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PII: S0890-5096(22)00446-0

DOI: https://doi.org/10.1016/j.avsg.2022.07.004

Reference: AVSG 6431

To appear in: *Annals of Vascular Surgery*

Received Date: 20 April 2022

Revised Date: 23 June 2022

Accepted Date: 3 July 2022

Please cite this article as: Matthay ZA, Smith EJ, Flanagan CP, Wu B, Malas MB, Hiramoto JS, Conte MS, Iannuzzi JC, Association of Intraoperative and Perioperative Transfusions with Postoperative Cardiovascular Events and Mortality after Infrainguinal Revascularization, *Annals of Vascular Surgery* (2022), doi: https://doi.org/10.1016/j.avsg.2022.07.004.

Association of Intraoperative and Perioperative Transfusions with Postoperative Cardiovascular Events and Mortality after Infrainguinal Revascularization

Short Title: Transfusions and Cardiovascular Events after Infrainguinal Revascularization

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Presentation Information: This study was presented at the Karmody ePoster Competition at the 48th Annual Symposium of the Society for Clinical and Vascular Surgery, Miami, Fl, March 2021.

Disclosures: The authors report no relevant conflicts of interest

Article Highlights

Type of Research: single center retrospective cohort study

Key Findings: Among 564 patients undergoing open or endovascular infrainguinal revascularization, intraoperative transfusion was associated with a more than four fold increased adjusted odds ($p<0.01$) of cardiovascular events with rates of 13% vs 4% among those transfused vs not transfused intraoperatively, independent of other risk factors including revised cardiac risk index, age, blood loss, and procedure type (open versus endovascular).

Take home Message: In patients undergoing open or endovascular infrainguinal revascularization, intraoperative transfusion is significant independent risk factor for adverse postoperative cardiovascular events.

Abstract

Background: Patients undergoing open or endovascular infrainguinal revascularization are at elevated risk for postoperative cardiovascular complications due to high rates of comorbidities and the physiologic stress of surgery. Transfusions are known to be associated with adverse events, but knowledge of specific risks associated with transfusion timing, product type, and long-term outcomes while accounting for preoperative cardiovascular risk factors is not well understood in this population.

Aim: This study aimed to characterize the association of intraoperative and perioperative transfusion, anemia, and cardiovascular risk factors with cardiovascular events and mortality in patients undergoing infrainguinal revascularization.

Methods: A single-center retrospective study was performed on 564 infrainguinal revascularization procedures, including both open (n=250) and endovascular (n=314) approaches (2016-2020). Comprehensive clinical data were collected including patient demographics, cardiovascular risk factors, preoperative hemoglobin, and detailed transfusion data. Multivariable logistic regression tested the association of transfusions with composite 30-day outcomes of cardiac complications (postoperative myocardial infarction [postop-MI], congestive heart failure [CHF], or dysrhythmia) and with major adverse cardiovascular events (MACE- postop-MI or death). Kaplan-Meier analysis and cox-proportional hazard modeling examined the association of transfusions, anemia, and cardiovascular risk factors with mortality up to 1 year.

Results: Intraoperative transfusion was performed in 15% of cases and 13% underwent transfusion in the early postoperative period. Intraoperative transfusion was associated with higher Revised Cardiac Risk Index (RCRI), lower preoperative hemoglobin, increased blood loss and open procedures (all $p<0.05$). Within each RCRI score, intraoperative transfusion was associated with

2-4 fold increased MACE at 30 days. Intraoperative pRBC transfusion and early postoperative pRBC transfusion was associated with more than 2-fold adjusted odds of any cardiovascular complication and intraoperative transfusion was also associated with MACE (all $p<0.05$). Intraoperative transfusion was associated with mortality at one year on unadjusted analysis, but after adjustment for RCRI, age, and preoperative hemoglobin, only RCRI scores of 2 and 3+ and preoperatively hemoglobin remained significant risk factors for mortality.

Conclusions: Intraoperative and early perioperative transfusions are strongly associated with worse cardiovascular outcomes after infrainguinal revascularization. These findings may have prognostic value for further risk stratifying patients perioperatively at high risk for complications. However, prospective studies are needed to elucidate whether optimizing transfusion strategies mitigates these risks.

Keywords: blood transfusion, myocardial infarction, peripheral arterial disease, perioperative care

Background

Due to high rates of cardiovascular comorbidities, chronic kidney disease, and advanced age, patients undergoing infrainguinal revascularization for peripheral artery disease are at high risk for postoperative cardiovascular complications and death.[1,2] Preoperative risk stratification with the revised cardiac risk index (RCRI) is a validated tool to estimate perioperative cardiovascular risk based on comorbidities and the anticipated physiologic stress of the procedure.[3] The RCRI is known to perform less well specifically in patients undergoing vascular surgery compared to other non-cardiac surgical procedures and may underestimate patient risk for this population.[4,5] Consideration of additional preoperative and perioperative risk factors may better guide surgeons in assessing risk of cardiovascular events after vascular surgery.

