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Original Article

# Intraoperative Plasma Transfusion Volumes and Outcomes in Cardiac Surgery

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*Objective:* Assess outcomes after intraoperative plasma transfusion in patients undergoing cardiac surgery.
*Design:* Retrospective study of adult cardiac surgical between 2011 and 2015. Relationships between plasma transfusion volume, coagulation test values, and a primary outcome of early postoperative red blood cell (RBC) transfusion were assessed via multivariable regression analyses. Secondary outcomes included hospital mortality, intensive care unit and hospital-free days, intraoperative RBCs, estimated blood loss, and reoperation for bleeding.
*Setting:* Academic tertiary referral center.
*Participants:* A total of 1,794 patients received intraoperative plasma transfusions during the study period.
*Interventions:* None.
*Measurements and Main Results:* Higher plasma transfusion volumes were associated with worse clinical outcomes, with each 1-unit increase being associated with greater odds for postoperative RBCs [odds ratio (OR) 1.12 (confidence interval [CI] 1.04-1.20); $p = 0.002$], intraoperative [OR 1.85 (CI 1.69-2.03); $p < 0.001$], and fewer hospital-free days [mean −0.20 (−0.39, −0.01); $p = 0.04$]. Each 0.1 increase in pretransfusion International Normalized Ratio (INR) was associated with increased odds of postoperative and intraoperative RBCs, reoperation for bleeding, and fewer intensive care unit and hospital-free days. For given plasma volumes, patients achieving greater reduction in elevated pretransfusion INR values experienced more favorable outcomes.
*Conclusions:* In patients undergoing cardiac surgery who received intraoperative plasma transfusion, higher plasma transfusion volumes were associated with inferior clinical outcomes. Higher pretransfusion INR values also were associated with worse outcomes; however, those achieving a greater degree of INR correction after plasma transfusion demonstrated more favorable outcomes. Prospective studies related to plasma transfusion are needed to address this important topic.


*Key Words:* plasma; INR; cardiac surgery; coagulation; bleeding, transfusion

PERIOPERATIVE BLEEDING necessitating allogeneic transfusion is common in cardiac surgery with a prior study citing overall transfusion rates in excess of 50%.[1] Intraoperative transfusion rates for plasma in patients undergoing cardiac surgery exceeds 20% in some studies.[1,2] The coagulopathy associated with cardiac surgery utilizing cardiopulmonary bypass (CPB) is complex and multifactorial. There can be a quantitative reduction of coagulation factors resulting from both hemodilution and consumption. Fibrinolysis and platelet abnormalities (quantitative/qualitative) can further contribute

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to microvascular bleeding in the immediate post CPB period.[3] Additionally, the presence of residual anticoagulants (eg, heparin, warfarin, etc) and ongoing surgical site bleeding can contribute to further derangements in the coagulation cascade. The historical mainstay of therapy to combat intraoperative bleeding owing to coagulation factor deficiencies not related to congenital causes (ie, hemophilia) has been allogeneic plasma transfusion.[4] The American Society of Anesthesiologists (ASA) Practice Guidelines for Perioperative Blood Management endorses the use of plasma for microvascular bleeding when the International Normalized Ratio (INR) is >2.0.[5] Additionally, more liberal plasma transfusion strategies (eg, triggered by INR >1.6) have been suggested in cardiac surgical patients with microvascular bleeding.[6] While the INR has long been recognized for its inadequacies in predicting bleeding risk, it remains a commonly utilized laboratory modality for assessing perioperative coagulation status as well as patient-specific responses to plasma transfusion.

Despite the guidelines mentioned above, there is an overall paucity of data to guide clinicians regarding intraoperative plasma transfusion in the cardiac surgical population. A prior study assessed outcomes related to intraoperative plasma administration amongst all surgical patients at the authors' institution and determined that higher intraoperative plasma transfusion volumes were associated inferior clinical outcomes.[7] However, the impact of intraoperative plasma transfusion in cardiac surgical patients remain incompletely defined.

The purpose of this study was to assess the relationships between intraoperative plasma transfusion volume, changes in coagulation test results, and the associations with clinical outcomes in patients undergoing cardiac surgery. The authors hypothesized that patients receiving higher intraoperative plasma volumes would have inferior clinical outcomes.

