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DETERMINANTS OF VARIATION IN PERIOPERATIVE RED BLOOD CELL TRANSFUSION DURING ADULT CORONARY ARTERY BYPASS GRAFT SURGERY

BY

David C. Fitzgerald, MPH, CCP

A doctoral project submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree Doctor of Health Administration in the College of Health Professions

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In Partial Fulfillment of the Requirements for the
Degree of Doctor of Health Administration

DETERMINANTS OF VARIATION IN PERIOPERATIVE RED BLOOD CELL TRANSFUSION DURING ADULT CORONARY ARTERY BYPASS GRAFT SURGERY

By

David C. Fitzgerald, M.P.H., C.C.P.

Chairperson: Annie N. Simpson, Ph.D.
Committee: Donald S. Likosky, Ph.D.; Robert A. Baker, Ph.D., C.C.P.

Background: Despite evidence-based guidelines informing indications for transfusions, unwarranted variability in performance exists across cardiac surgical programs. We aimed to identify to what extent distinguishing patient and procedural characteristics can explain center-level transfusion variation during coronary artery bypass grafting (CABG) surgery.

Methods: We evaluated 22,272 adult patients undergoing isolated CABG using cardiopulmonary bypass between July 1, 2011 and July 1, 2017 across 43 centers. Iterative multilevel logistic regression models were constructed using patient demographic, preoperative risk factors, and intraoperative conservation strategies to progressively explain center-level transfusion variation.

Results: Nearly one-third (n=7241, 32.5%) of patients received at least one transfusion. Rates varied between 10.9% to 59.9% across centers. Among the models explaining center-level transfusion variability, the intraclass correlation coefficients varied between 0.072 to 0.136, while the coefficient of variation varied between 0.29 to 0.40.

Conclusion: The results suggest that variation in center-level RBC transfusion cannot be explained by patient and procedural factors alone. Investigating organizational culture and programmatic infrastructure may be necessary to better understand variation in transfusion practices.

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I. INTRODUCTION

Background and Need

Frequency of Transfusions

Allogeneic blood transfusions are considered a potentially life-saving and routine medical procedure administered in healthcare systems around the world (Sharma *et al*, 2011). The American Red Cross (2018) estimates that each donated unit of blood can save up to three lives. A 2013 statistical brief from the Healthcare Cost and Utilization Project (HCUP) indicated that blood transfusion was the most common all-listed procedure performed during 2010 U.S. hospitalizations, accounting for up to eleven percent of all hospital stays with a procedure (Pfunter *et al*, 2013). Despite the relatively stable rate of hospitalization over the fourteen-year HCUP reporting period, the rate of blood transfusion in this population nearly doubled during this time (Pfunter *et al*, 2013). The majority of blood collected in high and middle-income countries are separated into components, including red blood cell (RBC) concentrates, plasma, cryoprecipitate, and platelet concentrates (World Health Organization, 2018).

RBC transfusions are the most common blood components administered, as they are frequently indicated to treat symptomatic anemia, acute blood loss, and inherited blood disorders (Sharma *et al*, 2011). Since anemia is common complication associated with critically-ill patients, optimizing red blood cell mass for oxygen transport and physiology is essential to preserving adequate tissue perfusion (Arias-Morales *et al*., 2017). The U.S. Department of Health and Human Services estimates that eighty-five million units of RBCs are transfused worldwide every year (Carson, 2012), with up to fifteen million units administered in U.S. hospitals (Bennett-Guerrero *et al*., 2010). Adult patients undergoing cardiac surgery are most at risk to receive an RBC transfusion, as the level of complexity, extent of hemodilution and blood

loss, and demographic aging may warrant transfusion (Geissler *et al*., 2015). Three to four million RBC transfusions are estimated to occur across U.S. cardiac surgical programs annually (Refaai & Blumberg, 2013), accounting for between fifteen to twenty percent of all RBC units (Spiess, 2002; Crescenzi *et al*, 2012). These reported rates are not endemic to the United States. In Australia, cardiac surgery is the second most common indication for RBC transfusion (McQuilten *et al*, 2014). Similar rates have been reported from surgical programs across the United Kingdom and other European countries (Patel & Murphy, 2018; Boer *et al*., 2018). A 2014 report from the Society of Thoracic Surgeons (STS) National Database indicates that the rate of RBC transfusion for patients that received isolated coronary artery bypass graft (CABG) surgery across participating centers was 44.5% (Bracey, 2015).

Risks of Transfusion

Mortality and Morbidity

Despite the perceived benefits of RBC transfusion, exposure to allogeneic blood products can also be associated with risks to patient health and overall surgical outcome (*Figure 1*). Over the last two decades, an increasing body of evidence has weighed the benefits and harms of transfusion (Spiess, 2004). While nucleic acid testing has increased the safety of the blood donor pool from viral infection, adverse events associated with immunomodulation can negatively impact patient morbidity and mortality (Geissler *et al*., 2015). These transfusion-related complications may include but not be limited to, acute injuries of the lung, kidneys, myocardium, and systemic tissue and bloodstream infections from the transmission of microorganisms (Tempe & Khurana, 2018).

In a retrospective cohort study of adult cardiac surgery patients, Murphy *et al* aimed to analyze the association between red blood cell transfusion and clinical outcome (Murphy *et al*,

2007). Primary endpoints included composite infection and ischemic outcomes (stroke, renal injury, and myocardial infarction). Secondary end points included resource allocation, hospital costs, and patient survival. Inclusion criteria included patients greater than sixteen years of age that presented for cardiac surgery from April 1996 to December 21, 2003, yielding 8598 subjects for analysis. Regression modeling was performed to quantify adjusted odds ratios for both primary outcome measures. Subjects transfused with RBCs were 3.38 and 3.35 times more likely than non-transfused subjects to acquire an infection or experience an ischemic event, respectively. Additionally, patients receiving transfusion experienced a forty-two percent increase in hospital costs, and thirty-seven percent less likelihood of surviving to hospital discharge. Limitations of the study include the observational design and the potential bias of sicker patients more likely to require transfusion.

Postoperative Infection

A systematic review conducted by Ang *et al* evaluated the association between mediastinitis and blood transfusion in cardiac surgery. Seven studies in adult cardiac surgery published between January 1990 and December 2010 met the inclusion criteria (Ang *et al*, 2012). Exclusion criteria included patients undergoing cardiac transplant or ventricular assist device procedures due to the associated presence of immunosuppression. Five of the studies reported an independent association between mediastinitis and RBC transfusion. Among these, two demonstrated a dose-dependent relationship, as an increasing exposure to RBC units increased the likelihood of mediastinal infection. Despite these findings, the authors identified several limitations in the review. Of the thirteen studies assessed for eligibility, there were only seven that met the inclusion and outcome reporting criteria. Further, studies were restricted to those published in the English language.

Other lesser known but significant adverse clinical effects of transfusion have been reported (Refaai & Blumberg, 2013). These would include allergic and febrile non-hemolytic reactions, transfusion associated circulatory overload (TACO), post-transfusion purpura (PTP), and transfusion-associated graft-versus-host disease. In patients treated with massive transfusion protocols, secondary complications may include hyperkalemia, citrate toxicity, iron overload, and hypothermia (Refaai & Blumberg, 2013).

End-Organ Dysfunction

Transfusion Related Acute Lung Injury (TRALI) is one of the most recognized and reported severe transfusion reactions. From 2010-2014, the U.S. Food and Drug Administration reported 72 deaths with a positive diagnosis of TRALI (Varghese & Jhang, 2015). This represented forty-one percent of all non-infectious transfusion associated deaths. However, other pulmonary complications from transfusion are either underreported or undiagnosed due to the incomplete understanding of the mechanism for injury. In a prospective cohort design of two university-based hospitals in the Netherlands, Vlaar *et al* reported an association between RBC transfusion and pulmonary capillary leakage (Vlaar *et al*, 2012). The Pulmonary Leak Index (PLI) is an early indicator of acute lung injury. Lower levels of pulmonary edema may manifest more frequently than an episode of acute respiratory that would trigger a TRALI diagnosis. In this study, a PLI was measured in all subjects that met the inclusion criteria. This included adult elective cardiac surgical patients consenting to on-pump CABG and/or valve surgery that were free of immunosuppressive drugs. The PLI was measured within three hours after surgery. Of the forty patients included for study, there was a significant increase in PLI for subjects receiving RBC transfusions versus non-transfused patients. This increase was isolated to RBC exposure, as plasma and platelet transfusions did not significantly increase PLI values. Moreover, this

association between PLI values and RBC units was dose dependent. Aside from the limited sample size, the authors suggest that there may be other pathways outside of TRALI that may contribute to depressed pulmonary function.

Acute Kidney Injury (AKI), generally defined as an abrupt decrease in renal function characterized by a >50% increase in serum creatinine or >25% reduction in glomerular filtration rate (GFR), may occur in more than 30% of patients undergoing cardiac surgery (Karkouti, 2012). Acute kidney injury has been associated with increases in morbidity, infection, length of stay, and overall hospital costs (Kindzelski *et al*, 2018). In a review of the literature involving cardiac surgical AKI and transfusion, Karkouti concludes that while the role of severe anemia has been the focus of many study variables, blood transfusion also appears to be independently associated with AKI (Karkouti, 2012). Eighteen of the twenty-two observational studies identified in the review demonstrated a relationship between AKI and transfusion. Although the exact nature of this relationship is not fully understood, possible causes of injury may be attributed to the pro-inflammatory mediators that are found in allogeneic bank blood. As these markers accumulate during storage, the resultant biochemical changes may impair oxygen delivery and renal oxidative stress.

Research has also indicated that postoperative deep vein thrombosis (DVT) may be associated with transfusion (Ghazi *et al*, 2015). Even with therapeutic thromboprophylaxis, the rate of DVT can exceed ten percent following cardiac surgery and has been reported as high as 40% (Ghazi *et al*, 2015). The most commonly reported form is pulmonary embolism (PE), which is considered life-threatening but largely preventable. In a single center retrospective review of 1070 cardiac surgical patients, Ghazi *et al* found a dose-dependent response between the incidence of postoperative DVT and RBC transfusion (Ghazi *et al*, 2015). The adjusted odds

ratio of DVT increased from 1.95 to 3.19 for patients receiving 1-3 units and ≥ 7 units of RBCs, respectively. Silvain and colleagues performed a series of RBC transfusions in an in-vitro model using healthy donors to determine the impact of platelet activation (Silvain *et al*., 2010). Using light transmission aggregometry and flow cytometry, ABO compatible blood from transfusion packs was mixed with whole blood from healthy donors to measure in-vitro platelet aggregation and p-selectin expression. The significant increases observed in both platelet reactivity and p-selectin release may provide an explanation of the deleterious effects of ischemia subsequent to RBC transfusion. A similar explanation was proposed in a narrative review by Rao *et al*, involving acute coronary syndrome patients with non-ST segment elevation (Rao *et al* (2007). Although bleeding can be associated with an increased risk of myocardial infarction, blood transfusions are also independently associated with ischemic events. In a review of the literature, Dubovoy & Engoren report an increased risk venous thrombosis, stroke, and myocardial ischemia in both cardiac surgical patients and patients diagnosed with acute coronary syndrome (Dubovoy & Engoren, 2016).

Effects on Long-Term Outcomes

The impact of RBC transfusion can extend beyond the episode of hospitalization, affecting both quality of life and long-term outcome. In a single-center retrospective review of 1,915 patients undergoing first-time isolated CABG, researchers aimed to determine if perioperative blood transfusions influence long-term mortality (Engoren *et al*., 2002). Hospital outcome data were matched to survival data secured through the U.S. Social Security Death Index database. The relationship between blood transfusions (and timing) and five-year mortality was assessed. After adjusting for comorbidities and preoperative risk factors, blood transfusions of any kind were associated with a seventy percent risk of five-year mortality (Engoren *et al*., 2002). Despite

the strong association between transfusion and survival, the authors were not able to determine causality (Engoren *et al*., 2002). Other limitations of the study included the lack of reported hemoglobin values and the inability to determine cause of reported death.

Transfusion and Resource Utilization

Exposure to allogeneic RBC transfusions may not only negatively impact clinical outcome, but may prolong length of hospital stay, resource utilization, and costs. Galas and colleagues analyzed the association between transfusion rate and hospital length of stay in a single center prospective randomized controlled trial- the Transfusion Requirements After Cardiac Surgery (TRACS) study (Galas *et al*., 2013). Of the enrolled 502 elective patients undergoing CABG, valve, or CABG/valve surgery, 48% received 1-3 units of red cells, and 12% received more than 3 units. In the multivariate analysis, age, Euroscore, valvular surgery and combined procedures, low ejection fraction, and > 3 RBC transfusions were predictive of a prolonged length of hospital stay. The most significant limitation is the inability to explain the causal relationship between transfusion and study endpoints.

Transfusions with allogeneic blood products also carry the burden of increased hospital costs. The most recent National Blood Collection and Utilization Survey (NBCUS) published in 2015 reported that the median price paid by the hospital for each unit of leukocyte-reduced RBCs was $211 (IQR $197-$228) (Ellingson *et al*., 2017). However, this estimate significantly underestimates the financial impact of blood acquisition, storage, and administration. In an activity-based cost model established across four U.S. and European acute care surgical hospitals, Shander *et al* determined that the direct and indirect overhead costs ranged between $522 and $1183 (mean $761, StdDev $294) for each unit of RBCs administered (Shander *et al*., 2010). This model included all relevant personnel, capital, and consumable resources, as well as

follow-up for acute transfusion reactions. The cost models were restricted to immediate transfusion reactions, thus not including long-term complications or post-discharge follow-up. These findings align with a previously published cost analysis of allogeneic transfusions in hip-replacement surgery (Blumberg *et al*, 1996). When accounting for outdating and wastage, incremental nursing and clerical time, and medical coverage, each unit of blood was associated with an incremental cost estimated between $1000 to $1500 (Blumberg *et al*, 1996).

With the aforementioned reported health risks and costs, clinicians must carefully weigh the benefits and harm of exposing patients to an allogeneic transfusion. Several multi-disciplinary clinical practice guideline documents have been developed to guide decisions in transfusion management (Boer *et al*., 2018; Ferraris *et al*., 2011; Menkis *et al*., 2012; Ferraris *et al*., 2007). These evidence-based recommendations identify patient blood management (PBM) strategies to aimed to not only minimize hemodilution and surgical blood loss but reduce the incidence of uninformed and potentially unnecessary blood transfusions. Such interventions are an essential aspect of improving the quality of care delivered to adult cardiac surgical patients.

The Shelf Life of Allogeneic RBCs

Several large observational and meta-analyses suggest that the transfusion of older stored blood can have a negative impact on surgical recovery and long-term survival. Depending on the type of preservative used during blood storage, RBC shelf life may be extended to 42 days (Buchholz *et al*, 1999). Although the extended lifespan of red cells would increase available resources and reduce wastage, the biochemical changes that occur in the blood bag can have a deleterious effect on oxygen delivery, inflammation, and infection.

A retrospective cohort study of patients who underwent CABG, valve or combined surgery at the Cleveland Clinic were divided into two groups according to the storage date of the RBC units (Koch *et al*., 2008). Patients receiving newer blood that was less than 14 days old were compared with patients receiving blood greater than 14 days of age. The median duration of storage was 11 and 20 days for the newer and older blood groups, respectively. Patients that were exposed to older blood experienced a significantly higher rate of in-hospital mortality, mechanical ventilation time, and sepsis. These findings were supported by a recently published retrospective review of patients who underwent either hip fracture or CABG surgery at single center between 2008-2013 (Khan *et al*., 2018). In this cohort study, RBC units that were stored for more than 28 days were associated with a higher inpatient and 30-day mortality in both surgical groups. A larger pooled meta-analysis by Wang *et al* identified twenty-one studies in cardiac and trauma surgery that examined the age of donor blood (Wang *et al*, 2012). Of the nearly 410,000 total patients included for study, there was a significant association between older blood transfusion and the risk of death that was unrelated to patient demographics or the quantity of units transfused. Conversely, other studies have failed to demonstrate a cause and effect relationship between RBC unit storage time and adverse outcomes out to one-year after hospitalization (Desmarets *et al*., 2016; Lelubre & Vincent, 2013). Even though there may be clear consensus regarding the safe storage age allogeneic blood, the use of autologous blood salvage strategies has been recommended to avoid the donor storage lesions that result in red cell deformity and impairment (Salaria *et al*., 2014).