Transfusion of packed red blood cells (pRBCs) and anemia are two important factors known to be associated with cardiovascular complications across vascular procedures, but knowledge regarding the harms versus benefits of specific transfusion strategies is evolving.[6–9] Furthermore, the impact of transfusion timing and the risks associated with platelets and fresh frozen plasma (FFP) are not well characterized in this population. Additional study is needed to understand the relationship of postoperative cardiovascular events with transfusions, preoperative anemia, blood loss, and the RCRI risk factors in patients undergoing infrainguinal revascularization.

Better understanding the specific risks associated with transfusion of blood products and timing may help guide transfusion strategies, post-operative monitoring of cardiac enzymes, and the level of care appropriate for high-risk patients after infrainguinal revascularization. In this study, we aimed to better characterize the impact of transfusions on cardiovascular events up to 30 days after infrainguinal revascularization, hypothesizing that intraoperative transfusions would be

most associated with adverse events. We further aimed to examine the longer-term relationship of preoperative anemia and perioperative transfusions with mortality up to 1 year after infrainguinal revascularization.

Methods:

A single-center retrospective study was performed on 564 infrainguinal revascularization procedures, including both open/hybrid (n=250) and endovascular (n=314) approaches, for disabling claudication or chronic limb threatening ischemia (2016-2020). Comprehensive patient characteristics and clinical outcomes were recorded by chart review on all patients. Complete transfusion data of pRBCs, platelets, and FFP were obtained from an institutional blood bank database and matched to each patient's record. Intraoperative transfusion was defined as transfusion of any blood product during surgery, while early perioperative transfusions were defined as transfusion of blood products postoperatively within 48 hours. Postoperative myocardial infarction (MI) was defined as a rise in troponin above the 99th percentile with at least one of the following: documented EKG changes consistent with ischemia, associated ischemic symptoms, or imaging findings consistent with myocardial infarction.[10] Congestive heart failure (CHF) exacerbations were defined as documented CHF exacerbation requiring treatment or monitoring in a higher level of care (telemetry unit or intensive care unit) or readmission after discharge within 30 days. New onset dysrhythmias were defined as onset of new symptomatic cardiac rhythm disturbance requiring medical treatment or intervention.

Bivariate analyses compared demographics and outcomes by those transfused any blood product intraoperatively using Student's t-tests for continuous and normally distributed variables, Wilcoxon-rank sum tests for continuous and skewed variables, and chi squared tests for categorical variables. Multivariable logistic regression tested the associations of transfusions (pRBCs,

platelets, and FFP) with composite outcomes at 30 days: 1) Major adverse cardiovascular event (MACE), defined as postop-MI or death, and 2) Any cardiac complication: Postoperative myocardial infarction (postop-MI), congestive heart failure (CHF), or dysrhythmia (postop-MI/CHF/dysrhythmia). To build our multivariable models, we identified known cardiovascular risk factors as well as potential confounders in the relationship between transfusions and post-operative cardiovascular events including the Revised Cardiac Risk Index, age, estimated blood loss, open versus endovascular approach, preoperative hemoglobin, and indication (chronic limb threatening ischemia versus claudication). We then used forward stepwise logistic regression with $p<0.3$ as criteria for inclusion in the model to develop the final models.

Lastly, Kaplan-Meier analysis and cox-proportional hazard modeling examined the association of transfusions, preoperative hemoglobin, age, and the RCRI score with survival with follow-up time up to 1 year. Schoenfeld residuals testing confirmed there were no violations of the proportional hazards assumption in our models. All data analysis was performed in Stata version 15 (StataCorps, Texas). This study was approved by the institutional review board at the University of California, San Francisco (study number 20-30624). Informed consent was waived due to the retrospective and minimal risk nature of this study.

Results

Overall, mean age was 70 ($\pm$11) years, 66% were male, and cardiovascular comorbidities were common including 32% with coronary artery disease and 18% with congestive heart failure (Table I). Thirty two percent of patients had insulin dependence, a smaller proportion had a history of stroke/TIA (12%), and CKD-5 or creatinine>2 (13%) (Table I). When comparing patients by their RCRI risk factors, most patients (63%) had a at least one risk factor- 33% with just one, 19% with two, and 11% had three or more (Table I). Transfusion occurred intraoperatively in 15% of

cases, 13% were transfused pRBCs in the first 48 hours postoperatively, while less than 5% were transfused PLT and FFP in the intra or postoperative period (Supplemental Figure 1). Those who were transfused intraoperatively were more likely to have a history of CAD, insulin dependence, and undergo an open procedure (all p<0.01, Table I). Transfusion was associated with lower preoperative hemoglobin (11.7 vs 10.5g/dL) and higher estimated blood loss (median of 20ml vs 300ml) (both p<0.01) (Table I). Those transfused intraoperatively also had increased 30-day rates of postoperative myocardial infarction and dysrhythmia and composite outcomes of postop-MI/CHF/dysrhythmia and MACE at 30 days, as well as increased mortality at 1 year (all p<0.05) (Table I).

