greater rates of hospital readmission than those discharged with higher hemoglobin levels,¹⁵ suggesting the possibility of poor physiologic tolerance of severe post-surgical anemia in this high-risk patient group. Beyond cardiac surgery, in a study of more than 150,000 hospitalizations including both medical and surgical patients, the severity of anemia at the time of hospital discharge was strongly associated with 30-day hospital readmissions.²⁴

Consistent with this previous work, it is possible that distinct patient groups may benefit from higher hemoglobin levels at hospital discharge. In this investigation, patients that required postoperative ICU cares and were subsequently discharged with severe anemia experienced increased readmission rates at 30 days. This relationship was not seen in those that did not require ICU admission postoperatively, suggesting that more critically ill patients may be less likely to tolerate low hemoglobin concentrations (i.e. <8 g/dL) at hospital discharge following non-cardiac surgery with intraoperative transfusion. However, it is important to note that postoperative RBC transfusions, which were greatest in critically ill patients with severe discharge anemia, did not modify anemia-outcome relationships; hence, there is no evidence to suggest that postoperative RBC transfusions are indicated for hemoglobin optimization prior to hospital discharge. Rather, it is likely that the use of practical non-transfusion-based strategies to prevent and/or attenuate the severity of anemia perioperatively (e.g. preoperative optimization, minimization of iatrogenic blood loss, reducing unnecessary phlebotomy, correcting nutritional deficiencies, addressing treatable causes of anemia) may have beneficial clinical effects extending beyond hospitalization; though this will warrant dedicated clinical investigation.

Interestingly, patients discharged with higher hemoglobin concentrations had a paradoxical increase in the composite outcome of new myocardial infarction or stroke (33% increase for each 1 g/dL increase in hemoglobin). There are three possible explanations. The first is residual confounding, such that patients deemed to be at highest risk for these complications were deliberately maintained at higher hemoglobin concentrations during their hospital stay. Indeed, those with severe anemia had the lowest prevalence of preoperative coronary or cerebrovascular disease. The second relates to the infrequency of these events (<2% incidence of myocardial infarction or stroke in those with discharge hemoglobin $\geq$ 10 g/dL) such that chance may have played a role in between group differences, particularly with the

limited sample size of those with severe anemia. A third explanation relates to potential adverse effects of RBC transfusion, in which administration of additional RBCs for the attainment of higher hemoglobin concentrations may actually have detrimental clinical effects. It is important to note that we are limited in our ability to make any meaningful inference regarding the mechanisms underlying observed exposure-outcome relationships. Future studies are warranted to explore optimal discharge hemoglobin targets in those at highest risk for myocardial infarction and stroke with careful consideration of the potential influence of RBC transfusion.

There are several limitations of this investigation. First, residual confounding is always a concern in observational research even with a well-established and pre-specified statistical plan with multivariable adjustment for relevant clinical and demographic variables. This may have influenced the observed relationships between discharge anemia and clinical outcomes, and such relationships should be considered hypothesis-generating rather than a reflection of causality. Second, this study was explicitly designed to examine patients that experienced intraoperative anemia and/or bleeding severe enough to warrant allogeneic transfusion, thereby providing an assessment of the relationships between post-transfusion hemoglobin targets and outcomes. Patients not receiving intraoperative RBC transfusion were excluded. Therefore, it is not possible to discuss clinical outcomes that may be related to withholding transfusion therapies and/or optimizing perioperative hemoglobin with entirely non-transfusion based approaches. This is clearly a topic that warrants focused clinical evaluation. Third, our study utilized myocardial infarction and cerebral ischemia as potential markers of inadequate end-organ oxygen delivery. It is possible that these events were underdiagnosed, as screening tests are not routinely performed during or after hospitalization. Additionally, patients with established risk factors for these outcomes may have been screened disproportionately. There are other surrogate markers of end-organ ischemia that could be pursued in future investigations (e.g. alterations in peripheral or splanchnic microcirculatory flow, changes in imaging biomarkers of tissue oxygenation, alterations in cognition in the absence of clinical stroke, renal ischemia). Fourth, the findings represent the experience of a single tertiary care medical center and may not be generalizable to other surgical populations. Fifth, individual patient responses are likely to vary from the cohort average such that some patients are likely to receive differential benefit (or harm) from any given discharge hemoglobin target. Finally, many factors may impact readmission rates, and it is unclear if readmissions were directly linked to the surgical episode of care. It is also possible that some readmissions may have been planned, though there is no evidence to suggest that this would preferentially affect one anemia group versus another. Furthermore, some readmissions could have occurred at hospitals not affiliated with the primary medical center and hence would have been missed, though we attempted to attenuate this possibility by limiting the analyses to patients residing in our local geographic location. Future investigations are warranted to assess heterogeneity in clinical responses to discharge hemoglobin values.