Clinical Practice Guidelines and Patient Blood Management

Despite the multitude of available clinical practice guidelines, the appropriateness of transfusion still remains in question. A 2012 national summit on overuse, organized by The

Joint Commission and the American Medical Association, identifies unnecessary blood transfusions as a waste of limited resource (The Joint Commission & the American Medical Association, 2012). Overuse was defined by the committee as *the provision of treatment that provides negligible benefit to patients*. Recommendations aimed to reduce overuse in blood management included better management of anemia, identifying variability in transfusion practice, and educating key stakeholders on the alternatives to transfusion.

While guidelines may be replete with clinical practice recommendations, their adoption across the industry is unevenly distributed and often slow to become incorporated into clinical practice (Committee on Quality Health Care in America, Institute of Medicine, 2001). Following the release of the 2007 STS Blood Conservation Guidelines, a survey conducted by Likosky and colleagues assessed the clinical practices and responses among perfusionists and anesthesiologists across North American cardiac surgical practices (Likosky *et al*., 2010). Of the 1,402 surveys received from 1,061 institutions, only 20% of the respondents reported that their institution engaged in formal discussions about the guidelines. Only 14% reported that institutional monitoring of blood transfusions was present. Moreover, only four of the thirty-eight recommendations published in the guidelines were reported by more than five percent of the survey respondents. The authors concluded that only minor changes to institutional blood management programs were attributed to the guidelines. These guidelines, while intended to provide clear and actionable recommendations to assist in practitioner decision-making, were not being utilized to improve the effectiveness and efficiency of care. When the indications for transfusion are not well established, significant variation may occur across clinical practice. While the indications for transfusion are believed to be attributed to patient-related clinical factors, practitioners may weigh these clinical characteristics differently in the absence of formal institutional protocols. Clinical transfusion triggers may also be influenced by environmental

factors such as computer decision support, motivation to adopt guidelines, and support for colleagues (Sim *et al*, 2015). The incorporation of patient-centered blood management (PBM) programs provide hospitals the opportunity to decrease transfusion rates, decrease practice variation, and improve patient outcomes (Hohmuth *et al*, 2014).

Problem Statement

Given the perceived benefits and risks of allogeneic RBC transfusion, the need to identify the factors that explain variation in transfusion practice is paramount to optimize patient care and outcome. Exposure to as little as 1 to 2 units of donor packed red blood cells has been associated with significant increases in postoperative morbidity, mortality, and hospital costs among low-risk coronary artery bypass grafting (CABG) procedures (Paone *et al*., 2014; Surgenor *et al*, 2006; Surgenor *et al*, 2009) Conventional wisdom suggests that differences in baseline patient risk may be predominant drivers of difference in center transfusion rates in cardiac surgery. Nonetheless, other studies suggest modifiable intraoperative factors may help explain center performance. Few studies have empirically tested the independent effect that both pre- and intraoperative factors have on overall RBC transfusion rates. Preoperative factors include patient demographics, risk factors and patient comorbidities, and laboratory assays. Intraoperative procedural variables include equipment and blood conservation modalities. Each of these variables were identified in a consensus statement describing the minimal reporting criteria for CPB-related red blood cell transfusions (Likosky et al, 2018).

In an observational cohort of 102,470 isolated CABG patients in the STS Adult Cardiac Surgical database, the rate of allogeneic RBC transfusion reported between cardiac surgical programs ranged from 7.8% to 92.8% (Bennett-Guerrero *et al*., 2010). After adjusting for patient-specific risk factors, there was significant variation observed in hospital transfusion rates regarding geographic location (P=0.007), academic status (P=0.03), and hospital volume (P<0.001). However, these characteristics only explained 11.1% of the variation in RBC administration. The procedural case-mix only accounted for approximately 20% of the total

variation. As such, it remains plausible that additional variation in RBC exposure may be attributed to the clinicians' perceived clinical benefits of and harms of transfusion.

The variability in human behaviors around the attitudes and beliefs of transfusion exist more broadly across international surgical programs. Snyder-Ramos *et al* investigated transfusion practices across 70 surgical centers in sixteen different countries (Snyder-Ramos *et al*., 2008). The incidence of intraoperative RBC transfusion ranged from 9 to 100 percent, and 25-87% for postoperative transfusions (Snyder-Ramos *et al*., 2008). These results suggest that a clear international consensus is necessary to identify the drivers associated with variation in RBC transfusion.

Hospital-level variation was also described in patients undergoing major non-cardiac surgery. In a retrospective analysis of the University HealthSystem Consortium database, Qian *et al* reported a wide variability in RBC transfusions for patients undergoing total hip replacement (THR), colectomy, and pancreaticoduodenectomy (Qian *et al*., 2013). Using hierarchical logistic regression modeling with random hospital intercepts, models were formed to adjust for patient-level demographic risk factors. Hospitals were categorized by transfusion terciles, ranging from low to high transfusion thresholds. There was significant variability in RBC exposure, ranging from 1.5% to 77.8% for THR surgery, 1.7% to 47.9% for colectomy, and 0% to 90.9% for pancreaticoduodenectomies. Patients that were operated on at high transfusion centers were 2.4 times more likely to receive RBC units than patients at average transfusion centers. Conversely, patients at low transfusion programs were about 50% less likely to receive allogeneic RBCs.

The combined results from each of these three studies strongly suggest that variances in RBC transfusion may be attributed to factors beyond patient demographics and disease characteristics (Bennett-Guerrero *et al*., 2010; Snyder-Ramos *et al*., 2008; Qian *et al*., 2013). These differences

also do not appear to be attributed to institutional procedural case-mix or hospital characteristics. For these reasons, we examine patient and procedural determinants of center-level variation in perioperative transfusions in the setting of CABG surgery.

Research Hypothesis

The primary aim of this research project is to identify to what extent distinguishing patient and procedural characteristics that are known prior to allogeneic RBC transfusion can explain center-level variation in transfusion rates across adult isolated coronary artery surgical procedures. It is hypothesized that variation in center-level transfusion rates may be explained by patient and procedural risk factors that are known prior to the initiation of cardiopulmonary bypass (CPB).

II. LITERATURE REVIEW

Anemia vs Transfusion

Although the risks and adverse effects of allogeneic RBC transfusion are well-described in the literature, severe anemia has also been associated with increased surgical morbidity and mortality. Anemia is broadly described as reduced levels of hemoglobin (Hgb) that impair oxygen delivery and induce tissue hypoxia (Dhir & Tempe, 2017). In a review article weighing the importance of anemia avoidance in blood management programs, Dhir & Tempe report the incidence of anemia in cardiac surgery over 30% (Dhir & Tempe, 2017). Patients with low perioperative Hgb content were more likely to experience perioperative complications and all-cause mortality. These harmful effects of anemia not only translated into a reduced carrying capacity for oxygen but are also attributed to impairments of the rheological characteristics of circulating blood, exacerbation of chronic illness and inflammation, and increased tissue ischemia *(*Lobel *et al*, 2015). These impairments may lead clinicians to question whether anemia or transfusion contributes more to an adverse outcome. To what degree of anemia is safe for patients to reduce the exposure to allogeneic blood? Moreover, what effect would both anemia and RBC transfusion have on overall patient care and outcomes?

Engoren *et al* conducted a single-center retrospective cohort study of 922 patients who underwent isolated CABG surgery (Engoren *et al*, 2014). The study aim was to determine whether preoperative anemia (defined as < 12g/dl for men; < 11g/dl for women) would significantly interact with allogeneic RBC transfusions. Receiving a transfusion for anemia would either provide a protective or harmful effect on patient survival out to four years. Four groups were assigned from the study population, each describing the exposure to anemia and

blood transfusion. A subsequent analysis included a propensity match to control for all variables except for anemia and transfusion. The results indicated that the interaction of both anemia and transfusion was associated with nearly three-fold greater hazard of dying (HR = 2.918, 95% C.I = 1.512-5.633, $p = 0.001$). Additionally, patients that experienced both anemia and transfusion had twice the hazard of dying as those who experienced anemia but not transfusion (HR = 2.087, 95% C.I. = 1.004-4.336, $p = 0.049$). Similar findings were observed in the propensity scoring analysis, as anemic subjects transfused with blood had a significantly higher hazard of mortality. Limitations in the study included the single-center observational design, transfusion of RBCs using hemoglobin triggers only, and the power insufficiency to detect all of the adverse effects of anemia alone. The authors concluded that the exposure to transfusion created the greatest risks of postoperative mortality, in both anemia and non-anemic populations.

Lapar and colleagues undertook an observational analysis of 33,411 patients undergoing isolated CABG surgery between January 2007 to December 2017 at any of 19 cardiac surgical centers participating in the Virginia Cardiac Surgical Quality Initiative (VCSQI) Registry. The investigators used hierarchical logistic regression modeling to determine the relationship between preoperative hematocrit (HCT) and RBC transfusion and the effects on morbidity and mortality (Lapar *et al*., 2018). Generalized linear mixed regression was used to estimate the effects between the model covariates baseline HCT and PRBC transfusion on the outcome variable, major morbidity and mortality. The mean baseline preoperative HCT was 39.1% (36-42%), and the STS predicted risk of mortality was 1.8 +/- 3.1%. After adjusting for patient risk, exposure to RBC transfusions was associated with an increased odds of mortality (OR- 4.3; $P < 0.001$), renal failure (OR-6.3; $P = 0.0001$), and postoperative stroke (OR- 2.4; $P < 0.0001$). While these associations with morbidity were not as strong using HCT, a 1-point increase in preoperative HCT was attributed to a decreased odds of mortality (OR, 0.97; $P= 0.0001$) and

renal failure (OR, 0.94; $P < 0.0001$). The investigators concluded that RBC transfusion had a higher association with morbidity and mortality than with the continuous nonlinear relationship to preoperative HCT alone, thus supporting the proposal that efforts be made in decreasing the incidence of 'unnecessary' allogeneic blood transfusions. Modifiable risk factors such as limiting systemic hemodilution and avoiding anemia should be considered. Aside from the observational nature of the study design, there were several other limitations to the findings. First, not all adverse outcome variables were identified in the endpoints. Events such as TRALI, infection, or transfusion reaction were not reported. The changes in perioperative HCT were also not recorded, so the impact that nadir HCT and average HCT values has on both RBC transfusion and outcome were not included for study.

The implications and management of anemia in cardiac surgery were described in a literature review by Loor *et al* (Loor *et al*, 2012). Given the negative consequences that both anemia and allogeneic transfusion have on outcome, strategies should be considered to optimize hemoglobin levels prior to surgery. One strategy would be to delay elective operations for patients presenting with anemia. Other interventions identified included iron supplementation, diuresis, and the avoidance of specific types of platelet inhibitors prior to surgery. *Figure 2* is a composite graph summarizing the effects of preoperative anemia on postoperative outcome (Loor *et al*, 2012). Intraoperative strategies that aim to minimize surgical blood loss, limit systemic hemodilution, and maximize autologous red blood cell recovery have also been demonstrated to reduce the incidence the consequences of anemia (*Figure 3*) (Goldberg *et al*, 2016; Loor *et al*, 2012).

Liberal vs Restrictive Transfusion

Navigating through the paradox that exists between the unfavorable outcomes from both anemia and transfusion can be a challenge for surgical care teams. Traditional protocols

previously supported the transfusion of patients when the hemoglobin level dropped below 10g/dl (Adams & Lundy, 1942). As the risks associated with transfusion became more evident, several published guidelines have advocated for a more restrictive approach blood transfusion. Additional consensus statements have also recommended against a single criterion to transfuse patients (Carson *et al*, 2002). Best practices in blood management would incorporate laboratory and physiologic markers in the decision-making process.

In 1999, a landmark multicenter, prospective, randomized trial was published describing the two different transfusion thresholds for critical care patients in Canada (Hebert *et al*., 1999). Previous randomized controlled trials had been conducted on blood transfusion practices; however, a multicenter design involving critically-ill patients had not yet been reported. Critical care patients who presented with a hemoglobin less than 9.0 g/dl within 72 hours of admission were randomized into either a liberal RBC transfusion protocol (Hgb 10-12 g/dl, n=420 pts.) or a restrictive transfusion protocol (Hgb 7-9 g/dl, n=418 pts.). Patients were prospectively followed to determine all-cause death at 30 days, hospital mortality rates, organ dysfunction, and intensive care unit and hospital length of stay. Overall 30-day mortality was not different between the two groups (18.7% vs 23.3%, p=0.11). Acute Physiology and Chronic Health Evaluation (APACHE) II scores significantly favored the restrictive group over the liberal group (8.7% vs 16.1%, p=0.03), respectively. The restrictive group also experienced a significantly lower hospital mortality rate than the liberal group (22.2% vs 28.1%, p=0.05). However, there was no significant differences in outcome noted in patients diagnosed with cardiac disease. Hebert and colleagues concluded that a restrictive approach to RBC transfusion is at least as safe and possibly superior to a liberal strategy in critical care patients without unstable angina (Hebert *et al*, 1999).

In another multicenter randomized trial, 5,243 patients undergoing cardiac surgery (TRICS III Clinical Trial) were prospectively assigned to a liberal or a restrictive transfusion protocol immediately before surgery (Mazer *et al*., 2017). The threshold for liberal transfusion was a Hgb below 9.5 g/dl in the operating room and intensive care unit (ICU), or a Hgb below 8.5 g/dl in the postoperative telemetry ward. Restrictive threshold subjects were transfused if the Hgb was below 7.5 g/dl at any point of care. The primary endpoints for this non-inferiority study design was all-cause death, MI, stroke, and post-operative renal failure requiring dialysis. Secondary outcomes included RBC transfusion and other clinical markers. Patients were enrolled for study across 73 sites in 19 countries. These were patients considered at moderate to high risk of death, as defined by the Euroscore I score. After study withdrawal and exclusions, 5092 patients entered the modified intention-to-treat population, and 4860 patients were included for per-protocol analysis. Among these patients, 26.1% received CABG only, 27.7% had CABG with another procedure, and 46.2% underwent a non-CABG procedure. The overall mean Hgb value at study baseline was 13.1 +/- 1.8 g/dl. The results indicated that a restrictive transfusion strategy was not inferior to a liberal threshold. While there were no significant differences noted in primary outcomes, RBC transfusion occurred in 52.3% of the restrictive group and 72.6% in the liberal threshold group (OR, 0.41; 95% CI, 0.37 to 0.47). A subgroup analysis also demonstrated a significant benefit in outcome for restrictive group among 75 years of age or greater (OR, 0.70; 95% CI, 0.54 to 0.89). These findings suggest that a restrictive transfusion protocol can be implemented safely in cardiac surgical patients that have a predicted moderate to high risk of hospital death.

Murphy *et al* conducted a multicenter transfusion threshold across 17 cardiac surgical programs in the United Kingdom (Murphy *et al*, 2015). In this study, adult patients were prospectively enrolled into a liberal (< 9g/dl) or a restrictive threshold (< 7.5 g/dl) once the Hgb

decreased < 9.0 g/dl following cardiac surgery. The primary outcomes were serious infection and ischemic events. All-cause mortality and hospital index costs were also estimated out to 90 days after surgery. A total of 2003 patients were randomized and included for analysis. Transfusion rates after randomization were 53.4% and 92.2% for the restrictive and liberal groups, respectively. The results from this study differ from other reported transfusion threshold trials, as a restrictive transfusion was not found to be equivalent to a liberal approach. There was a significant increase in deaths in the restrictive vs liberal group, 4.2% vs 2.6%, respectively (P = 0.045). There was also a reduction in primary outcome events favoring the liberal group, but this did not reach statistical significance. The discrepancy in these findings may be attributed to several key study limitations. Randomization in the trial did not take place until the postoperative period. Many of the patients were exposed to allogeneic transfusions prior to enrollment. Mortality was indicated as a secondary outcome (which was added after the trial began). Using the intention-to-treat protocol, the authors reported relatively high rates of nonadherence, 30% and 45.2% for the restrictive and liberal threshold groups, respectively. Further, severe nonadherence (significant enough to change the classification of the subject), was observed in 9.7% and 6.2% in both groups.