To further describe the incidence of postoperative cardiovascular events among those who were transfused, we examined rates of MACE stratified by intraoperative transfusion and RCRI scores. This demonstrated that while rates of MACE increased in stepwise fashion with higher RCRI scores, rates were higher for each corresponding RCRI score in the transfused group (Figure 1). For each RCRI score, comparing those not transfused to those transfused intraoperatively, rates of MACE were 1.1% (2/186) vs 7.4% (2/27) (p=0.02) for scores of 0, 3.3% (5/153) vs 12.5% (4/32) (p=0.03) for scores of 1, 6.6% (8/91) vs 14 .3% (2/14) (p=0.31) for scores of 2, and 12.0% (6/50) vs 27.3% (3/11) (p=0.19) for scores of 3+ (Figure 1).

On unadjusted logistic regression, intraoperative transfusion, early postoperative transfusion, and any transfusion of FFP and PLTs were all significantly associated with both MACE and postop-MI/CHF/dysrhythmia (all p<0.05, Supplemental Table I). When examining the RCRI risk factors individually, a history of CAD and CHF were both significantly associated with MACE and postop-MI/CHF/dysrhythmia (all p<0.01), a history of CKD-5/creatinine>2 was significantly associated with MACE (p<0.01), but prior stroke/TIA and insulin dependent diabetes

mellitus were not associated with either outcome (Supplemental Table I). The total number of RCRI risk factors showed significant increasing odds of both MACE and postop-MI/CHF/dysrhythmia- those with 3 or more risk factors had 9-fold increased odds of MACE and 7-fold increased odds of postop-MI/CHF/dysrhythmia (both $p<0.01$, Supplemental Table I. Lastly, age>80 and open procedures were associated with increased odds of any cardiovascular complication but not with MACE, while estimated blood loss >200 ml was associated with MACE (Supplemental Table I).

We then performed multivariable logistic regression to test the association of intraoperative and postoperative transfusions with cardiovascular events, adjusting for age, RCRI score, and blood loss. Both intraoperative transfusion and early postoperative transfusion were associated increased adjusted odds of postop-MI/CHF/dysrhythmia (ORs 2.5; CI 1.1-5.7 and 2.1; CI 0.9-4.7, respectively) and intraoperative transfusion but not postoperative transfusion was associated with increased adjusted odds of MACE at 30 days (OR 4.7; CI 1.7-13.2) (Figure 2a and 2b, supplemental table II). Transfusion of FFP was significantly associated with increased odds of MACE (OR 6.6; CI 2.3-18.7) and with increased odds of MI, CHF, or dysrhythmia (OR 2.8; CI 1.0-7.8) (Figure 2a and 2b, supplemental table II). Platelet transfusions were not independently associated with MI, CHF, or dysrhythmia and MACE (Figure 2a and 2b, supplemental table II).

Lastly, we examined the association of transfusions with survival time (up to 1 year) to better understand the relationship between transfusion status, cardiovascular risk factors, and lower hemoglobin with mortality. Median follow up time was 390 days (IQR 120-759 days). Intraoperative transfusion was significantly associated with survival time (up to 1 year) on Kaplan Meier analysis (log-rank p=0.01) (Figure 3). The RCRI score stratified patients well: the group with no RCRI risk factors had lowest mortality at 3.2% (CI 2.6-6.8%), followed by 6.5% (CI 3.7-

11.1%), 10.5% (CI 5.9-18.1%), and 14.8% (CI 8.0-26.4%) for the groups with 1, 2, and 3 or more RCRI risk factors respectively (log rank $p<0.01$, figure 4). On multivariable cox proportional hazard modeling, intraoperative transfusion was no longer statistically significantly associated with increased mortality (HR 1.74; CI 0.84-3.60), but presence of 2 RCRI risk factors (HR 3.2; CI 1.2-8.4) and 3 or more RCRI risk factors (HR 4.8, CI 1.7-13.1) as well as lower preoperative hemoglobin (HR 0.8; CI 0.7-1.0) were each independently associated with mortality (Table II).

Discussion

In this study, we identified the relationships between intraoperative and early postoperative blood product transfusions with adverse cardiovascular events after lower extremity revascularization. These relationships remained significant even after adjustment for the RCRI risk factors, age, hemoglobin, blood loss, and the presence of chronic limb threatening ischemia, suggesting transfusions are an important independent perioperative risk factor for cardiovascular complications in this population. These findings are generally consistent with prior studies demonstrating associations of pRBC transfusions with adverse cardiovascular events after vascular surgery.[8,9,11,12] We further build upon this knowledge base by additionally examining specific risks associated with FFP and platelet transfusions and adjusting for the RCRI score. Additionally, we report the longer-term mortality associated with increasing number of RCRI risk factors and lower preoperative hemoglobin.