Conclusion:

In patients that received allogeneic RBC transfusion during non-cardiac surgery, the severity of discharge anemia was not associated with 30-day hospital readmission rates but was

associated with higher rates of post-hospitalization RBC transfusion. Additionally, readmission rates were significantly higher in ICU patients that were discharged with severe anemia, and postoperative RBC transfusions prior to hospital discharge did not modify anemia and hospital readmission relationships. These findings suggest that common-sense approaches to attenuate or prevent the development of severe anemia after surgery (i.e. minimizing iatrogenic blood loss, reducing unnecessary phlebotomy, correcting nutritional deficiencies, addressing treatable causes of anemia) should be considered a practical goal for perioperative specialists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

ASA – American Society of Anesthesiology Physical Classification; Hb – hemoglobin; RBC – red blood cell

Fig. 2.
Histogram plot showing the distribution of discharge hemoglobin concentrations for the study cohort.

Table 1:
Patient Demographic and Clinical Characteristics By Hemoglobin at Hospital Discharge*

Variable	<8.0 g/dL (N=165)	8.0-9.9 g/dL (N=1962)	10.0 g/dL (N=1002)	P Value
<u>Baseline Features</u>				
Age	62.2 (49.9, 73.7)	67.3 (56.4, 77.6)	69.1 (57.0, 78.3)	<.001
Female Sex	95 (58%)	1008 (51%)	532 (53%)	0.25
BMI (kg/m ² , n=158/1778/79)	28.6 (24.1, 34.3)	28.1 (24.3, 33.1)	26.6 (23.0, 30.9)	<.001
Charlson comorbidity score	5 (3, 8)	6 (3, 9)	6 (3, 9)	<.001
History of CAD	29 (18%)	469 (24%)	250 (25%)	0.12
History of stroke	10 (6%)	158 (8%)	84 (8%)	0.60
<u>Hemoglobin Features (g/dL)</u>				
Preoperative, n=163/1937/981	9.7 (8.6, 11.5)	10.1 (8.8, 11.7)	10.7 (9.2, 12.4)	<.001
Lowest postoperative	7.4 (7.0, 7.7)	8.1 (7.4, 8.8)	9.1 (7.8, 10.2)	<.001
Hospital discharge	7.7 (7.4, 7.9)	9.0 (8.6, 9.5)	10.6 (10.3, 11.2)	-
<u>Surgery & Postoperative Features</u>				
Emergency surgery	24 (15%)	358 (18%)	226 (23%)	0.005
General anesthesia	162 (98%)	1935 (99%)	993 (99%)	0.43
Length of procedure (min)	202 (132, 325)	221 (133, 356)	228 (136, 354)	0.58
Estimated blood loss (ml)	600 (250, 1300)	600 (200, 1200)	582 (200, 1300)	0.80
ASA PS				0.06
1-2	53 (32%)	502 (26%)	237 (24%)	
3-5 [†]	112 (68%)	1459 (74%)	765 (76%)	
Postop AKI	37 (22%)	438 (22%)	163 (16%)	<.001
AKI stage				0.41
1	29 (78%)	325 (74%)	119 (73%)	
2	3 (8%)	72 (16%)	32 (20%)	
3	5 (14%)	41 (9%)	12 (7%)	
Postoperative myocardial infarction	0 (0%)	37 (2%)	24 (2%)	0.11
Postoperative stroke	0 (0%)	25 (1%)	11 (1%)	0.33
Postoperative ICU admission	67 (41%)	1098 (56%)	622 (62%)	<.001
Any postoperative anticoagulation	38 (23%)	433 (22%)	182 (18%)	0.04