A 2017 meta-analysis of restrictive versus liberal transfusion strategies was conducted by Shehata *et al* to measure all-cause mortality and secondary clinical outcomes among adult and pediatric patients that underwent cardiac surgery (Shehata *et al*, 2018). Of the thirteen trials included for analysis (8 adult studies), 4545 patients were assigned do the restrictive group and 4547 patients were assigned to the liberal strategy. There were no significant differences observed in the relative risks associated with mortality, myocardial infarction, stroke, renal failure, or infection (*Figure 4*) (Shehata *et al*, 2018). Despite the lack of a subgroup analysis comparing high risk and low risk cardiac surgery patients and the pooling of adult and pediatric

cardiac procedures, a restrictive RBC transfusion strategy was not inferior to a liberal threshold protocol.

Predictors of Transfusion

Models that can accurately predict a patient's risk of receiving a perioperative blood may help facilitate appropriate blood management techniques. A preoperative patient risk stratification would not only allow clinicians to identify those patients considered at high risk of transfusion, but such a scoring system may also recognize an individual's risk for potentially discretionary 1-2 RBC unit allocations. Prediction modeling can be used to inform treatment decisions.

Moskowitz *et al* conducted an observational study of 307 consecutive patients undergoing CABG, valve, or combined procedures at a single cardiac surgical center (Moskowitz *et al*, 2004). Using a multivariate analysis of preoperative patient risk factors, patients with a calculated transfusion probability of at least 5% were used to identify intraoperative predictors. Preoperative independent transfusion predictors included red blood cell mass, surgery type, procedural status, number of diseased vessels, serum creatinine, and preoperative thrombin time. Intraoperative factors included CPB time, number of CABG grafts, amount of acute normovolemic hemodilution (ANH) blood harvested, and total crystalloid volume. The overall rate of perioperative transfusion was 13%. Applying the formula to a validation group of 246 subjects resulted in a predicted risk of transfusion range from 0.01% to 90%, with median and mean values of 4% and 12%, respectively. Fourteen percent of the patients received a blood transfusion. One of the most significant limitations of these findings was the small number of subjects used for both the prediction formula and validation. Moreover, the overall transfusion rate of 11% observed in the preoperative risk factor multivariate analysis may not have been

large enough of an exposure to capture all of the conventional factors commonly associated with blood transfusion.

In a multicenter regional perfusion outcome registry study of 20,377 adult CABG patients, Likosky *et al* identified preoperative factors to develop a prediction model for RBC transfusion (Likosky *et al*, 2017). Variables used in the univariate analysis included patient demographics, medical history, procedural status, admission status, comorbidities, cardiac anatomy, and institutional demographics. The population was divided into the development and validation samples to create the multivariate model and assess model fit and discrimination. The sixteen variables that were included in the model were age, gender, race, body surface area (BSA), last pre-op HCT, preoperative total albumin, last preoperative creatinine, congestive heart failure, dialysis, history of cerebrovascular disease, peripheral artery disease, previous cardiac surgery, three vessel disease, ejection fraction, acuity, and year of surgery. The final prediction model discriminated well and achieved satisfactory correlation ($ROC_{development}$: 0.81; $ROC_{validation}$: 0.82). Among the observed limitations were the inability to discriminate between the number of exposed RBC units administered, the lack of inclusion of non-red cell blood products, and the homogeneity in the study population according to surgery type and region. The authors recognize the importance of conducting an external validation against a larger and more diverse population of surgical patients.

Two other risk prediction score models were developed and compared to three previously existing scores (Goudie *et al*., 2015). Clinical data collected from 27 cardiac surgical programs from the U.K and Europe were used to create prediction models for exposure to RBC transfusions and for large amount transfusion volumes (≥4 RBC units). These resultant risk models were compared to the Transfusion Risk and Clinical Knowledge Score (TRACK), the

Transfusion Risk Understanding Scoring Tool (TRUST), and the Papworth Bleeding Risk Score (BRiSc). The receiver operating characteristic curve demonstrated agreement (AUC = 0.77, 95% CI, 0.77-0.77) for any RBC exposure, and for large blood volume scores (AUC = 0.80, 95% CI, (0.79-0.80). The AUC values for the TRACK and TRUST scores any for any RBC exposure were 0.71 and 0.71, respectively. The AUC for the LVBT and BRiSc score was 0.69. These findings suggest that transfusion risk models can effectively discriminate in patient transfusion risk stratification (Goudie *et al*, 2015). This may further inform clinical decision making and encourage evidence-based blood management practices.

Multidisciplinary Teams in Blood Management

As the pursuit for patient-centered blood management programs continues to expand across the cardiac surgical community, the importance of optimizing multidisciplinary team collaboration cannot be overstated. There is clear consensus that a multidisciplinary approach involving institutional key stakeholders improves both the process of care and surgical outcome in blood conservation programs. The 2011 Update Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines identifies the following recommendation with the highest level of support (Ferraris *et al*., 2011):

> *A multidisciplinary approach involving multiple stakeholders, institutional support, enforceable transfusion algorithms supplemented with point-of-care testing, and all of the already mentioned efficacious blood conservation interventions limits blood transfusion and provides optimal blood conservation for cardiac operations. (Class I-Level of evidence A)*

In addition to surgeons and anesthesiologists, clinical perfusionists were key contributors to this practice guideline revision. The authors concluded that when supported with guidelines and institutional protocols, multidisciplinary teams make better decisions in the management of blood resources.

The taskforce on patient blood management for adult cardiac surgery established by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anesthesia (EACTA) support the team approach to treat anemia, identifying cardiologists, surgeons, anesthesiologists and perfusionists as key stakeholders with the following recommendation (Boer *et al*., 2018):

> *It is recommended that the members of the multidisciplinary team discuss the optimal surgical strategy based on clinical status, comorbidities, bleeding risk and team expertise. (Class I, Level of Evidence C)*

Both the STS and EACTS documents emphasize the importance of team effort and collaboration in blood management. Numerous professional disciplines across the continuum of care should serve as key stakeholders in developing effective blood management programs. Presumably, both the strength and implementation of these guidelines may be extended through collaborations with other professional societies.

Support for team-approached blood management also exists in professional practice standards and guidelines. The 2017 update to the American Society of Extracorporeal Technology (AmSECT, 2017) identifies the minimum practice standards and recommendations the membership believe support reliable, safe, and effective perfusion blood management programs. Among the recommendations in Guideline 13.1 are the following (AmSECT, 2017):

- *Participate in pre-operative briefings (discussions) with the surgical care team (Standard 5.1) regarding transfusion strategies and target hematocrit values.*
- *Participation in a multidisciplinary blood management team.*

Properly leveraging multidisciplinary teams across the surgical program starts with capturing clinical data and outcome measures. In an observational review of a multi-institutional clinical perfusion database, Likosky *et al* describe the value that clinical registries may have in identifying practice variation relative to published clinical practice guidelines (Likosky *et al*, 2016). Specifically, the review aimed to understand center-level variation of two blood conservation strategies, Retrograde autologous priming (RAP), and acute normovolemic hemodilution (ANH). The 2011 STS/SCA Update assigned a Class IIB, Level of Evidence B recommendation for both of these blood management techniques (Ferraris *et al*., 2011). The IIb designation suggests these interventions may be considered but their overall effectiveness is unclear. Using the Perfusion Measures and Outcomes (PERForm) registry, the authors identified the reported use in CABG surgery across 27 contributing centers over a four-year period. The overall use of ANH was reported at 11.6% (0 - 75.7%), and the employment of RAP was 71.4% (0 – 99%). Despite a similar level of evidence in the 2011 update, a significant difference was observed in practice adoption. The use of the database not only helped identify center-level practice variation, but such systems may better explain variability in RBC transfusion rates.

Organizational Culture and Non-Technical Drivers of Transfusion

Previous literature has identified both modifiable and non-modifiable clinical factors associated with the increased exposure to allogeneic RBC units (Shaw *et al*, 2015; Cote *et al*, 2015; Shehata *et al*, 2007). Additional investigation into nonclinical factors (e.g., provider transfusion triggers, organizational culture, blood management protocols) may improve our

understanding of center-level differences (Camaj *et al*, 2017). Organizational culture, broadly defined as the basic assumptions and values that guide organizations may be associated with variances in clinical practice (Schneider *et al*, 2013). Using multilevel mixed-effect logistic and linear regression models, Jin *et al* examined variation in blood transfusion practices among 5,744 isolated CABG procedures performed by 42 surgeons at 12 hospitals within the same health system (*Jin et al*, 2013). Observed variances in RBC transfusions at the hospital level (0.82) were over twice as high as surgeons practicing at the same hospital (0.35), suggesting a correlation between organizational culture and transfusion practice through factors such as team familiarity, quality improvement and data sharing, and standardized clinical practices (Jin *et al*, 2013).

Likosky *et al* compared perioperative RBC transfusion rates for both CABG and percutaneous coronary intervention (PCI) at 33 Michigan cardiac surgical programs (Likosky *et al*, 2013). While perhaps somewhat surprising, the investigators found that an institution's CABG transfusion rate was significantly correlated with its PCI rate. Both crude (0.48, p=.005) and adjusted (0.53, p=.001) RBC transfusion correlations between CABG and PCI existed independent of patient case mix. These findings suggest that factors beyond patient-level risk (e.g., transfusion protocols, practice patterns, organizational culture) may help explain center-level differences in transfusion practices.

A retrospective single center analysis of 4,823 patients by Cote *et al* found that differing practice patterns among cardiac surgeons and anesthesiologists were independent predictors of perioperative transfusion (Cote *et al*, 2015). Patients who underwent off-pump or emergency surgery were excluded from analysis. The surgical team consisted of 5 attending surgeons, 7 anesthesiologists, and 7 perfusionists. The primary outcome of interest was transfusion, defined as at least 1 unit of blood (RBC, fresh frozen plasma, cryoprecipitate, platelets, or factor 8

inhibitor bypass activity) administered within the first 24 hours after surgery. The overall rate of blood transfusion was 40%. Significant variation was observed between surgeons (32.4% to 51.5%, $p<.0001$) and anesthesiologists (34.4% to 51.9%, $p<.0001$). There were also significant differences in transfusion rates across the reporting year, from 28.2% in 2004 to 48.8% in 2008. After adjusting for pre- and intraoperative variables, physician and year of procedure contributed to variation in blood transfusion rates.

III. METHODOLOGY

Study Design and Hypotheses

We evaluated determinants of center variability in intra-or postoperative RBC transfusion rates across adult cardiac surgical programs performing isolated CABG surgery. The primary aim was to identify determinants of center variability in allogeneic RBC transfusions following adult isolated coronary artery surgical procedures.

Patients and Methods

This study (HUM00151098) was approved by the University of Michigan's Institutional Review Board.

The PERFusion measures and outcomes (PERForm) registry was established in 2010 as a voluntary database. Current efforts are focused on identifying perfusion practices associated with improved outcomes and providing benchmarking opportunities to support local and multi-institutional quality improvement initiatives. The PERForm registry is structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC), a cardiac surgeon–led quality collaborative embedded in the Michigan Society of Thoracic and Cardiovascular Surgeons. The membership of the MSTCVS-QC, which became partially funded by Blue Cross/Blue Shield of Michigan in 2005, convenes quarterly to review processes and outcomes and to facilitate and evaluate quality improvement studies. All programs in the MSTCVS-QC use The Society of Thoracic Surgeons (STS) data collection form and submit data on a quarterly basis to both the STS database and the MSTCVS-QC data warehouse. The PERForm registry complements data from the STS by focusing on the care and conduct of

cardiovascular perfusion practices (The Michigan Society of Thoracic Cardiovascular Surgeons and The MSTCVS Quality Collaborative, 2018). Each record from the PERForm registry is merged with a record from each center's surgical data (Paugh *et al*., 2012).

The study population included adult patients undergoing isolated CABG surgery using CPB support between July 1, 2011 and July 1, 2017. Data were collected from 43 cardiac surgical centers participating in both the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) and the PERForm registry. After exclusions (*Figure 5*), our final dataset included 22, 272 patients.

The primary outcome is allogeneic RBC transfusions administered during the intraoperative and/or postoperative periods.

Statistical Analysis

We considered possible variables that are present prior to at the time of an RBC transfusion decision. For instance, we considered patient and disease characteristics, equipment selection, laboratory assay results, and intraoperative blood conservation strategies.

We performed median and mode imputation for continuous and categorical covariates with an observed data missingness of less than 10% to ensure that all hospitals were included during the modeling process. Specifically, missing preoperative risk factor data variables such as CHF, diabetes, history of cerebrovascular disease, peripheral arterial disease, dialysis status, and prior myocardial infarction were imputed as no disease. Missing data for operative status was considered as elective surgery. Missing data fields including last preoperative hematocrit and serum creatinine levels were imputed to their conditional median on gender. Variables with a higher than 10% missingness remained by creating missing indicators.

The distribution of demographic variables was reported according to quartile categories of crude transfusion rates. The observed-to-expected (OE) ratio for perioperative RBC transfusion was calculated using the observed rates from the data and the expected rates derived from the risk prediction model previously described by Likosky *et al* (Likosky *et al*., 2017).

To quantify the degree to which hospitals, patient and procedural factors influence variation in center-level transfusion rates, a series of mixed effect logistic regression models (Model 1-4) were constructed (*Table 1*):

- Model 1: No covariates- contain only hospital random intercepts.
- Model 2: Model 1 + Preoperative patient demographics, risk factors, comorbidities, and laboratory values.
    - Patient demographics: age (yrs), gender, body surface area (m^2) & admission status (elective, urgent, emergent/salvage).
    - Patient comorbidities and risk factors: chronic lung disease (y/n), diabetes mellitus (y/n), cardiogenic shock (y/n), cerebrovascular disease (y/n), peripheral artery disease (y/n), dialysis (y/n), three vessel disease (y/n), reoperative status (y/n), previous MI (y/n), left ventricular ejection fraction (EF), current smoker (y/n), anticoagulation medications < 48 hrs (y/n), hypertension (y/n).
    - Laboratory assay values: preoperative HCT (%), platelet count (x10000), serum albumin (g/dl), serum creatinine (mg/dl).
- Model 3: Model 1 + intraoperative blood conservation strategies
    - Perfusion equipment: arterial roller pump (y/n), cardioplegia type (% of cases w/non-traditional blood based cardioplegia- del Nido), autotransfusion usage (y/n)

    - Fluid management: autologous CPB circuit prime (y/n), acute normovolemic hemodilution (y/n), CPB net prime volume (indexed to BSA, ml/m^2)
- Model 4: Model 1 + Model 2 + Model 3

From each model, the random effect variance on the logit scale was computed and intraclass correlation coefficient (ICC) is calculated using both the simulation method and latent variable method as described by Merlo *et al* (Merlo *et al*., 2006) . In Model 1 with only hospital random effect, ICC is the proportion of total observed variance in transfusion that is attributable to the systematic differences between hospitals. In Models 2-4 with covariates adjustment, the ICC is interpreted as the proportion of the residual variation after accounting other variables in the model that is attributable to the hospital differences. Continuous variables are presented as median and interquartile range (25^{th}, 75^{th} percentile), and categorical variables are presented as counts and percentages. Pearson's Chi-Square and Fisher's Exact tests were performed for categorical variables, as appropriate, and the Wilcoxon rank-sum test was performed for continuous variables. A *p* value less than 0.05 was considered for all two-tailed significance testing. Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.2.

IV. ARTICLE MANUSCRIPT

DETERMINANTS OF HOSPITAL VARIABILITY IN PERIOPERATIVE RED BLOOD CELL TRANSFUSIONS DURING CORONARY ARTERY BYPASS GRAFT SURGERY

Abstract

Background: Despite the continued emergence of clinical practice guidelines describing the indications for allogeneic RBC blood transfusion, wide variability in transfusion rates persist across cardiac surgical programs. While the determinants underlying this variability include patient and procedural-related factors, evaluation of these key factors has not been fully explored. With this in mind, we aimed to identify to what extent distinguishing patient and procedural characteristics can explain center-level RBC transfusion variation during coronary artery bypass grafting (CABG) surgery.