In one of the larger studies examining transfusions after common vascular procedures, Obi *et al*. identified that perioperative blood transfusion was associated with a 7-8 fold increased adjusted odds of death and myocardial infarction up to 30 days post procedure, though they did not compare intraoperative versus postoperative transfusion in their multivariable analysis.[12] In a more recent study by Heafner *et al*., the authors did examine differences in intraoperative versus

postoperative transfusions with the risk of postoperative myocardial infarction.[9] Those receiving intra- and post-operative transfusions as well those receiving only postoperative transfusions had significantly increased risk of postoperative MI, but this relationship did not reach statistical significance for the group only transfused intraoperatively.[9] This is in contrast to the findings reported in this study demonstrating intraoperative transfusion were associated with 2.5-4 fold increased adjusted odds of MACE and postop MI/CHF/dysrhythmia, but the association was less pronounced (although still significant) for early postoperative transfusion. These interstudy differences may be due distinct study populations- this analysis only included those undergoing lower extremity revascularization, while Heafner *et al*. additionally included a large proportion of aortic aneurysm repairs. Given the very high rate of blood transfusions during open AAA repairs, intraoperative transfusion may be a less discriminatory risk factor for cardiovascular complications compared to transfusion during infrainguinal vascular procedures which is a less common occurrence (15% in this study).

Few studies have specifically examined the association of transfusions with cardiovascular complications in patients undergoing infrainguinal procedures.[8,11] A NSQIP analysis of open lower extremity revascularization identified intraoperative transfusion as an independent risk factor for 30-day mortality, as well as for a composite outcome of any major postoperative complication.[8] A large retrospective study of using VQI data by Osborne *et al*. similarly identified associations of pRBC transfusion with both mortality and postop-MI after lower extremity bypass on multivariable analysis, though data on transfusion timing was not available.[11] We additionally included endovascular infrainguinal revascularization in this analysis, though notably, open versus endovascular approach did not modify the association of transfusions with MACE or postop MI/CHF/dysrhythmia on sensitivity analysis.

While this study and others support that perioperative transfusion is an important independent risk factor for cardiovascular events after vascular surgery, it is less clear what the mechanistic pathway is. These findings are consistent with multiple hypotheses including: residual confounding related to sicker patients requiring transfusions, the association of transfusions with more complex and physiologically stressful procedures, or potential harms directly attributable to transfusions themselves. In the setting of significant blood loss, the benefits of transfusions include correction of anemia and restoration of intravascular blood volume that may improve oxygen delivery and minimize myocardial ischemia. However, transfusions may also put patients at risk for transfusion associated circulatory overload that may precipitate CHF exacerbations, dysrhythmias, or increase myocardial stress, particularly in patients with underlying heart and renal disease.[13,14] Paradoxically, some studies have demonstrated reduced oxygen delivery in response to red blood cell transfusions, particularly in blood with prolonged storage time.[15,16] The transfusions administered in this study were administered at the discretion of the treating surgeon and anesthesiologist and not according to a rigid institutional protocol. Therefore, inferences about specific transfusion thresholds cannot be inferred from this study's findings. However, current studies are underway to better delineate the optimal hemoglobin transfusion threshold in vascular surgery patients.

This study also highlights the important impact of the RCRI risk factors on rates of cardiovascular complications and death in the setting of transfusions. A large prospective study examining the RCRI criteria found event rates of 2.2% for RCRI of 0, 8.2% for RCRI of 1, 5.3% for RCRI of 2, and 36% for RCRI of $\geq$3.[4] Our findings demonstrate comparable trends with 30-day rates of MACE of 1.8%, 4.9%, 7.6%, and 14.8% for RCRI scores of 0, 1, 2, and $\geq$3 respectively. However, these rates were strongly impacted by transfusion status- rates of MACE

were 2-4 fold higher in each RCRI score group when transfused intraoperatively. These data could be used to inform perioperative monitoring for cardiovascular events and further risk stratify patients. Additionally, RCRI scores of 2 and 3+ and preoperative hemoglobin were all significantly associated with longer term mortality up to 1 year in this analysis on multivariable regression, further reinforcing the value of these measures as independent risk factors for poor outcome in patients undergoing vascular surgery.[4,7,17–19]