Variable	<8.0 g/dL (N=165)	8.0-9.9 g/dL (N=1962)	10.0 g/dL (N=1002)	P Value
Warfarin	5 (3%)	25 (1%)	14 (1%)	0.18
LMW heparin	6 (4%)	44 (2%)	14 (1%)	0.10
Heparin	27 (16%)	372 (19%)	156 (16%)	0.07
Any postoperative antiplatelet therapy	26 (16%)	294 (15%)	137 (14%)	0.58
<u>Transfusion Features</u>				
Intraoperative RBC volume (mL)	330 (330, 660)	660 (330, 660)	660 (330, 990)	<.001
Postoperative RBCs	71 (43%)	852 (43%)	424 (42%)	0.85
RBC volume (mL)	660 (330, 990)	610 (330, 1242)	660 (330, 1302)	0.54
Perioperative Platelets	11 (7%)	202 (10%)	107 (11%)	0.28
Platelet volume (mL)	433 (279, 602)	351 (267, 836)	422 (278, 832)	0.97
Perioperative Plasma	21 (13%)	238 (12%)	125 (12%)	0.95
Plasma volume (mL)	553 (512, 597)	577 (298, 1124)	577 (455, 1132)	0.42
<u>Hospital Discharge Features</u>				
Hospital length of stay (d)	6.9 (4.3, 14.6)	8.0 (5.1, 15.4)	8.2 (5.3, 15.7)	0.05
Discharge disposition				0.10
Home	85 (52%)	990 (50%)	541 (54%)	
Home with HHC	19 (12%)	158 (8%)	92 (9%)	
Skilled nursing facility	48 (29%)	693 (35%)	319 (32%)	
Other [§]	13 (8%)	121 (6%)	50 (5%)	

AKI – acute kidney injury, ASA PS – American Society of Anesthesiologists Physical Status, BMI – body mass index, CAD – coronary artery disease, HHC – home health care, ICU – intensive care unit, LMW – low molecular weight, RBC – red blood cell.

* Continuous variables are summarized as median (Q1, Q3) and compared with Kruskal-Wallis rank-sum tests. Categorical variables are summarized as n (%) and compared with Chi-square tests except for factor concentrates and direct thrombin inhibitors which were compared with Fisher's exact tests.

[†] ASA 3-5 includes patients with ASA PS 5 (n=16, 28, and 15 in the 8.7, 8.8-10.2, and 10.3 groups respectively).

[§] Other includes acute care hospital transfer, hospice, long-term acute care, rehab, and swing bed.

Table 2 -

Associations between hospital discharge anemia and clinical outcomes *

	Total N	Events (%)	Univariate		Multivariable	
			Hazard Ratio (95% CI)	Overall p-value	Hazard Ratio (95% CI)	Overall p-value
30-day hospital readmission[§]				0.058		0.216
Mild anemia (Hb 10 g/dL)	1002	189 (18.9%)	1.00 (ref)		1.00 (ref)	
Moderate anemia (Hb 8-9.9 g/dL)	1962	361 (18.4%)	0.97 (0.81, 1.16)		0.90 (0.74, 1.09)	
Severe anemia (Hb <8 g/dL)	165	42 (25.5%)	1.43 (1.02, 2.00)		1.16 (0.81, 1.68)	
90-day RBC transfusion[§]				<.001		<.001
Mild anemia (Hb 10 g/dL)	1002	102 (10.2%)	1.00 (ref)		1.00 (ref)	
Moderate anemia (Hb 8-9.9 g/dL)	1962	268 (13.7%)	1.39 (1.10, 1.74)		1.20 (0.94, 1.53)	
Severe anemia (Hb <8 g/dL)	165	41 (24.8%)	2.81 (1.96, 4.04)		2.17 (1.45, 3.25)	
90-day mortality[‡]				0.153		0.219
Mild anemia (Hb 10 g/dL)	1002	54 (5.4%)	1.00 (ref)		1.00 (ref)	
Moderate anemia (Hb 8-9.9 g/dL)	1962	140 (7.1%)	1.34 (0.98, 1.83)		1.30 (0.93, 1.81)	
Severe anemia (Hb <8 g/dL)	165	13 (7.9%)	1.50 (0.82, 2.75)		1.64 (0.84, 3.20)	
90-day Stroke or MI^{**}				0.092		0.081
Hb 10 g/dL	1002	18 (1.8%)	1.00 (ref)		1.00 (ref)	
Hb <10 g/dL	2127	23 (1.1%)	0.59 (0.32, 1.09)		0.57 (0.31, 1.07)	

Hb – hemoglobin, MI – myocardial infarction, RBC – red blood cell.

* The number and percentage of each event occurring within the categories of hemoglobin is presented. Analysis results are from proportional hazards analysis.