Methods: 22,272 adult patients undergoing isolated CABG using CPB support between July 1, 2011 and July 1, 2017 were included for analysis using the PERFusion measures and outcomes (PERForm) registry. Iterative multilevel logistic regression models were constructed using patient demographic, preoperative risk factors, and intraoperative conservation strategies to progressively explain center-level RBC transfusion variation.

Results: 7241 (32.5%) of the 22,272 study subjects received at least one unit of allogeneic RBCs (10.9% - 59.9%). When compared to subjects who were not transfused, patients that received at least one unit of RBCs were older (68 vs 64 years, $p<0.001$), female gender (41.5% vs 15.9%, $p<0.001$), lower BSA (1.93m^2 vs 2.07m^2, $p<0.001$), and less likely to be electively admitted for surgery (34.5% vs 42.1%), respectfully. Among the models explaining center-level transfusion

variability, the Intraclass correlation coefficients (ICC) were 0.07 for Model 1 (hospital random intercepts only), 0.12 for Model 2 (patient factors+ Model 1), 0.14 for Model 3 (intraoperative factors+ Model 1), and 0.11 for Model 4 (Models 1 + 2 +3). The coefficient of variation for center-level transfusion rates by model were 0.31, 0.29, 0.40 and 0.30 for models 1 through 4, respectively. The majority of center-level variation could not be explained through the combined models.

Conclusion: The results suggest that variation in center-level RBC transfusion cannot be explained by patient and procedural factors alone. Investigating organizational culture and programmatic infrastructure may be necessary to better understand variation in transfusion practices.

Approximately 85 million allogeneic red blood cell (RBC) units are administered worldwide every year, with cardiac surgery accounting for 15 to 20% of all transfusions (1-3). Almost half of all patients undergoing isolated coronary artery bypass grafting (CABG) receive at least one RBC unit during the hospital episode of care (4). Despite the perceived clinical benefits in treating symptomatic anemia and hemorrhage, exposure to as little as one or two RBC units has been independently associated with significantly increased postoperative morbidity and mortality following CABG surgery (5).

Several randomized controlled trials and metanalyses have suggested that that a more 'restrictive' strategy for RBC exposure may be noninferior to a liberal transfusion threshold (6-8). Current multidisciplinary clinical practice guidelines identify interventions aimed to reduce bleeding and unnecessary blood transfusions in cardiac surgery (9-11). While guidelines may provide practical recommendations for institutional blood conservation programs, their dissemination and direct impact on clinical care may not be fully realized (12). Wide variation in blood transfusion rates has been reported across institutions even after adjusting for patient risk (13, 14). Prior work has identified hospital geographic location, academic status, surgical case volume, and procedural mix as risk factors for transfusion (15). Few studies have empirically tested the independent effect that both pre and intraoperative factors have on blood transfusion rates prior to the initiation of cardiopulmonary bypass (CPB). As such, determinants of center-level variation in RBC rates have not been explained.

We evaluated determinants of center variability in intra-or postoperative RBC transfusion rates across adult cardiac surgical programs performing isolated CABG surgery. The primary aim is to identify to what extent distinguishing patient and procedural characteristics that are known prior to allogeneic RBC transfusions may help explain center-level variation in transfusion rates across adult isolated coronary artery surgical procedures.

Patients and Methods

This study (HUM00151098) was approved by the University of Michigan's Institutional Review Board.

The PERFusion measures and outcomes (PERForm) registry was established in 2010 as a voluntary database. Current efforts are focused on identifying perfusion practices associated with improved outcomes and providing benchmarking opportunities to support local and multi-institutional quality improvement initiatives. The PERForm registry is structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC), a cardiac surgeon–led quality collaborative embedded in the Michigan Society of Thoracic and Cardiovascular Surgeons. The membership of the MSTCVS-QC, which became partially funded by Blue Cross/Blue Shield of Michigan in 2005, convenes quarterly to review processes and outcomes and to facilitate and evaluate quality improvement studies.

All programs in the MSTCVS-QC use The Society of Thoracic Surgeons (STS) data collection form and submit data on a quarterly basis to both the STS database and the MSTCVS-QC data warehouse. The PERForm registry complements data from the STS by focusing on the care and conduct of cardiovascular perfusion practices (16). Each record from the PERForm registry are merged with a record from each center's surgical data (17) .

The study population included adult patients undergoing isolated CABG surgery using CPB support between July 1, 2011 and July 1, 2017. Data were collected from 43 cardiac surgical centers participating in both the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) and the PERForm registry. Each surgical record was merged with the perfusion record from the PERForm registry. After exclusions (*Figure 1*), our final dataset included 22, 272 patients.

The primary outcome is allogeneic RBC transfusions administered during the intraoperative and/or postoperative periods.

Statistical Analysis

We considered possible variables that are present prior to at the time of an RBC transfusion decision. For instance, we considered patient and disease characteristics, equipment selection, laboratory assay results, and intraoperative blood conservation strategies (*Figure 2*).

We performed median and mode imputation for continuous and categorical covariates with an observed data missingness of less than 10% to ensure that all hospitals were included during the modeling process. Specifically, missing preoperative risk factor data variables such as diabetes, history of cerebrovascular disease, dialysis status, and prior myocardial infarction were imputed as no disease. Missing data for operative status was considered as elective surgery. Missing data fields including last preoperative hematocrit and serum creatinine levels were imputed to their conditional median on gender. Variables with a higher than 10% missingness such as CHF and PVD remained by creating missing indicators.

The distribution of demographic variables was reported according to quartile categories of crude transfusion rates. The observed-to-expected (OE) ratio for perioperative RBC transfusion was calculated using the observed rates from the data and the expected rates derived from the risk prediction model previously described by Likosky *et al* (18).

To quantify the degree to which hospitals, patient and procedural factors influence variation in center-level transfusion rates, a series of mixed effect logistic regression models (Model 1-4) were constructed (*Figure 2*). This approach is similar to a model previously reported by Xian *et al* (19). Model 1 contained hospital random intercepts and no covariates. Model 2 included the previous Model 1 hospital random effect plus patient-related risk factors:

patient demographic data (age, gender, body surface area, admission status), preoperative laboratory serum assay results (hematocrit, platelet count, albumin level, serum creatinine), and preoperative risk factors (smoking status, cardiac history, lung disease, cerebrovascular disease, hypertension, peripheral vascular disease, diabetes, preoperative dialysis, anticoagulant medications within 48 hours). Model 3 contained Model 1 plus intraoperative blood conservation techniques and equipment aimed to reduce hemodilution and anemia (arterial roller head usage, autotransfusion usage, autologous CPB circuit priming, acute normovolemic hemodilution, del Nido cardioplegia usage, CPB net crystalloid volume indexed to patient BSA). Model 4 included all of the previous models of 1 through 3. Patient and procedural covariates were selected according to the consensus minimal reporting criteria for CPB-related RBC transfusions reported by Likosky *et al* (20).

From each model, the random effect variance on the logit scale was computed and intraclass correlation coefficient (ICC) is calculated using both the simulation method and latent variable method as described by Merlo *et al* (21). In Model 1 with only the hospital random effect, the ICC is the proportion of total observed variance in transfusion that is attributable to the systematic differences between hospitals. In Models 2-4 with covariate adjustment, the ICC is interpreted as the proportion of the residual variation after accounting other variables in the model that is attributable to the hospital differences. Continuous variables are presented as median and interquartile range (25^{th}, 75^{th} percentile), and categorical variables are presented as counts and percentages. Pearson's Chi-Square and Fisher's Exact tests were performed for categorical variables, as appropriate, and the Wilcoxon rank-sum test was performed for continuous variables. A p value less than 0.05 was considered for all two-tailed significance testing. Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.2.

Results

Table 1 describes patient demographic and procedural variables according to perioperative RBC transfusion. There were 7241 (32.5%) of the 22,272 study subjects that received at least one unit of allogeneic RBCs. Among those, 3,884 (53.6%) subjects were transfused in the postoperative period only. Overall, the median age was 65 years (IQR 58, 72), with males comprising 75.8% of the population. Arterial rollerheads were used in 44.5% of procedures, and 14.6% utilized del Nido cardioplegia solution. When compared to subjects who were not transfused, patients that received at least one unit of RBCs were older (68 vs 64 years, $p<0.001$), female sex (41.5% vs 15.9%, $p<0.001$), lower BSA (1.93m^2 vs 2.07m^2, $p<0.001$), and less likely to be electively admitted for surgery (34.5% vs 42.1%), respectfully. The transfusion group also had a significantly higher prevalence of preoperative risk factors including previous MI (60.1% vs 51.5%, $p<0.001$), chronic lung disease (13.5% vs 8.5%, $p<0.001$), congestive heart failure (14.5% vs 9.6%, $p<0.001$), peripheral vascular disease (16.1% vs 11.6%, $p<0.001$), cardiogenic shock (3.3% vs 0.9%, $p<0.001$), preoperative dialysis (6.2% vs 0.7%, $p<0.001$), diabetes (52.5% vs 44.9%, $p<0.001$), cerebrovascular disease (28.4% vs 17.4%, $p<0.001$), and anticoagulant medication within 48 hours of surgery (50.7% vs 44.0%, $p<0.001$). Similar differences between groups were also observed across all perioperative HCT values; Preoperative HCT (35.9% vs 41%, $p<0.001$), last HCT before CPB (31% vs 36%, $p<0.001$), and first HCT measured on CPB (23% vs 28%, $p<0.001$). Transfused patients were also less likely to receive blood conservation therapies such as ANH volume (8.1% vs 17.2%, $p<0.001$), and autologous CPB circuit priming (77% vs 80.8%, $p<0.001$). Additionally, the transfusion group received significantly larger indexed amounts of asanguineous crystalloid volume via anesthesia

intravenous infusion (11.79 ml/kg vs 10.32 ml/kg, $p<0.001$) and total CPB prime volume (640.6 ml/m^2 vs 604.2 ml/m^2, $p<0.001$).

Demographic and procedural variables were distributed across quartiles of crude center-level perioperative RBC transfusion rates (*Table 2*). Center-level RBC transfusion rates ranged from 10.9 to 59.9%. The observed-to-expected (O/E) ratios for RBC transfusion were 0.71 (0.60, 0.77), 0.89 (0.82, 0.95), 1.10 (1.07, 1.24), and 1.28 (1.20, 1.52), for quartiles 1-4, respectively. Patients in the highest quartile group were more likely to be female (27.5% vs 22% for Q4 and Q1, respectively; $p < 0.0001$), undergo urgent procedures (59.9% vs 55.6% for Q4 and Q1, respectively; $p < 0.0001$), and receive anticoagulant medications within 48 hours of surgery (50.5% vs 41.6% for Q4 and Q1, respectively; $p < 0.0001$). There were significant differences across transfusion across quartiles with perfusion equipment and intraoperative blood conservation techniques. Arterial pump usage (35.5%, 51.1%, 78.9%, 8.7%, $p < 0.0001$), Acute normovolemic hemodilution (ANH) harvest (17.3%, 16.1%, 13.5%, 9.9%, $p < 0.0001$), autologous CPB circuit priming (89.2%, 59.7%, 89.2%, 77.4%, $p < 0.0001$), and del Nido cardioplegia usage (14.2%, 23.9%, 14.9%, 5.5%, $p < 0.0001$) were reported for Q1-Q4, respectively.

The random effect variance and intra-class correlation coefficients (ICC) are displayed in *Table 3*. The Model 1 (hospital intercepts only) random effect variance was 0.256. Model 2 (adding patient-related factors to Model 1) increased the random effect variance to 0.453. The calculated variance for intraoperative equipment and blood conservation modalities (Model 3) was 0.519. However, nesting of all models together (Model 4) resulted in a decrease in the calculated variance, 0.420. The ICC from the null model was 0.072, implying that 7.2% of the individual variation in transfusion is due to systematic differences between hospitals, while 92.8% is due to systematic differences between patients. Model 2 (ICC = 0.12), indicates that

the residual variation (unexplained variation) in transfusion after adjusting for patient risk factors due to hospital differences was 12%, and 88% was due to systematic differences between patients. Model 3 (ICC= 0.136) indicates that the unexplained variation after adjusting for intraoperative factors due to hospital differences was 13.6%, and 86.4% was due to systematic differences between patients. The ICC from Model 4 was 0.113, implying that 11.3% of the individual variation in transfusion after controlling for patient risk and intraoperative factors was due to systematic differences between hospitals, and while 88.7% of the individual variation in transfusion is due to systematic differences between patients. Similar trends were obtained for ICC with simulation approach (0.052, 0.0618, 0.0616, 0.0636 for M1-M4, respectively).

The direct standardized hospital transfusion rate by model is illustrated in the turnip plot (*Figure 3)*. The turnip plot displays the coefficient of variation, defined as the ratio of the standard deviation to the mean hospital center transfusion rate. Each dot represents a hospital that is centered symmetrically on the horizontal axis based on RBC transfusion rate. The coefficient of variation for each of the models were 0.33 (observed), and 0.31, 0.29, 0.40, and 0.30 for models 1-4, respectively.

Discussion

Previous literature has identified both modifiable and non-modifiable clinical factors associated with the increased exposure to allogeneic RBC units (22-24). Conventional wisdom suggests that differences in baseline patient risk may be the predominant drivers of differences in center transfusion rates following CABG surgery. With this in mind, we aimed to assess the contributions that pre- and intraoperative factors have in explaining hospital variation in blood transfusion rates. In this large, contemporaneous, multi-center study, we found that the addition of intra-operative factors known at the time of transfusion decision-making did not appreciably

improve our understanding of determinants of variation in RBC transfusion during CABG surgery.

The turnip plot, first utilized in the *Dartmouth Atlas of Health Care* reports, illustrates the dispersion of hospital transfusion variation around the mean rates (25). Only small differences in variation were observed across each of the covariate-adjusted models. When all of the covariates were taken account (model 4), the coefficient of variation decreased. The ICC and random effects variance tests measured the relatedness of transfusions between hospitals. Even after adjusting for many of the patient and procedural factors that are reported to be associated with RBC exposure (20), there was little conformity in transfusion rates among hospitals. Guidelines for interpreting the ICC reported by Koo & Li recommend that values less than 0.5 are indicative of poor reliability (26). Our results indicate that the clinical factors we believed were key determinants in transfusion decisions did not explain the variability in RBC transfusions between hospitals. Additional investigation into nonclinical factors (e.g., provider transfusion triggers, organizational culture, blood management protocols) may improve our understanding of center-level differences (27).

In an observational cohort of 102,470 patients from 798 clinical sites undergoing isolated CABG surgery, Bennett-Guerrero *et al* reported significant variation in hospital risk-adjusted transfusion rates according to geographic location (p=0.007), academic status (p=0.03), and hospital volume (p<0.001) (15). Although these factors only attributed for 11.1% of the observed variance, procedural case mix accounted for only 20% of the total variation. Likosky *et al* examined regional-specific discretionary (1-2 units) RBC transfusions for isolated CABG procedures across five regional cardiac surgical quality collaboratives (The IMPROVE Network) (28). The analysis included 11,200 patients across the 56 participating centers who received 0,1, or 2 units of RBCs during the index admission. Significant variation in RBC units and volume

was observed across regions and remained so after pre- and intraoperative risks (9.1% - 31.7%, $p<0.001$) (28). These findings suggest differences in regional transfusion practices.

Organizational culture, broadly defined as the basic assumptions and values that guide organizations (29), may be associated with variances in clinical practice. Using multilevel mixed-effect logistic and linear regression models, Jin *et al* examined variation in blood transfusion practices among 5,744 isolated CABG procedures performed by 42 surgeons at 12 hospitals within the same health system (30). Observed variances in RBC transfusions at the hospital level (0.82) were over twice as high as surgeons practicing at the same hospital (0.35), suggesting a correlation between organizational culture and transfusion practice through factors such as team familiarity, quality improvement and data sharing, and standardized clinical practices (30). Likosky *et al* compared perioperative RBC transfusion rates for both CABG and percutaneous coronary intervention (PCI) at 33 Michigan cardiac surgical programs (31). (32)A total of 16,568 CABG and 94,634 PCI patients were included for analysis. There was wide variation in transfusion rates observed across centers for both CABG (26.5% to 71.3%) and PCI (1.6% to 6.0%). While perhaps somewhat surprising, the investigators found that an institution's CABG transfusion rate significantly correlated with the PCI rate (31). These findings suggest that factors beyond patient-level risk may help explain center-level differences in transfusion practices.