There are several important limitations to consider for this study. First, this is a retrospective analysis and therefore subject to additional unmeasured confounders not accounted for in our analysis. While transfusions are known to be associated with adverse cardiovascular events, it is not possible in this analysis to determine to what extent the cardiovascular events are attributable to transfusions themselves versus the associated physiologic stress, preoperative anemia, and blood loss of the procedures performed. Prospective, randomized controlled trials are needed to better define optimal transfusion strategies in patients undergoing infrainguinal revascularization, which may be especially relevant in non-urgent settings where preoperative correction of anemia with transfusion may be feasible. The sample size is relatively modest and the results in several our multivariable models have wide confidence intervals which may suggest a lack of statistical power (especially for examining platelet and FFP transfusions) and some degree of model overfitting which is another limitation of this retrospective study. This analysis included both open and endovascular procedures increasing its generalizability, but it should be noted that the rate of transfusion was much lower in the endovascular group. Additionally, few patients in the endovascular compared to the open group had significant blood loss which is an important consideration in untangling the relationship of transfusions with cardiovascular events. Further analyses with larger sample sizes may be warranted to further examine differences in

effects of transfusions in patients undergoing open versus endovascular procedures. We additionally investigated the risks associated with platelet and FFP transfusions, though the absolute number of patients receiving these products was low, limiting our ability to draw conclusions regarding transfusion of these blood products.

In conclusion, this study quantified important risks associated with transfusion of blood products in patients undergoing infrainguinal revascularization. We further build on prior studies by examining the role of transfusion timing and the important additive risks of transfusion combined with RCRI risk factors for postoperative cardiovascular events and death. Lastly, we identified longer term relationships of preoperative anemia, RCRI score, and transfusion with mortality in this cohort. These results may inform patient risk assessment and the design of future prospective studies of transfusions in patients undergoing infrainguinal vascular procedures.

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Table I. Patient Characteristics and Outcomes by Intraoperative Transfusion

	Not Transfused intraoperatively N=480	Transfused intraoperatively N=84	P-value
Patient Characteristics			
Age	70 (11)	72 (11)	0.06
Sex – Male/Female	66% / 34%	63% / 37%	0.52
Race			0.71
American Indian or Alaskan Native	2%	0%	
Asian	10%	13%	
Black or African American	12%	11%	
Native Hawaiian or Pacific Islander	1%	1%	
White	60%	63%	
More than 1 race	0%	0%	
Unknown	15%	12%	
Hispanic or Latinx	10%	7%	0.37
Coronary Artery Disease	30%	43%	0.02
Congestive Heart Failure	17%	25%	0.09
Prior Stroke or TIA	12%	12%	0.10
CKD-5 or creatinine>2	13%	15%	0.49
Insulin Dependence	33%	23%	0.05
Diabetes	59%	45%	0.01
RCRI Score			0.49
RCRI=0	39%	32%	
RCRI=1	32%	38%	
RCRI=2	19%	17%	
RCRI=3+	10%	13%	
Preop Hemoglobin, g/dL	11.7 (2.0)	10.5 (2.0)	<0.01
Preop Platelet count, $x10^9$/L	239 (82)	254 (108)	0.21
Open Procedure	37%	88%	<0.01
CLTI	71%	74%	0.55
Estimated Blood Loss, ml	20 (10-100)	300 (200-675)	<0.01
Outcomes within 30 days			
Postop MI	2.1%	8.3%	<0.01
Postop CHF	1.5%	3.6%	0.18
Postop Dysrhythmia	1.5%	9.5%	<0.01
Postop MI, CHF, or dysrhythmia	5.2%	21.4%	<0.01
MACE	4.0%	13.1%	<0.01
Major amputation	2.3%	6.0%	0.06
Mortality at 30 days	2.5%	4.8%	0.25
Mortality at 1 year*	5.8% (4.1-8.3%)	13.1% (7.5-22.4%)	0.01

Binary variables presented as percent (%), normally distributed continuous variables as mean with standard deviation, and non-normally distributed continuous variables as median with interquartile range. RCRI-revised cardiac risk index score; CLTI- chronic limb threatening ischemia; MI- myocardial infarction; CHF-congestive heart failure, MACE- major adverse cardiovascular event defined as postoperative MI or death

*Mortality at 1 year presented as estimate with 95% confidence interval based on life table analysis, *p*-value based on log-rank test comparison

Table II. Multivariable Cox Proportional Hazards Model for Mortality up to 1 year

	Hazard Ratio	P-Value	CI-Low	CI-High
Intra-op Transfusion	1.74	0.14	0.84	3.60
RCRI Score (0-reference)	1.00			
1	1.82	0.21	0.71	4.64
2	3.17	0.02	1.20	8.38
3+	4.76	<0.01	1.73	13.06
Preop Hgb	0.83	0.05	0.69	1.00
Age (<60=reference)	1.00			
61-70	0.66	0.42	0.24	1.79
71-80	0.65	0.41	0.24	1.81
>80	2.18	0.09	0.87	5.41

N=564
C-statistic=0.73
RCRI-revised cardiac risk index. Hgb-hemoglobin (g/dL)