[§]Covariates included age, sex, BMI, Charlson score, coronary artery disease (CAD), preoperative hemoglobin, emergency surgery, ASA PS, surgery type, general anesthesia, duration of surgery, estimated blood loss, intraoperative RBC platelet, and plasma transfusion volume, lowest postoperative hemoglobin, admission to the ICU postoperatively, hospital length of stay, hospital discharge location, postoperative complications of acute kidney injury, MI, and stroke, use of aspirin, warfarin, low molecular weight heparin, and heparin; perioperative transfusion volumes of RBC, platelets, and plasma.

[‡]Covariates included age, Charlson score, surgery type, preoperative hemoglobin, lowest postoperative hemoglobin, total perioperative RBC transfusion volume, acute kidney injury, postoperative admission the ICU, and hospital length of stay.

^{**}Covariates included age, preoperative hemoglobin, history of stroke/CAD, total perioperative RBC transfusion volume.

Table 3 -

Associations between hemoglobin concentrations (per 1 g/dL) at hospital discharge and outcomes *

	Multivariable	
	Hazard Ratio (95% CI)	p-value
30-day hospital readmission[§]	1.00 (0.93, 1.10)	0.853
90-day RBC transfusion[§]	0.87 (0.78, 0.97)	0.013
90-day mortality[‡]	0.91 (0.78, 1.05)	0.192
90-day Stroke or MI^{**}	1.33 (1.03, 1.70)	0.027

MI – myocardial infarction, RBC – red blood cell.

* Outcomes were assessed per 1 g/dL increase in hemoglobin concentration utilizing proportional hazards analysis.

[§] Covariates included age, sex, BMI, Charlson score, coronary artery disease, preoperative hemoglobin, emergency surgery, ASA PS, surgery type, general anesthesia, duration of surgery, estimated blood loss, intraoperative RBC, platelet, and plasma transfusion volume, lowest postoperative hemoglobin, admission to the ICU postoperatively, hospital length of stay, hospital discharge location, postoperative complications of acute kidney injury, MI, and stroke, use of aspirin, warfarin, low molecular weight heparin, and heparin; perioperative transfusion volumes of RBCs, platelets, and plasma.

[‡] Covariates included age, Charlson score, surgery type, preoperative hemoglobin, lowest postoperative hemoglobin, total perioperative RBC transfusion volume, postoperative acute kidney injury, postoperative admission the ICU, and hospital length of stay.

^{**} Covariates included age, Charlson score, history of coronary artery disease or stroke, perioperative RBC transfusion volume.

Associations between number of RBC units transfused during and after surgery and post-hospitalization outcomes in multivariable analysis*

Table 4 -

	30-Day Readmission [§]		90-Day RBC Transfusion [§]		90-Day Mortality [‡]		90-Day Stroke or MI ^{**}	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Intraoperative RBCs	1.04 (0.99, 1.09)	0.11	1.01 (0.97, 1.06)	0.58	1.01 (0.96, 1.07)	0.67	1.02 (0.98, 1.06) [#]	0.27 [#]
Postoperative RBCs	1.00 (0.97, 1.03)	0.99	0.98 (0.94, 1.02)	0.31	1.00 (0.96, 1.04)	0.84		

MI – myocardial infarction, RBC – red blood cell.

* Outcomes were assessed per 1 unit increase (i.e. 330 ml) in RBC transfusion volume utilizing proportional hazards analysis.

[§] Covariates included age, sex, BMI, Charlson score, coronary artery disease, preoperative hemoglobin, emergency surgery, ASA PS, surgery type, general anesthesia, duration of surgery, estimated blood loss, intraoperative RBC, platelet, and plasma transfusion volume, lowest postoperative hemoglobin, admission to the ICU postoperatively, hospital length of stay, hospital discharge location, postoperative complications of acute kidney injury, MI, and stroke, use of aspirin, warfarin, low molecular weight heparin, and heparin; perioperative transfusion volumes of RBC, platelets, and plasma.

[‡] Covariates included age, Charlson score, surgery type, preoperative hemoglobin, lowest postoperative hemoglobin, total perioperative RBC transfusion volume, postoperative acute kidney injury, postoperative admission to the ICU, and hospital length of stay.

^{**} Covariates included age, Charlson score, history of stroke, history of coronary artery disease.

[#] Due to limited outcome events for stroke or MI, the association displayed is for perioperative RBCs defined by the summation of intraoperative and postoperative RBCs.