A number of studies have evaluated the association between clinical providers and RBC transfusions. A retrospective single center analysis of 4,823 patients by Cote *et al* found that differing practice patterns among cardiac surgeons and anesthesiologists were independent predictors of perioperative transfusion (23). Significant differences in perioperative transfusion rates were reported between surgeons (32.4% to 51.5%, $P<.0001$), anesthesiologists (34.4% to 51.9%, $P<.0001$), and year of hospital admission (28.2% in 2004 to 48.8% in 2008, $P<.0001$).

Differences in transfusion rates among practitioners were found after adjustment for baseline and intraoperative covariates (23). Previous surveys conducted among critical care practitioners reported significant individual variation in acceptable hemoglobin concentrations prior to transfusion (33, 34). While differences in transfusion triggers may be attributed to patient-related clinical factors, physicians may weigh these clinical characteristics differently in the absence of formal institutional protocols. Clinical transfusion triggers may also be influenced by environmental factors such as computer decision support, motivation to adopt guidelines, and support for colleagues (35).

Despite the reported benefits of team familiarity on clinical effectiveness and surgical teamwork (36-38), its association with blood transfusion behaviors has not been previously described. Shared work experiences and familiarity among team members has been reported to contribute to improved anticipation, coordination, and productivity (39). Conversely, clinicians that experience a high level of dispersion across larger and unfamiliar teams may lack the bonds and interpersonal relationships for effective collaboration. Poor communication between unfamiliar team members may lead to avoidable transfusions, as team members may not compensate for unfamiliarity with increased communication (40). These effects may be exacerbated by increased staff turnover, surgical case volume, and education. It is conceivable that centers with fewer team member combinations can establish a quicker consensus regarding transfusion best practices. Decisions among intraoperative care members are improved with teamwork and experience (41, 42). Although we reported the number unique staffing pairs among surgeons and perfusionists (*Table 2*), we were unable to capture anesthesia personnel. This data may have provided a more reliable estimate of explanatory transfusion variation within and across centers.

Although single and multi-center studies have reported reductions in potentially discretionary transfusions through programmatic guideline development, education, and feedback/audit activities (43-46), these activities are not considered mandatory research reporting criteria (20). Our findings highlight the importance of identifying and comparing programmatic differences in blood management. Such variables may include the presence of transfusion triggers, protocols, and institutional blood management committees. Variability in practice may exist in circumstances when multiple clinicians are empowered to make transfusion decisions. Differences in clinical opinion combined with multiple triggers may not support standardized transfusion algorithms. The single-center experience of Cote and colleagues describes a joint process on intraoperative transfusion decisions that collectively involve the surgeon, anesthesiologist and perfusionist (23). However, once the patient is admitted to the postoperative care arena it was predominately the surgeon who decides. The incorporation of these practices is not currently captured in clinical outcome registries.

There were several limitations to our study. First, as in any observational cohort study, we cannot rule out the impact of unmeasured confounding. Nonetheless, we adjusted for commonly reported risk factors associated with the risk of transfusion (18). Additionally, our analysis was restricted to variables that are known prior to the initiation of CPB support and before a transfusion decision is made. Second, there may also be potential collinearity among the model covariates that could influence the regression coefficient. For example, net CPB prime volume was included in the intraoperative procedural model and is a function of the difference between CPB static prime volume (in ml) and autologous blood prime volume (in ml). As such, we removed the autologous CPB prime volume from the model as a separate covariate. All attempts were made to omit any of the independent variables that demonstrated strong correlation. Third, we recognize that our findings are generalizable only to the institutions

participating in the PERForm registry. Last, we recognize that we are unaware of the primary reasons underlying RBC transfusions across centers. Observational research may be limited in capturing the appropriate circumstances associated with transfusion medicine.

In summary, our analysis was unable to explain the majority of perioperative RBC transfusion variation across centers performing CABG surgery. Variation across hospitals could not be explained by conventional patient and procedural factors present at the time of transfusion decision. Further investigation is warranted to consider the impact of human factors and the non-technical aspects of transfusion medicine. The degree to which institutions adopt transfusion algorithms is relatively unknown. Clinical guidelines that are not uniformly applied will continue to influence local hospital decisions and have limited effect on individual provider practices. Changes in organizational culture and reporting are necessary to help ensure the transfusion decisions we make are the right ones.

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References

1. Speiss BD. Transfusion and outcome in heart surgery. *The Annals of Thoracic Surgery*. 2002 Oct 1,;74(4):986.

2. Carson JL. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. *Annals of Internal Medicine*. 2012 Mar 26,:E.

3. Crescenzi G, Torracca L, Capestro F, Matteucci MLS, Rossi M. Allogenic Blood Transfusion in Cardiac Surgery. *Journal of Cardiac Surgery*. 2012 Sep;27(5):594-9.

4. Bracey A. Bloodless cardiac surgery: a strategy for few or the future standard of care? *Transfusion*. 2015 Dec;55(12):2773-4.

5. Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM, et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg*. 2014 Jan;97(1):94.

6. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. *The New England Journal of Medicine*. 2017 Nov 30,;377(22):2133-44.

7. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B, et al. Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery. *The New England Journal of Medicine*. 2018 Aug 26,;379(13):1224-33.

8. Hajjar LA, Vincent J, Galas, Filomena R. B. G, Nakamura RE, Silva CMP, Santos MH, et al. Transfusion Requirements After Cardiac Surgery: The TRACS Randomized Controlled Trial. *JAMA*. 2010 Oct 13,;304(14):1559-67.

9. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011 Mar;91(3):944-82.

10. Menkis AH, Martin J, Cheng DCH, Fitzgerald DC, Freedman JJ, Gao C, et al. Drug, devices, technologies, and techniques for blood management in minimally invasive and conventional cardiothoracic surgery: a consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) 2011. *Innovations*. 2012 Jul;7(4):229-41.

11. Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg*. 2018 Jan 01,;53(1):79-111.

12. Likosky DS, FitzGerald DC, Groom RC, Jones DK, Baker RA, Shann KG, et al. The effect of the perioperative blood transfusion and blood conservation in cardiac surgery Clinical Practice Guidelines of the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists upon clinical practices. *The Journal of Extracorporeal Technology*. 2010 Jun;42(2):114.

13. Qian F, Osler TM, Eaton MP, Dick AW, Hohmann SF, Lustik SJ, et al. Variation of blood transfusion in patients undergoing major noncardiac surgery. *Annals of surgery*. 2013 Feb;257(2):266-78.

14. Snyder-Ramos SA, Möhnle P, Weng Y, Böttiger BW, Kulier A, Levin J, et al. The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion*. 2008 Jul;48(7):1284-99.

15. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB, Peterson ED, Gammie JS, et al. Variation in Use of Blood Transfusion in Coronary Artery Bypass Graft Surgery. *JAMA*. 2010 Oct 13,;304(14):1568-75.

16. The Michigan Society of Thoracic and cardiovascular Surgeons and The MSTCVS Quality Collaborative. About PERForm. 2018 [cited April 1, 2019]. Available from: https://mstcvs.org/home/perform-registry/.

17. Paugh TA, Dickinson TA, Theurer PF, Bell GF, Shann KG, Baker RA, et al. Validation of a perfusion registry: methodological approach and initial findings. *The Journal of Extracorporeal Technology*. 2012 Sep;44(3):104.

18. Likosky DS, Paugh TA, Harrington SD, Wu X, Rogers MAM, Dickinson TA, et al. Prediction of Transfusions after Isolated Coronary Artery Bypass Grafting Surgery. *Ann Thorac Surg*. 2017(103):764-72.

19. Xian Y, Chen AY, Thomas L, Roe MT, Subherwal S, Cannon CP, et al. Sources of hospital-level variation in major bleeding among patients with non-st-segment elevation myocardial infarction: a report from the National Cardiovascular Data Registry (NCDR). *Circulation*. Cardiovascular quality and outcomes. 2014 Mar;7(2):236-43.

20. Likosky DS, Baker RA, Dickinson TA, Fitzgerald DJ, Somer MF, Groom RC, et al. Special Report: Report from AmSECT's International Consortium for Evidence-Based Perfusion Consensus Statement: Minimal Criteria for Reporting Cardiopulmonary Bypass-Related Contributions to Red Blood Cell Transfusions Associated with Adult Cardiac Surgery. *Journal of Extracorporeal Technology*. 2015;47:83-89.

21. Merlo J, Chaix B, Ohlsson H, Beekman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *Journal of Epidemiology and Community Health* (1979-). 2006 Apr 1,;60(4):290-7.

22. Shah A, Stanworth SJ, McKechnie S. Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia*. 2015 Jan;70(s1):e3.

23. Cote C, MacLeod JB, Yip, AM, Ouzounian M, Brown CD, Forgie, R, Pelletier MP, Hassan A. Variation in transfusion rates within a single institution: Exploring the effect of differing practice patterns on the likelihood of blood product transfusion in patients undergoing cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery*, The. 2015;149(1):297-302.

24. Shehata N, Naglie G, Alghamdi AA, Callum J, Mazer CD, Hebert P, et al. Risk factors for red cell transfusion in adults undergoing coronary artery bypass surgery: a systematic review. *Vox Sanguinis*. 2007 Jul;93(1):1-11.

25. The Center for the Evaluative Clinical Sciences, Dartmouth Medical School. *The Dartmouth Atlas of Health Care*. Wennberg JE and Cooper MM, editors. Chicago, IL: American Hospital Publishing; 1996.

26. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*. 2016 Jun;15(2):155-63.

27. Camaj A, Zahuranec DB, Paone G, Benedetti BR, Behr WD, Zimmerman MA, et al. Organizational Contributors to the Variation in Red Blood Cell Transfusion Practices in Cardiac Surgery: Survey Results From the State of Michigan. *Anesthesia and analgesia*. 2017 Sep;125(3):975-80.

28. Likosky DS, Al-Attar PM, Malenka DJ, Furnary AP, Lehr EJ, Paone G, et al. Geographic Variability in Potentially Discretionary Red Blood Cell Transfusions After Coronary Artery Bypass Grafting Surgery. *The Journal of Thoracic and Cardiovascular Surgery*. 2014 Aug 14,;148(6):3084-9.

29. Schneider B, Ehrhart MG, Macey WH. Organizational Climate and Culture. *Annual review of Psychology*. 2013;64(1):361-88.

30. Jin R, Zelinka ES, McDonald J, Byrnes T, Grunkemeier GL, Brevig J. Effect of Hospital Culture on Blood Transfusion in Cardiac Procedures. *Annals of Thoracic Surgery*. 2013;95(4):1269-74.

31. Likosky DS, Zhang M, Paone G, Collins J, DeLucia A, Schreiber T, Theurer P, Kazziha S, Leffler D, Wunderly DJ, Gurm HS, Prager, RL. Impact of institutional culture on rates of transfusions during cardiovascular procedures: The Michigan experience. *American Heart Journal*. 2016;174:1-6.

32. Likosky, Donald S., PhD|Zhang, Min, PhD|Paone, Gaetano, MD, MHSA|Collins, John, MD|DeLucia, Alphonse, MD|Schreiber, Theodore, MD|Theurer, Patty, BSN, RN|Kazziha, Samer, MD|Leffler, Dale, DO|Wunderly, Douglas J., MD|Gurm, Hitinder S., MD|Prager, Richard L., MD. Impact of institutional culture on rates of transfusions during cardiovascular procedures: The Michigan experience. *American Heart Journal*. 2015;174:1-6.

33. Kranenburg FJ, Willems SA, Le Cessie S, Marang-van de Mheen, P. J, Bom JG, Arbous MS. Variation in red cell transfusion decisions in the intensive care unit – a nationwide survey in the Netherlands. *Vox Sanguinis*. 2018 May;113(4):378-85.

34. Hébert PCP. A Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. *Crit Care Med*. 1998 -3;26(3):482-7.

35. Sim V, Kao LS, Jacobson J, Frangos S, Brundage S, Wilson CT, Simon R, Glass NE, Pachter HL, Todd SR. Can old dogs learn new "transfusion requirements in critical care": a survey of packed red blood cell transfusion practices among members of The American Association for the Surgery of Trauma. *The American Journal of Surgery*. 2015 July;1(210):45-51.

36. Avgerinos E, Gokpinar B. Team Familiarity and Productivity in Cardiac Surgery Operations: The Effect of Dispersion, Bottlenecks, and Task Complexity. *Manufacturing & Service Operations Management*. 2017 Feb;19(1):19-35.

37. Maruthappu M, Duclos A, Zhou CD, Lipsitz SR, Wright J, Orgill D, et al. The impact of team familiarity and surgical experience on operative efficiency: a retrospective analysis. *Journal of the Royal Society of Medicine*. 2016 Apr;109(4):147-53.

38. Xu R, Carty M, Orgill D, Lipsitz S, Duclos A. The Teaming Curve: A Longitudinal Study of the Influence of Surgical Team Familiarity on Operative Time. *Annals of Surgery*. 2013 Dec;258(6):953-7.

39. Sexton K, Johnson A, Gotsch A, Hussein AA, Cavuoto L, Guru KA. Anticipation, teamwork and cognitive load: chasing efficiency during robot-assisted surgery. *BMJ Quality & Safety*. 2018 0201;27(2):148-54.

40. Lane L. Frasier, MS, Sudha R. Pavuluri Quamme, MS, Yue Ma, Douglas Wiegmann, et al. Familiarity and Communication in the Operating Room. *Journal of Surgical Research*. 2019;235:395-403.

41. Epstein NE. Multidisciplinary in-hospital teams improve patient outcomes: A review. *Surg Neuro Int*. 2014 Aug 28;5(Suppl 7):S303.

42. O'Daniel M, Rosenstein AH. Patient Safety and Quality: *An Evidence-Based Handbook for Nurses*. Hughes RG, editor. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008.

43. Tinmouth A, MacDougall L, Fergusson D, Amin M, Graham ID, Hebert PC, et al. Reducing the Amount of Blood Transfused: A Systematic Review of Behavioral Interventions to Change Physicians' Transfusion Practices. *Archives of Internal Medicine*. 2005 Apr 25,;165(8):845-52.

44. Marques MB, Polhill SR, Waldrum MR, Johnson JE, Timpa J, Patterson A, et al. How we closed the gap between red blood cell utilization and whole blood collections in our institution. *Transfusion*. 2012 Sep;52(9):1857-67.

45. Gutsche JT, Kornfield ZN, Speck RM., Patel PA, Atluri P, Augoustides JG. Impact of Guideline Implementation on Transfusion Practices in a Surgical Intensive Care Unit. *Journal of Cardiothoracic and Vascular Anesthesia*. 2013;27(6):1189-93.

46. LaPar DJ, Crosby IK, Ailawadi G, Ad N, Choi E, Spiess BD, Rich, JB, Kasirajan V, Fonner E, Kron IL, Speir AM. Blood product conservation is associated with improved outcomes and reduced costs after cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery*. 2013;145(3):796-804.