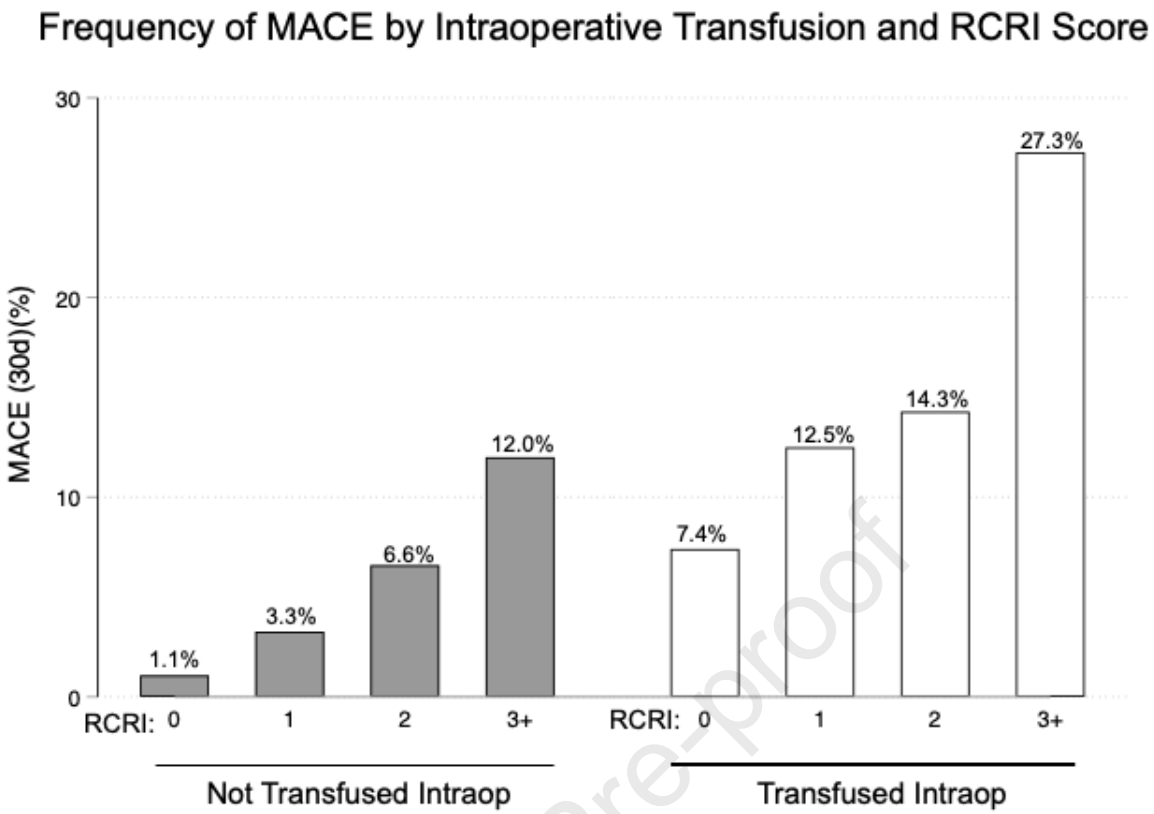


Figure 1. Stratification of MACE by Intraoperative Transfusion and RCRI Score. Numbers beneath each column specify number of RCRI risk factors. MACE=Major adverse cardiovascular events (postoperative myocardial infarction or death) up to 30 days.

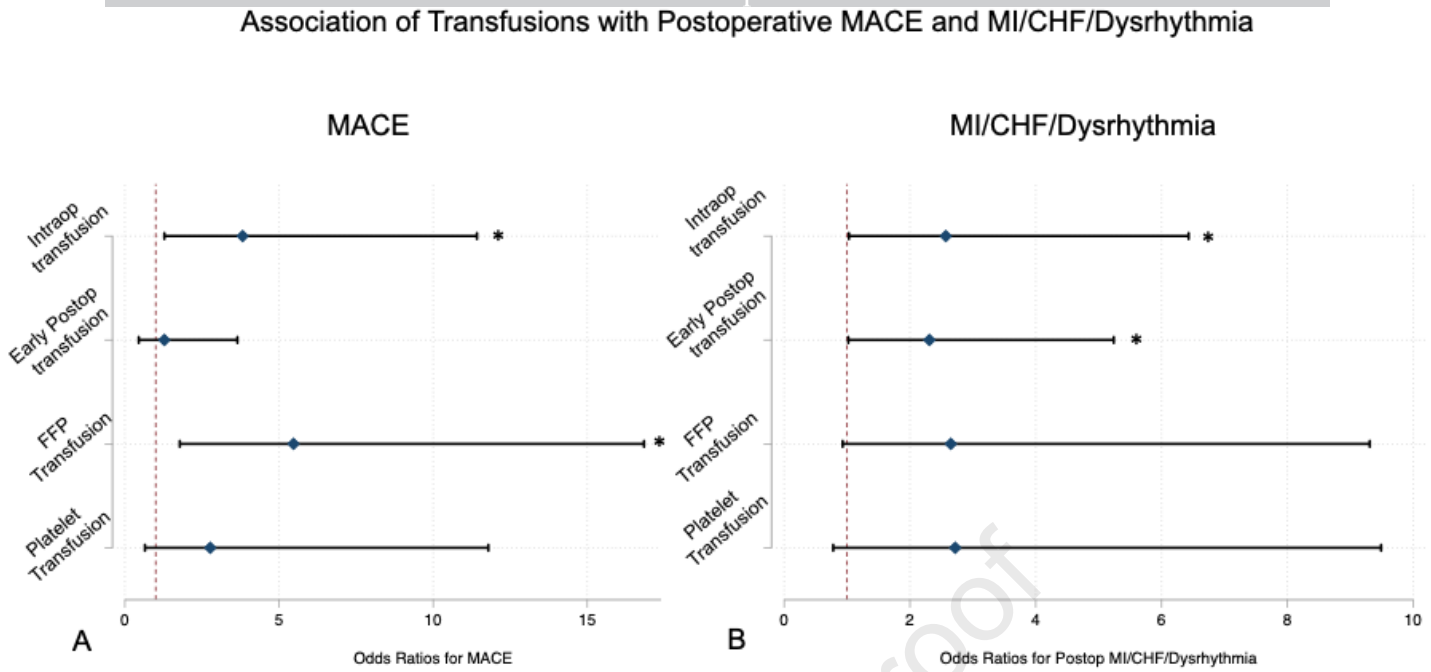


Figure 2. Coefficient plot showing adjusted odds ratios for the association of transfusions with postoperative myocardial infarction or death (MACE) in Panel A and with the composite outcome of postoperative myocardial infarction (postop MI), congestive heart failure (CHF), or dysrhythmia in Panel B. Early post op pRBC=RBC transfusion with 48 hours of surgery; FFP-fresh frozen plasma. All odds ratios adjusted for revised cardiac risk index score, blood loss, and age. * denotes $p<0.05$ for given odds ratio in the adjusted multivariable logistic regression model. See supplemental table II for complete model results.