Figure 1. Selection criteria for study population inclusion

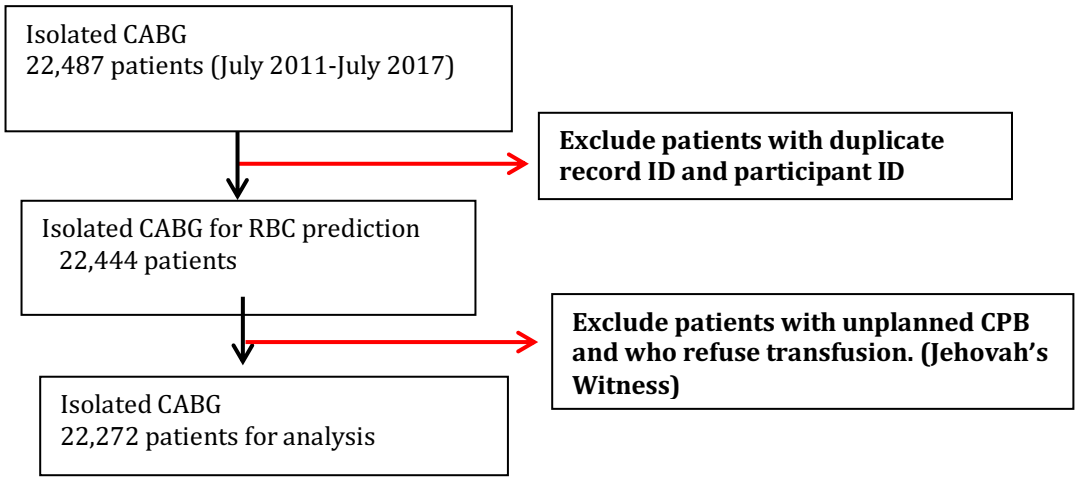


Figure 2. Multivariable Logistic Regression Models of RBC Transfusion Variables

	Description	Covariates
Model 1	Hospital random intercepts only	None
Model 2	Model 1 + Patient demographic, laboratory assay results, and preoperative risk factors	- Model 1 - Age (years) - Body Surface Area (m^2) - Sex (M/F) - Admission status (elective, urgent, emergent/salvage) - Preoperative Hematocrit (%) - Serum Albumin (g/dl) - Serum Creatinine (mg/dl) - Platelet count (x 10,000) - Current smoker (y/n) - Chronic lung disease (y/n) - Previous MI (y/n) - Congestive Heart Failure (y/n) - Cardiogenic Shock (y/n) - Peripheral Vascular Disease (y/n) - Cerebrovascular disease (y/n) - Diabetes Mellitus (y/n) - Dialysis (y/n) - Hypertension (y/n) - Anticoagulant medications <48 hrs (y/n) - Reoperative status (y/n) - Number of diseased vessels
Model 3	Model 1 + Perfusion Factors (Intraoperative Blood Conservation Procedural Factors)	- Model 1 - Arterial Roller Pump Use (y/n) - Acute Normovolemic Hemodilution (ANH) (y/n) - del Nido cardioplegia use (y/n) - Autotransfusion use (y/n) - Autologous CPB circuit prime (y/n) - Indexed Net CPB Prime (ml/m^2)
Model 4	(Hospital random intercepts) + (Patient demographic, laboratory assay results, and preoperative risk factors) + (Intraoperative Blood Conservation Procedural Factors)	- Model 1 - Model 2 - Model 3

Table 1. Descriptive Statistics of Patient and Procedural Variables According to Perioperative RBC Transfusion.

	Perioperative RBC transfusion			
	Overall	Transfusion (No)	Transfusion (yes)	Significance ($p< 0.05$)
	22272	15031	7241	
Intraoperative Only	1586	0 (0.0)	1586 (21.9)	
Postoperative transfusion only	3884 (17.4)	0 (0.0)	3884 (53.6)	<0.001
Intraoperative & Postoperative	1771	0 (0.0)	1771 (24.5)	
Intraoperative CPB equipment				
Roller pump	9914 (44.5)	6771 (45.0)	3143 (43.4)	0.022
Cardioplegia				<0.001
CDPG (non-del Nido)	18606 (83.5)	12474 (83.0)	6132 (84.7)	
del Nido only	3250 (14.6)	2311 (15.4)	939 (13.0)	
None	416 (1.9)	246 (1.6)	170 (2.3)	
Autotransfusion device	18978 (85.2)	12727 (84.7)	6251 (86.3)	0.001
Demographics				
Age (years)	65 [58, 72]	64 [57, 71]	68 [61, 75]	<0.001
BSA (m^2)	2.03 [1.87, 2.18]	2.07 [1.93, 2.21]	1.93 [1.77, 2.09]	<0.001
Female	5398 (24.2)	2391 (15.9)	3007 (41.5)	<0.001
Admission status				<0.001
Elective	8825 (39.6)	6326 (42.1)	2499 (34.5)	
Urgent	12834 (57.6)	8413 (56.0)	4421 (61.1)	
Emergent/emergent salvage	611 (2.7)	291 (1.9)	320 (4.4)	
Lab values				
Preoperative HCT (%)	40 [36, 43]	41 [38., 44]	36 [32, 39]	<0.001
Total albumin (g/dl)	3.80 [3.50, 4.10]	3.80 [3.60, 4.10]	3.70 [3.30, 4.00]	<0.001
Last creatinine (mg/dl)	1.00 [0.80, 1.19]	0.97 [0.80, 1.10]	1.00 [0.80, 1.30]	<0.001
Platelets count (x 10000)	20.80 [17.30, 25.00]	20.70 [17.30, 24.60]	21.00 [17.00, 26.00]	<0.001
Intraoperative blood conservation techniques				
1st HCT on CPB support	27.00 [23.00, 31.00]	28.00 [25.00, 32.00]	23.00 [21.00, 27.00]	<0.001
Last HCT prior to CPB	35.00 [31.00, 39.00]	36.00 [33.00, 40.00]	31.00 [27.00, 35.00]	<0.001
Anesthesia crystalloid volume (indexed to pt. kg weight) (ml/m^2)	10.74 [7.53, 14.77]	10.32 [7.30, 14.10]	11.79 [8.11, 16.50]	<0.001
Static prime volume (indexed to BSA) ml/m^2	1000.00 [900.00, 1220.00]	1050.00 [900.00, 1220.00]	1000.00 [850.00, 1250.00]	<0.001
Total prime volume (indexed to BSA) ml/m^2	614.10 [506.22, 722.91]	604.24 [498.32, 704.35]	640.61 [525.15, 766.03]	<0.001
Autologous Circuit Prime (count, %)	17714 (79.5)	12141 (80.8)	5573 (77.0)	<0.001

Autologous circuit volume (ml)	500.00 [200.00, 625.00]	500.00 [250.00, 650.00]	450.00 [200.00, 600.00]	<0.001
Acute normovolemic hemodilution (ANH)	3176 (14.3)	2591 (17.2)	585 (8.1)	<0.001
ANH volume (ml) [among ANH (yes)]	5.8 [4.6,8.2]	5.8 [4.7, 8.8]	5.8 [4.4, 6.2]	<0.001
Patient Risk factors				
Current smoker	5006 (22.5)	3575 (23.8)	1431 (19.8)	<0.001
Previous MI	12094 (54.3)	7744 (51.5)	4350 (60.1)	<0.001
Severe/moderate chronic lung disease	2264 (10.2)	1285 (8.5)	979 (13.5)	<0.001
CHF				<0.001
no	17058 (76.6)	12381 (82.4)	4677 (64.6)	
yes	2491 (11.2)	1439 (9.6)	1052 (14.5)	
unknown	2723 (12.2)	1211 (8.1)	1512 (20.9)	
PVD				<0.001
no	16633 (74.7)	12074 (80.3)	4559 (63.0)	
yes	2914 (13.1)	1745 (11.6)	1169 (16.1)	
unknown	2725 (12.2)	1212 (8.1)	1513 (20.9)	
Diabetes	10543 (47.3)	6743 (44.9)	3800 (52.5)	<0.001
Cardiogenic shock	382 (1.7)	140 (0.9)	242 (3.3)	<0.001
CVD	4673 (21.0)	2614 (17.4)	2059 (28.4)	<0.001
Preoperative dialysis	562 (2.5)	112 (0.7)	450 (6.2)	<0.001
Hypertension	19970 (89.7)	13290 (88.4)	6680 (92.3)	<0.001
Anticoagulant use (<48 hrs)	10287 (46.2)	6617 (44.0)	3670 (50.7)	<0.001
First cardiovascular surgery	21772 (97.8)	14783 (98.4)	6989 (96.5)	<0.001
Number of diseased vessels (3 or more)	17462 (78.4)	11598 (77.2)	5864 (81.0)	<0.001

Continuous variables expressed as median, [IQR], and categorical variables as count (%). CDPG indicates cardioplegia; BSA, body surface area; HCT, hematocrit; CPB, cardiopulmonary bypass; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease.

Table 2. Distribution of Demographic Variables According to Quartiles of Center-level Perioperative RBC Transfusion Rates.

Perioperative RBC transfusion rates (%)	**Overall 10.9-59.9**	**Q1 10.9-23.6**	**Q2 24.2-31.2**	**Q3 33.0-39.8**	**Q4 40.0-59.9**	**Significance (p<0.05)**
Patients (n)	22272	5807	5178	6005	5282	
Hospitals (n)	43	10	11	11	11	
Surgeons (n)	209	61	40	57	51	
Perfusionists (n)	294	68	63	74	89	
Unique pairs of surgeons and perfusionists	1421	336	314	460	407	
O/E Ratio of RBC Transfusion	0.98 (0.80, 1.23)	0.71 (0.60, 0.77)	0.89 (0.82, 0.95)	1.10 (1.07, 1.24)	1.28 (1.20, 1.52)	
Age (years)	65.0 (58.0,72.0)	65.0 (58, 72)	66.0 (59, 73)	65.0 (58, 72)	65.0 (57.0, 72)	<.0001
Sex (Female- %)	24.2	22	23.3	24.4	27.5	<.0001
Body Surface Area (m^2)	2.0 (1.9, 2.2)	2.0 (1.9, 2.2)	2.0 (1.9, 2.2)	2.0 (1.9, 2.2)	2.0 (1.8, 2.2)	<.0001
Elective Operative Status (%)						<.0001
Elective	39.6	41.7	35.5	43.4	37.1	
Urgent	57.6	55.6	61.4	54.4	59.9	
Emergent/emergent salvage	2.7	2.7	3.1	2.3	3	
Number of Diseased Vessels (>3)	78.4	78.8	78.6	78.1	78.1	0.72
Previous Myocardial Infarction (%)	54.3	55.1	54	51.9	56.5	<.0001
Reoperative Status (%)	2.2	2.3	2.8	1.7	2.3	0.0011
Diabetes Mellitus (%)	47.3	47.2	45.1	46.5	50.5	<.0001
Cerebrovascular Disease (%)	21.0	18.7	23.6	20	22.1	<.0001
Congestive Heart Failure (%)	11.2	10.4	10.5	12.4	11.4	<.0001
Cardiogenic Shock (%)	1.7	1.5	1.8	1.8	1.8	0.45
Peripheral Vascular Disease (%)	13.2	11.7	13.6	12.2	15.1	<.0001
Smoking (%)	22.5	20.9	20.3	22.9	25.9	<.0001
Chronic Lung Disease (%)	10.2	9.9	9.5	9.1	12.3	<.0001
Hypertension (%)	89.7	88.6	87.9	90.1	92.1	<.0001
Dialysis (%)	2.5	2.3	2.2	2.6	3.1	0.016
Left Ventricular Ejection Fraction (%)	55.0 (45.0,60.0)	55.0 (45.0,60.0)	55.0 (47.0,60.0)	55.0 (45.0,60.0)	55.0 (45.0,60)	<.0001
Preoperative Hematocrit (%)	39.9 (36.0, 43.0)	40.0 (36.0, 43.0)	39.9 (36.0, 42.8)	39.7 (35.9, 42.9)	39.3 (35.2, 42.8)	<.0001
Platelet Count (per µl)	208 (172, 251)	209 (173, 250)	205 (171, 246)	209 (173, 253)	209 (171, 255)	
Anticoagulant medications (< 48 hrs) (%)	46.2	41.6	43.3	49.4	50.5	<.0001
Creatinine (mg/dl)	1.0 (0.8, 1.2)	1.0 (0.8, 1.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	<.0001
Albumin (g/dl)	3.8 (3.5, 4.1)	3.8 (3.6, 4.1)	3.8 (3.4, 4.1)	3.8 (3.4, 4.0)	3.8 (3.5, 4.1)	<.0001
Arterial Roller Pump Use (%)	44.5	35.5	51.1	78.9	8.7	<.0001
Del Nido Cardioplegia Use (%)	14.6	14.2	23.9	14.9	5.5	<.0001

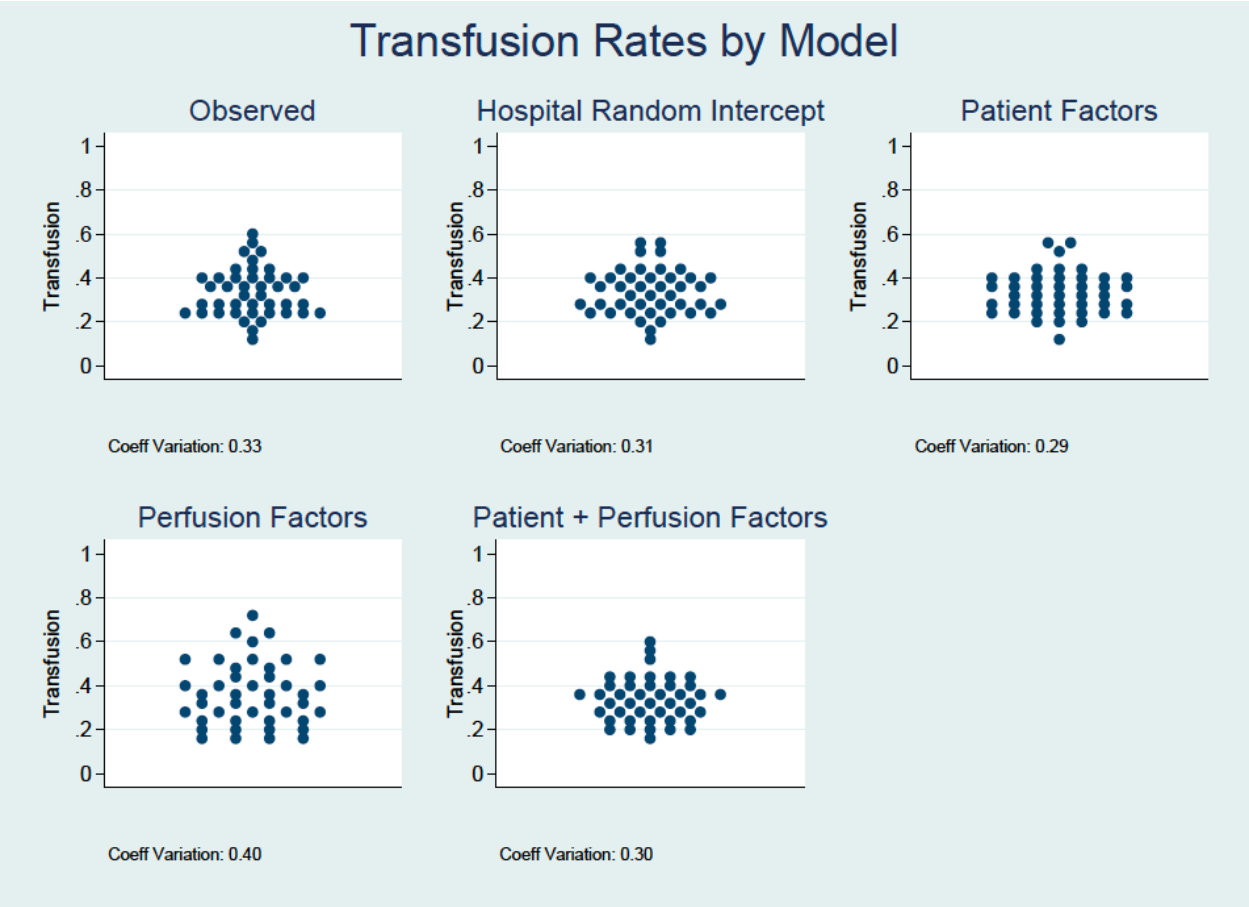
Autotransfusion Usage (%)	85.2	94.44	59.77	90.56	93.92	<.0001
Acute Normovolemic Hemodilution (y/n)	14.3	17.3	16.1	13.5	9.9	<.0001
Acute Normovolemic Hemodilution (ml)	450 (400, 900)	800 (400, 900)	500 (450, 900)	450 (400, 450)	350 (350, 450)	<.0001
Autologous Blood CPB Prime (RAP)	79.5	89.2	59.7	89.2	77.4	<.0001
Autologous Blood Prime (ml)	550 (400, 700)	600 (400, 650)	500 (400, 600)	600 (400, 750)	600 (400, 700)	<.0001
Static CPB prime, indexed to BSA (ml/m^2)	1000 (900,1220)	1200 (900,1215)	1000 (900,1200)	1100 (900,1500)	1000 (850, 1220)	<.0001
Net Prime Volume, Indexed to BSA (ml/m^2)	371.9 (258.5,514.3)	373.7 (262.4,505.1)	434.8 (286.7,640.1)	366.5 (250.6,483.7)	331.9 (233.3,456.9)	<.0001
Last Pre-CPB Hematocrit (%)	35.0 (31.0, 39.0)	35 (31,38)	36 (32, 39)	35 (30, 39)	35 (30, 38)	<.0001

Continuous variables expressed as median, [IQR], and categorical variables as count (%).