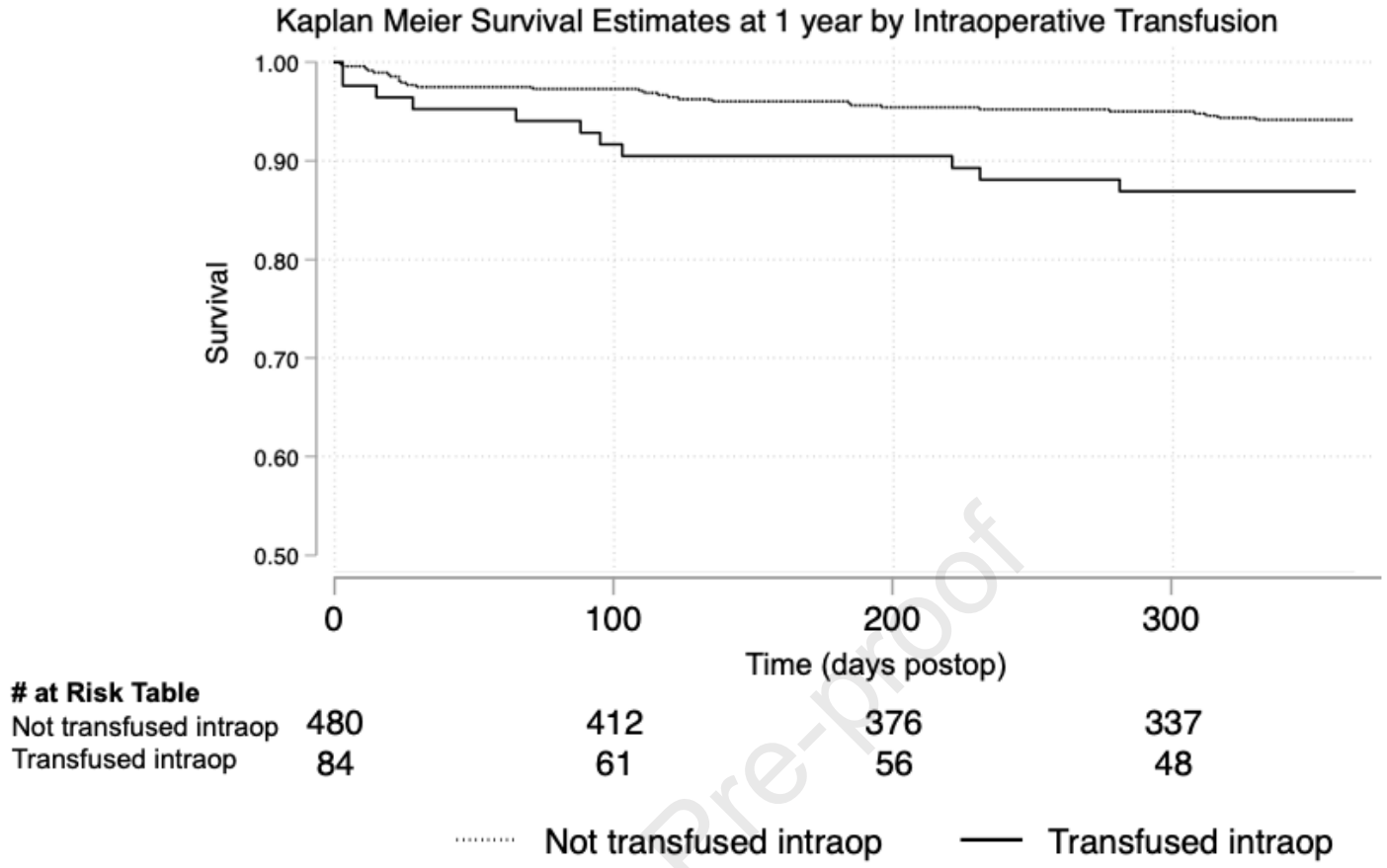
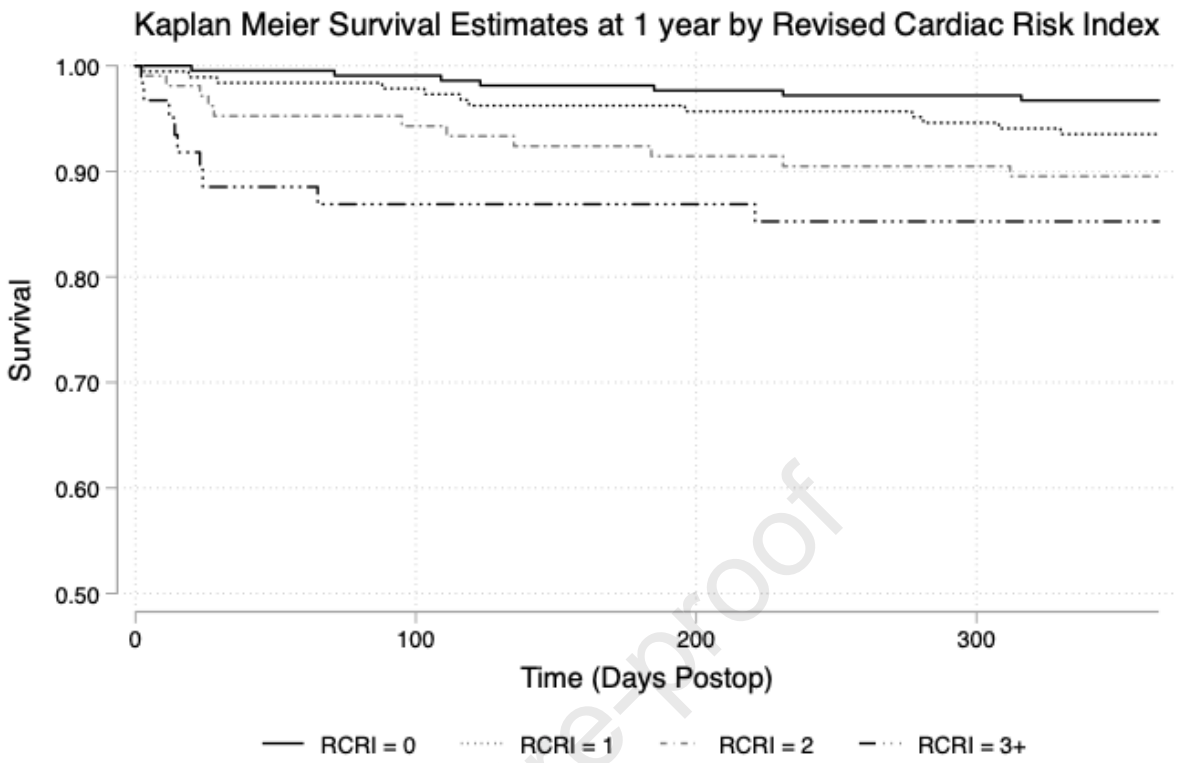


Figure 3. Kaplan Meier Curve Comparing 1 year Survival by intraoperative transfusion status. Logrank-*p*=0.01.



 # at Risk Table

RCRI = 0	213	184	166	145
RCRI = 1	185	156	142	128
RCRI = 2	105	88	81	74
RCRI = 3+	61	45	43	38

Figure 4. Kaplan Meier Curve Comparing Survival up to 1 year by number of RCRI risk factors. Logrank-$p<0.01$. RCRI-revised cardiac risk index.