Table 3. Random effect variance and ICC coefficient model results

	Model 1 (Hospital intercepts only)	**Model 2** (Model 1 + Patient demographic, laboratory assay results, and preoperative risk factors	**Model 3** (Model 1 + Intraoperative Blood Conservation Procedural Factors	**Model 4** (Model 1 + Model 2 + Model 3)
Random Effects Variance	0.256	0.453	0.519	0.420
ICC coefficient with latent variable approach	0.072	0.12	0.136	0.113
ICC coefficient with simulation approach	0.052	0.062	0.062	0.064

Figure 3. Turnip Plot of Direct Standardized Hospital Transfusion Rates by Models



REFERENCES

Adams RC, Lundy JS, (1942). Anesthesia in cases of poor surgical risk. Some suggestions for decreasing the risk**.** *Surg Gynecol Obstet,* 74***:*** *1011-1019*

AmSECT, (2017). American society of extracorporeal technology standards and guidelines for perfusion practice. Retrieved from http://www.amsect.org/p/cm/ld/fid=1617

Ang LB, Veloria E, Evanina E, Smaldone A. (2012). Mediastinitis and blood transfusion in cardiac surgery: A systematic review. *Heart & Lung: The Journal of Acute and Critical Care, 41*(3), 255-263. doi:10.1016/j.hrtlng.2011.07.012

Arias-Morales, C. E., Stoicea, N., Gonzalez-Zacarias, A. A., Slawski, D., Bhandary, S. P., Saranteas, T., . . . Papadimos, T. J. (2017). Revisiting blood transfusion and predictors of outcome in cardiac surgery patients: A concise perspective. *F1000Research, 6*, 168. doi:10.12688/f1000research.10085.1

Bennett-Guerrero, E., Zhao, Y., O'Brien, S. M., Ferguson, T. B., Peterson, E. D., Gammie, J. S., & Song, H. K. (2010). Variation in use of blood transfusion in coronary artery bypass graft surgery. *Jama, 304*(14), 1568-1575. doi:10.1001/jama.2010.1406

Blumberg, N., Kirkley, S. A., & Heal, J. M. (1996). A cost analysis of autologous and allogeneic transfusions in hip-replacement surgery. *The American Journal of Surgery, 171*(3), 324-330. doi:10.1016/S0002-9610(97)89635-3

Boer, C., Meesters, M. I., Milojevic, M., Benedetto, U., Bolliger, D., von Heymann, C., . . . Pagano, D. (2018). 2017 EACTS/EACTA guidelines on patient blood management for adult

cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia, 32*(1), 88-120. doi:10.1053/j.jvca.2017.06.026

Bracey, A. (2015). Bloodless cardiac surgery: A strategy for few or the future standard of care? *Transfusion, 55*(12), 2773-2774. doi:10.1111/trf.13365

Brescia, A. A., Rankin, J. S., Cyr, D. D., Jacobs, J. P., Prager, R. L., Zhang, M., . . . Likosky, D. S. (2018). Determinants of variation in pneumonia rates after coronary artery bypass grafting. *The Annals of Thoracic Surgery, 105*(2), 513-520. doi:10.1016/j.athoracsur.2017.08.012

Camaj A, Zahuranec DB, Paone G, Benedetti BR, Behr WD, Zimmerman MA, et al., (2017). Organizational Contributors to the Variation in Red Blood Cell Transfusion Practices in Cardiac Surgery: Survey Results From the State of Michigan. *Anesthesia and Analgesia*, 125(3):975-80.

Carson, J. L. (2012). Red blood cell transfusion: A clinical practice guideline from the AABB. *Annals of Internal Medicine,* , E. doi:10.7326/0003-4819-156-12-201206190-00429

Committee on Quality Health Care in America, Institute of Medicine, (2001). Crossing the quality chasm: a new health system for the 21st century. Washington, D.C. :*National Academy Press*,

Cote C, MacLeod JB, Yip, AM, Ouzounian M, Brown CD, Forgie, R, Pelletier MP, Hassan A., (2015). Variation in transfusion rates within a single institution: Exploring the effect of differing practice patterns on the likelihood of blood product transfusion in patients

undergoing cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery*, 149(1):297-302.

Crescenzi, G., Torracca, L., Capestro, F., Matteucci, M. L. S., & Rossi, M. (2012). Allogenic blood transfusion in cardiac surgery. *Journal of Cardiac Surgery, 27*(5), 594-599. doi:10.1111/j.1540-8191.2012.01522.x

Desmarets, M., Bardiaux, L., Benzenine, E., Dussaucy, A., Binda, D., Tiberghien, P., . . . Monnet, E. (2016). Effect of storage time and donor sex of transfused red blood cells on 1-year survival in patients undergoing cardiac surgery: An observational study. *Transfusion, 56*(5), 1213-1222. doi:10.1111/trf.13537

Dhir, A., & Tempe, D. K. (2017). Anemia and patient blood management in cardiac Surgery—Literature review and current evidence. *Journal of Cardiothoracic and Vascular Anesthesia,* doi:10.1053/j.jvca.2017.11.043

Dubovoy, T., & Engoren, M. (2016). Thrombotic risks in red blood cell transfusions. *Semin Thromb Hemost, 42*(2), 102-111. doi:10.1055/s-0035-1569069

Ellingson, K. D., Sapiano, M. R. P., Haass, K. A., Savinkina, A. A., Baker, M. L., Chung, K., . . . Basavaraju, S. V. (2017). Continued decline in blood collection and transfusion in the united States–2015. *Transfusion, 57*(S2), 1588-1598. doi:10.1111/trf.14165

Engoren, M. C., Habib, R. H., Zacharias, A., Schwann, T. A., Riordan, C. J., & Durham, S. J. (2002). Effect of blood transfusion on long-term survival after cardiac operation. *The Annals of Thoracic Surgery, 74*(4), 1180. Retrieved from http://ats.ctsnetjournals.org/cgi/content/abstract/74/4/1180

Ferraris, V. A., Brown, J. R., Despotis, G. J., Hammon, J. W., Reece, T. B., Saha, S. P., . . . Shann, K. G. (2011). 2011 update to the society of thoracic surgeons and the society of cardiovascular anesthesiologists blood conservation clinical practice guidelines. *The Annals of Thoracic Surgery, 91*(3), 944-982. doi:10.1016/j.athoracsur.2010.11.078

Galas, Filomena R B G, Almeida, J. P., Fukushima, J. T., Osawa, E. A., Nakamura, R. E., Silva, Carolina M P D C, . . . Hajjar, L. A. (2013). Blood transfusion in cardiac surgery is a risk factor for increased hospital length of stay in adult patients. *Journal of Cardiothoracic Surgery, 8*(1), 54. doi:10.1186/1749-8090-8-54

Geissler, R. G., Rotering, H., Buddendick, H., Franz, D., Bunzemeier, H., Roeder, N., . . . Schlenke, P. (2015). Utilisation of blood components in cardiac surgery: A single-centre retrospective analysis with regard to diagnosis-related procedures. *Transfusion Medicine and Hemotherapy, 42*(2), 75-82. doi:10.1159/000377691

Ghazi L, Schwann TA, Engoren MC, Habib RH, (2015). Role of blood transfusion product type and amount in deep vein thrombosis after cardiac surgery. *Thrombosis Research, 136*(6), 1204-1210. doi:10.1016/j.thromres.2015.10.041

Goldberg, J. B., Shann, K. G., Fitzgerald, D., Fuller, J., Paugh, T. A., Dickinson, T. A., . . . Likosky, D. S. (2016). The relationship between intraoperative transfusions and nadir hematocrit on post-operative outcomes after cardiac surgery. *The Journal of Extra-Corporeal Technology, 48*(4), 188. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27994259

Goudie, R., Sterne, J. A. C., Verheyden, V., Bhabra, M., Ranucci, M., & Murphy, G. J. (2015). Risk scores to facilitate preoperative prediction of transfusion and large volume blood

transfusion associated with adult cardiac surgery. *British Journal of Anaesthesia, 114*(5), 757-766. doi:10.1093/bja/aeu483

Hebert, P. C., Wells, G., Blajchman, M. A., Marshall, J., Martin, C., Pagliarello, G., . . . The Transfusion Requirements in Critical Care Investigators Canadian Critical Care Trials Group. (1999). A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *The New England Journal of Medicine, 340*(6), 409-417. doi:10.1056/NEJM199902113400601

Hohmuth, B., Ozawa, S., Ashton, M., & Melseth, R. L. (2014). Patient-centered blood management. *Journal of Hospital Medicine, 9*(1), 60-65. doi:10.1002/jhm.2116

Jin R, Zelinka ES, McDonald J, Byrnes T, Grunkemeier GL, Brevig J., (2013). Effect of Hospital Culture on Blood Transfusion in Cardiac Procedures. *Annals of Thoracic Surgery*, 95(4):1269-74.

Karkouti, K. (2012). Transfusion and risk of acute kidney injury in cardiac surgery. *British Journal of Anaesthesia, 109*, i38. doi:10.1093/bja/aes422

Khan, B. A., Khan, S. H., Devnani, R., LaPradd, M., Landrigan, M., Gray, A., . . . Li, X. (2018). Age of transfused red blood cells and health outcomes in two surgical cohorts. *Heart & Lung,* doi:10.1016/j.hrtlng.2018.08.012

Kindzelski, B. A., Corcoran, P., Siegenthaler, M. P., & Horvath, K. A. (2018). Postoperative acute kidney injury following intraoperative blood product transfusions during cardiac surgery. *Perfusion, 33*(1), 62-70. doi:10.1177/0267659117712405

Koch, C. G., Li, L., Sessler, D. I., Figueroa, P., Hoeltge, G. A., Mihaljevic, T., & Blackstone, E. H. (2008). Duration of red-cell storage and complications after cardiac surgery. *The New England Journal of Medicine, 358*(12), 1229-1239. doi:10.1056/NEJMoa070403

LaPar, D. J., Hawkins, R. B., McMurry, T. L., Isbell, J. M., Rich, J. B., Speir, A. M., . . . Ailawadi, G. (2018). Preoperative anemia versus blood transfusion: Which is the culprit for worse outcomes in cardiac surgery? *The Journal of Thoracic and Cardiovascular Surgery, 156*(1), 74.e2. doi:10.1016/j.jtcvs.2018.03.109

Lelubre, C., & Vincent, J. (2013). Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: A systematic review. *Critical Care, 17*(2), R66. doi:10.1186/cc12600

Likosky, D. S., Baker, R. A., Newland, R. F., Paugh, T. A., Dickinson, T. A., Fitzgerald, D., . . . Willcox, T. W. (2018). Is conventional bypass for coronary artery bypass graft surgery a misnomer? *The Journal of Extra-Corporeal Technology, 50*(4), 225. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30581229

Likosky, D. S., Paugh, T. A., Harrington, S. D., Wu, X., Rogers, M. A. M., Dickinson, T. A., . . . Pane, G. (2017). Prediction of transfusions after isolated coronary artery bypass grafting surgery. *Ann Thorac Surg,* (103), 764-72. doi:10.1016/j.athoracsur.2016.07.009

Likosky, D. S., Dickinson, T. A., & Paugh, T. A. (2016). Blood conservation-A team sport. *The Journal of Extra-Corporeal Technology, 48*(3), 99. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27729702

Likosky DS, Zhang M, Paone G, Collins DA, Schreiber T, Theurer P, Kazziha S, Leffler D, Wunderly DJ, Gurm HS, Prager RL, (2015). Impact of institutional culture on rates of transfusions during cardiovascular procedures: The Michigan experience. *American Heart Journal*, 174:1-6.

Likosky, D. S., FitzGerald, D. C., Groom, R. C., Jones, D. K., Baker, R. A., Shann, K. G., . . . Body, S. C. (2010). The effect of the perioperative blood transfusion and blood conservation in cardiac surgery clinical practice guidelines of the society of thoracic surgeons and the society of cardiovascular anesthesiologists upon clinical practices. *The Journal of Extra-Corporeal Technology, 42*(2), 114. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20648895

Lobel, G. P., Javidroozi, M., & Shander, A. (2015). Risks of anemia in cardiac surgery patients. *Seminars in Cardiothoracic and Vascular Anesthesia, 19*(4), 288-292. doi:10.1177/1089253215613792

Loor G, Koch CG, Sabik JF, Li L, Blackstone EH. (2012). Implications and management of anemia in cardiac surgery: Current state of knowledge. *Journal of Thoracic and Cardiovascular Surgery, The, 144*(3), 538-546. doi:10.1016/j.jtcvs.2012.04.014

Mazer, C. D., Whitlock, R. P., Fergusson, D. A., Hall, J., Belley-Cote, E., Connolly, K., . . . Shehata, N. (2017). Restrictive or liberal red-cell transfusion for cardiac surgery. *The New England Journal of Medicine, 377*(22), 2133-2144. doi:10.1056/NEJMoa1711818

McQuilten ZK, Andrianopoulos N, Wood EM, Cole-Sinclair MF, McNeil, JJ, Cameron PA, Reid CM, Newcomb AE, Smith JA, Phillips LE. (2014). Transfusion practice varies widely in

cardiac surgery: Results from a national registry. *Journal of Thoracic and Cardiovascular Surgery, The, 147*(5), 1690.e1. doi:10.1016/j.jtcvs.2013.10.051

Maxwell, MJ, Wilson, MJA, (2006). Complications in blood transfusion. *Continuing Education in Anaesthesia Critical Care & Pain*, 6(6):225-229. https://doi.org/10.1093/bjaceaccp/mkl053

Menkis, A. H., Martin, J., Cheng, D. C. H., Fitzgerald, D. C., Freedman, J. J., Gao, C., . . . Ad, N. (2012). Drug, devices, technologies, and techniques for blood management in minimally invasive and conventional cardiothoracic surgery: A consensus statement from the international society for minimally invasive cardiothoracic surgery (ISMICS) 2011. *Innovations (Philadelphia, Pa.), 7*(4), 229-241. doi:10.1097/IMI.0b013e3182747699

Merlo J, Chaix B, Ohlsson H, Beekman A, Johnell K, Hjerpe P, . . . Larsen K., (2006). A brief conceptual tutorial of multilevel analysis in social epidemiology: Using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *Journal of Epidemiology and Community Health (1979-), 60*(4), 290-297. doi:10.1136/jech.2004.029454

Moskowitz, D. M., Klein, J. J., Shander, A., Cousineau, K. M., Goldweit, R. S., Bodian, C., . . . Ergin, M. A. (2004). Predictors of transfusion requirements for cardiac surgical procedures at a blood conservation center. *The Annals of Thoracic Surgery, 77*(2), 626. Retrieved from http://ats.ctsnetjournals.org/cgi/content/abstract/77/2/626

Murphy, G. J., Pike, K., Rogers, C. A., Wordsworth, S., Stokes, E. A., Angelini, G. D., & Reeves, B. C. (2015). Liberal or restrictive transfusion after cardiac surgery. *The New England Journal of Medicine, 372*(11), 997-1008. doi:10.1056/NEJMoa1403612

Murphy, G. J., Reeves, B. C., Rogers, C. A., Rizvi, S. I. A., Culliford, L., & Angelini, G. D. (2007). Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation, 116*(22), 2544. doi:10.1161/CIRCULATIONAHA.107.698977

Paone, G., Likosky, D. S., Brewer, R., Theurer, P. F., Bell, G. F., Cogan, C. M., & Prager, R. L. (2014). Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *The Annals of Thoracic Surgery, 97*(1), 94. doi:10.1016/j.athoracsur.2013.07.020

Patel, N. N., & Murphy, G. J. (2018). Restrictive transfusion practice in cardiac surgery patients is safe, but what transfusion threshold is safe for my patient? *European Heart Journal,* doi:10.1093/eurheartj/ehy505

Paugh, T. A., Dickinson, T. A., Theurer, P. F., Bell, G. F., Shann, K. G., Baker, R. A., . . . Likosky, D. S. (2012b). Validation of a perfusion registry: Methodological approach and initial findings. *The Journal of Extra-Corporeal Technology, 44*(3), 104. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23198390

Pfunter A, Wier LM, Stocks C. (2013). *Most frequent procedures performed in U.S. hospitals, 2010. the HCUP report : Healthcare cost and utilization project (HCUP): Statistical briefs;2013 ASI 4186-20.149;statistical brief no. 149.* (). Retrieved from https://statistical.proquest.com/statisticalinsight/result/pqpresultpage.previewtitle?docType=PQSI&titleUri=/content/2013/4186-20.149.xml

Qian, F., Osler, T. M., Eaton, M. P., Dick, A. W., Hohmann, S. F., Lustik, S. J., . . . Glance, L. G. (2013). Variation of blood transfusion in patients undergoing major noncardiac surgery. *Annals of Surgery, 257*(2), 266-278. doi:10.1097/SLA.0b013e31825ffc37

Rao, S. V., Eikelboom, J. A., Granger, C. B., Harrington, R. A., Califf, R. M., & Bassand, J. (2007). Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. *European Heart Journal, 28*(10), 1193-1204. doi:10.1093/eurheartj/ehm019

Refaai, M. A., & Blumberg, N. (2013). The transfusion dilemma--weighing the known and newly proposed risks of blood transfusions against the uncertain benefits. *Best Practice & Research. Clinical Anaesthesiology, 27*(1), 17. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23590913

Salaria, O., Barodka, V., Hogue, C., Berkowitz, D., Ness, P., Wasey, J., & Frank, S. (2014). Impaired red blood cell deformability after transfusion of stored allogeneic blood but not autologous salvaged blood in cardiac surgery patients. *Anesthesia & Analgesia, 118*(6), 1179-1187. doi:10.1213/ANE.0000000000000227

Schneider B, Ehrhart MG, Macey WH., (2013). Organizational Climate and Culture. *Annual Review of Psychology*, 64(1):361-88.

Shander, A., Hofmann, A., Ozawa, S., Theusinger, O. M., Gombotz, H., & Spahn, D. R. (2010). Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion, 50*(4), 753-765. doi:10.1111/j.1537-2995.2009.02518.x

Shah A, Stanworth SJ, McKechnie S., (2015). Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia*, 70(s1):e3.

Sharma S, Sharma P, Tyler LN. (2011). Transfusion of blood and blood products: Indications and complications. *American Family Physician, 83*(6), 719-724. Retrieved from https://www.clinicalkey.es/playcontent/1-s2.0-S0002838X1160097X

Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, Scott DA, Hare GMT, Jüni P, Mazer CD, (2019). Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis, *European Heart Journal*, 40(13), 1081–1088.

Shehata N, Naglie G, Alghamdi AA, Callum J, Mazer CD, Hebert P, et al, (2007). Risk factors for red cell transfusion in adults undergoing coronary artery bypass surgery: a systematic review. *Vox Sanguinis*, 93(1):1-11.

Sim V, Kao LS, Jacobson J, Frangos S, Brundage S, Wilson CT, Simon R, Glass NE, Pachter HL, Todd SR, (2015). Can old dogs learn new "transfusion requirements in critical care": a survey of packed red blood cell transfusion practices among members of The American Association for the Surgery of Trauma. *The American Journal of Surgery*, 1(210):45-51.

Silvain, J., Pena, A., Cayla, G., Brieger, D., Bellemain-Appaix, A., Chastre, T., . . . Montalescot, G. (2010). Impact of red blood cell transfusion on platelet activation and aggregation in healthy volunteers: Results of the TRANSFUSION study. *European Heart Journal, 31*(22), 2816-2821. doi:10.1093/eurheartj/ehq209

Snyder-Ramos, S. A., Möhnle, P., Weng, Y., Böttiger, B. W., Kulier, A., Levin, J., & Mangano, D. T. (2008). The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion, 48*(7), 1284-1299. doi:10.1111/j.1537-2995.2008.01666.x

Speiss, B. D. (2002). Transfusion and outcome in heart surgery. *The Annals of Thoracic Surgery, 74*(4), 986. Retrieved from http://ats.ctsnetjournals.org/cgi/content/extract/74/4/986

Spiess, B. D. (2004). Transfusion of blood products affects outcome in cardiac surgery. *Seminars in Cardiothoracic and Vascular Anesthesia, 8*(4), 267-281. doi:10.1177/108925320400800402

Surgenor, S. D., DeFoe, G. R., Fillinger, M. P., Likosky, D. S., Groom, R. C., Clark, C., . . . O'Connor, G. T. (2006). Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. *Circulation, 114*(1 Suppl), 48. doi:10.1161/CIRCULATIONAHA.105.001271

Surgenor, S. D., Kramer, R. S., Olmstead, E. M., Ross, C. S., Sellke, F. W., Likosky, D. S., . . . O'Connor, G. T. (2009). The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. *Anesthesia and Analgesia, 108*(6), 1741-1746. doi:10.1213/ane.0b013e3181a2a696

Tempe, D. K., & Khurana, P. (2018). Optimal blood transfusion practice in cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia,* doi:10.1053/j.jvca.2018.05.051

The Michigan Society of Thoracic Cardiovascular Surgeons and The MSTCVS Quality Collaborative. (2018). About PERForm. Retrieved from: https://mstcvs.org/home/perform-registry/

The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris, V. A., Ferraris, S. P., Saha, S. P., Hessel, E. A., II, Haan, C. K., . . . Body, S. (2007). Perioperative blood transfusion and blood conservation in cardiac surgery: The society of thoracic surgeons and the society of cardiovascular anesthesiologists clinical practice guideline. *The Annals of Thoracic Surgery, 83*(5_Supplement), S86. doi:10.1016/j.athoracsur.2007.02.099

The Joint Commission & the American Medical Association. (2012). Proceedings from the national summit on overuse. Retrieved from https://www.jointcommission.org/assets/1/6/National_Summit_Overuse.pdf

Transfusion medicine reviews. *Transfusion Medicine Reviews,*

Varghese, R., & Jhang, J. (2015). Blood conservation in cardiac surgery. *Seminars in Cardiothoracic and Vascular Anesthesia, 19*(4), 293-301. doi:10.1177/1089253215613807

Vlaar, A. P. J., Cornet, A. D., Hofstra, J. J., Porcelijn, L., Beishuizen, A., Kulik, W., . . . Juffermans, N. P. (2012). The effect of blood transfusion on pulmonary permeability in cardiac surgery patients: A prospective multicenter cohort study. *Transfusion, 52*(1), 82-90. doi:10.1111/j.1537-2995.2011.03231.x

Wang, D., Sun, J., Solomon, S. B., Klein, H. G., & Natanson, C. (2012). Transfusion of older stored blood and risk of death: A meta-analysis. *Transfusion, 52*(6), 1184-1195. doi:10.1111/j.1537-2995.2011.03466.x

World Health Organization. (2018). Processing of donated blood . Retrieved from http://www.who.int/bloodsafety/processing/en/

Zou G, (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*, 159(7):702-706.

FIGURES AND TABLES

Figure 1: Early and Late Complications reported from Blood Transfusions (adapted from Maxwell & Wilson, 2006)

Early Reactions	Late Reactions
Hemolytic reactions	Viral transmission of infection
Non-hemolytic febrile reactions	Bacterial transmission
Allergic reactions to proteins, IgA	Parasitic transmission
Transfusion-related acute lung injury (TRALI)	Graft versus host disease
Bacterial contamination	Iron overload
Circulatory overload	Immune sensitization
Air embolism	
Thrombophlebitis	
Hyperkalemia	
Citrate toxicity	
Hypothermia	
Clotting abnormalities	

Figure 2: The effect of preoperative anemia on postoperative outcome (Loor et al, 2012)

TABLE 1. Investigations examining effect of preoperative anemia on postoperative outcomes

Investigation	Design	n	Effect
Zindrou et al[6]	Observational	2059	Increased mortality
Hung et al[3]	Observational	2688	Increased transfusion requirement, ICU stay, and mortality
van Straten et al[5]	Observational	10,626	Increased mortality
Ranucci et al[7]	Observational	3003	Prolonged ventilation, renal insufficiency, stroke, reoperations
Karkouti et al[9]	Observational	3500	Increased in-hospital death, stroke, or acute kidney injury
Kulier et al[4]	Observational	5065	Neurologic, renal, and GI complications
De Santo et al[8]	Observational	1214	Postoperative renal insufficiency
Kazmierski et al[10]	Observational	563	Postoperative delirium

ICU, Intensive care unit; *GI,* gastrointestinal.

Figure 3: Adverse events and anemia management. (Loor et al, 2012)

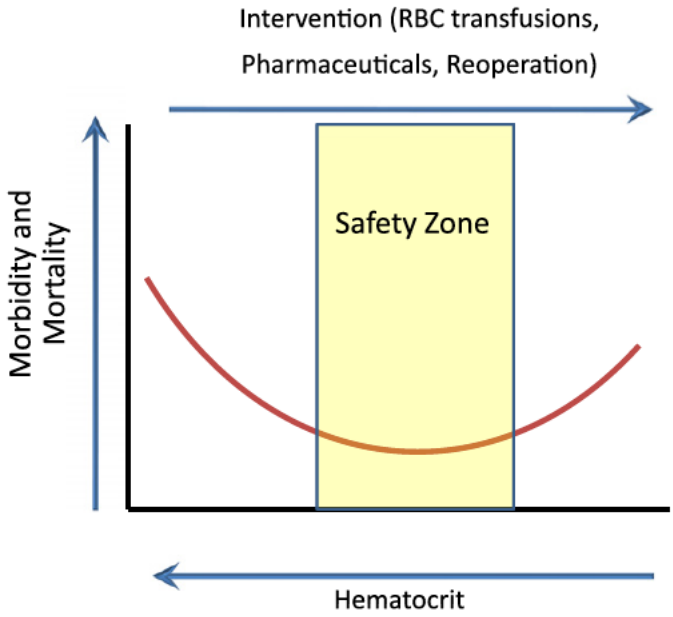
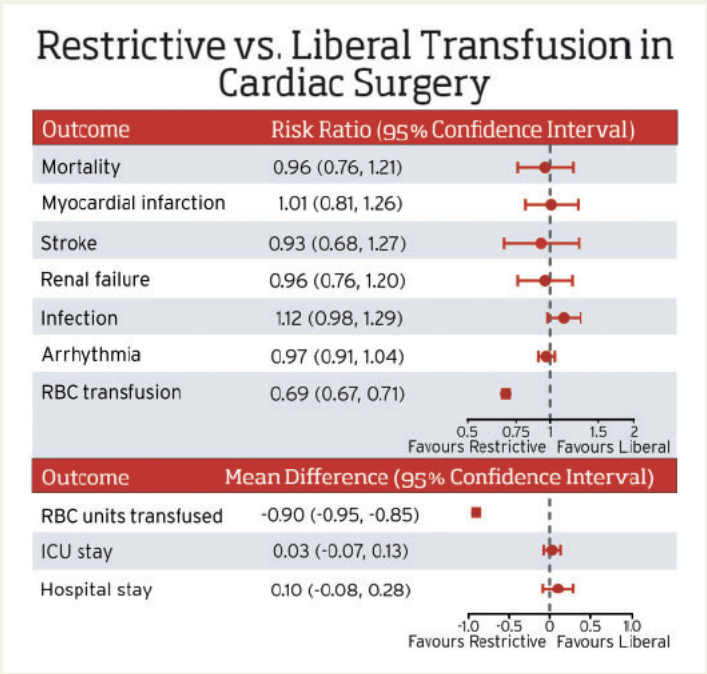


FIGURE 4. Pictorial representation of a U-shaped relationship that exists between adverse events related to degree of anemia on the left and degree of intervention on the right. The "safety zone" at the bottom of the curve reflects a balance between tolerable anemia and interventions to correct anemia. *RBC*, Red blood cell.

Figure 4: Restrictive vs Liberal Transfusion in Cardiac Surgery (Shehata et al, 2019)



Take home figure The current evidence suggests restrictive transfusion strategies are not inferior to liberal transfusion strategies in adult and pediatric patients undergoing cardiac surgery. RBC indicates red blood cell; ICU indicates intensive care unit. ICU stay and hospital stay are reported as days.

Figure 5. Selection criteria for study population inclusion

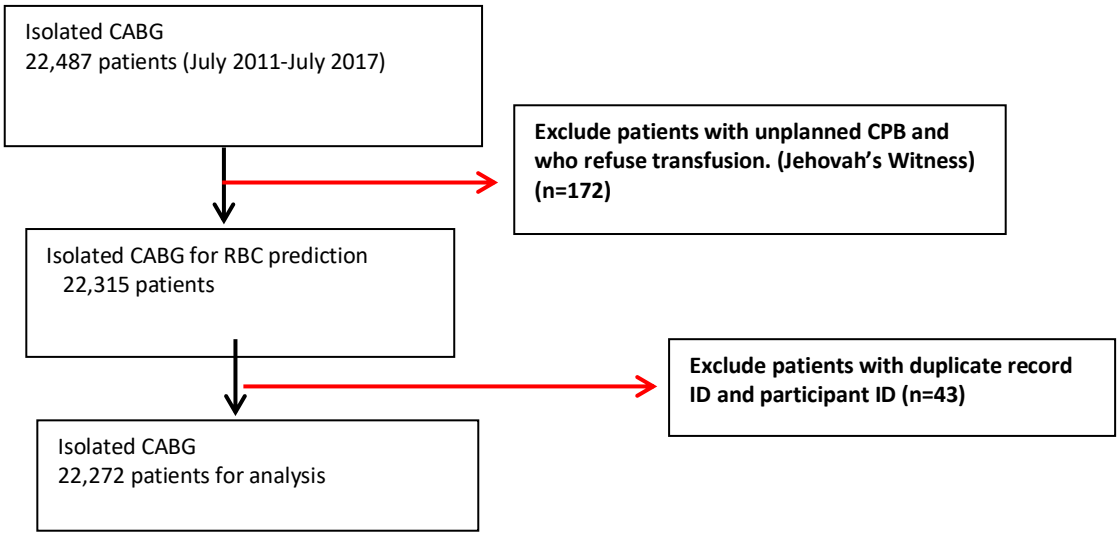


Table 1: *Multivariable Logistic Regression Models of RBC Transfusion Variables*

	Description	Covariates
Model 1	Hospital random intercepts only	None
Model 2	Model 1 + Patient demographic, laboratory assay results, and preoperative risk factors	- Model 1 - Age (years) - Body Surface Area (m^2) - Sex (M/F) - Admission status (elective, urgent, emergent/salvage) - Preoperative Hematocrit (%) - Serum Albumin (g/dl) - Serum Creatinine (mg/dl) - Platelet count (x 10,000) - Current smoker (y/n) - Chronic lung disease (y/n) - Previous MI (y/n) - Congestive Heart Failure (y/n) - Cardiogenic Shock (y/n) - Peripheral Vascular Disease (y/n) - Cerebrovascular disease (y/n) - Diabetes Mellitus (y/n) - Dialysis (y/n) - Hypertension (y/n) - Anticoagulant medications <48 hrs (y/n) - Reoperative status (y/n) - Number of diseased vessels
Model 3	Model 1 + Intraoperative Blood Conservation Procedural Factors	- Model 1 - Arterial Roller Pump Use (y/n) - Acute Normovolemic Hemodilution (ANH) (y/n) - del Nido cardioplegia use (y/n) - Autotransfusion use (y/n) - Autologous CPB circuit prime (y/n) - Indexed Net CPB Prime (ml/m^2)
Model 4	(Hospital random intercepts) + (Patient demographic, laboratory assay results, and preoperative risk factors) + (Intraoperative Blood Conservation Procedural Factors)	- Model 1 - Model 2 - Model 3