## Materials and Methods

This is a retrospective, single-center, cohort study conducted with approval from the Mayo Clinic (Rochester, Minnesota) Institutional Review Board with waived written informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were used in the design and conduct of this study, as well as in the reporting of results.[8]

Inclusion criteria were: (1) age ≥18 years; (2) cardiac surgery; (3) presence of an intraoperative INR value obtained before any intraoperative plasma transfusion(s); (4) presence of intraoperative plasma transfusion (occurring after the qualifying pretransfusion INR value and before surgical closure) between January 1, 2011 and December 31, 2015, and; (5) presence of a post-transfusion INR value, defined as the first INR value measured after the last unit of intraoperative plasma (within 24 hours). Only INR values and plasma transfusion episodes occurring after the cessation of CPB were included.

Exclusion criteria included: (1) lack of research authorization; (2) plasma utilized as part of therapeutic plasma exchange or apheresis; (3) a normal pretransfusion INR (ie, ≤1.1); (4) prior inclusion in the study; (5) noncardiac surgery; (6) congenital cardiac operations, ventricular assist device placement or exchange, and extracorporeal membrane oxygenator initiation; and (7) cardiac operations without use of CPB. For patients receiving intraoperative plasma transfusion during multiple surgical encounters during the study period, only the first intraoperative encounter was included.

Screening for potential study participants was performed using an institutional data warehouse called the OR DataMart, which captures transfusion data for all patients at the study institution.[9] In addition, this resource contains clinical and procedural data for all patients admitted to an acute care environment. Transfusion details were extracted from a related data warehouse called the Transfusion DataMart, which provides detailed information regarding all transfused blood products (eg, product type, volumes), exact transfusion timings (ie, order time, issue time, administration times), and related laboratory variables (eg, pretransfusion and post-transfusion hemoglobin, INR, platelet counts, and fibrinogen values). Additional pertinent baseline characteristics were obtained from a second validated database, the Advanced Cohort Explorer.[10] Both databases have undergone extensive validation with accuracy superior to manual data collection alone.[11] Data pertinent to cardiac surgical operations were obtained from The Society of Thoracic Surgeons (STS) database.

The primary exposure variables of interest were the volume of plasma transfused (aim 1) and the change in INR and R-time values (aim 2). Additional potentially confounding variables of interest included demographic features, surgical characteristics (eg, cardiac operation type, redo-sternotomy, surgery length, perfusion time and aortic cross-clamp time, emergency surgery, estimated blood loss), clinical features (eg, left ventricular ejection fraction, STS score, Charlson comorbidity scores, Sequential Organ Failure Assessment [SOFA] scores at the time of surgical incision, ASA physical status, comorbid medical conditions), perioperative transfusions, and perioperative laboratory tests. Cardiac operations were categorized as isolated coronary artery bypass surgery (CAB) or valve surgery (Valve), combined CAB+Valve, combined CAB+Valve+Other, or Other. The "Other" operations included, for example, aorta surgery, cardiac mass removal, myectomy, patent foramen ovale closure, left atrial appendage ligation, surgical MAZE procedure, or combinations of the above not classified elsewhere. Thromboelastography (TEG)-derived R-time values were included if the pretransfusion TEG was obtained within the hour preceding the first intraoperative plasma transfusion and the post-transfusion TEG was obtained within 6 hours after the last unit of intraoperative plasma. R-time values obtained after the first intraoperative unit but preceding additional units of intraoperative plasma were not included. Similarly, R-time values obtained after the last intraoperative plasma unit but without corresponding pretransfusion values were not included.

The primary outcome of interest was the need for early postoperative red blood cell (RBC) transfusion (defined as RBC transfusion in the first 24 postoperative hours), with secondary outcomes of reoperation for bleeding, hospital mortality, estimated blood loss (EBL) intensive care unit (ICU)-free days, and hospital-free days. Free days were defined by subtracting the ICU or hospital length of stay in days from 28, with patients dying during the ICU or hospital stay receiving a score of zero. Patients with ICU or hospital lengths of stay greater than

28 days also received a score of zero. For example, if a patient was discharged alive after a length of stay of 3 days, their hospital free days was 28-3 = 25. If, however, they died after 4 days, their hospital free days were 0. This outcome was chosen instead of simple length of stay to account for death, and avoid early death (hence short length of stay) being viewed as a favorable outcome statistically. Of note, intraoperative RBC transfusions and EBL were utilized as covariates to account for the severity of the surgical insult rather than outcome variables in primary analyses. However, recognizing that these variables may represent clinically important outcomes for intraoperative plasma transfusion, sensitivity analyses were performed utilizing 1) intraoperative RBC transfusions occurring after the first plasma unit, and 2) EBL as outcome variables. In these instances, only pretransfusion characteristics were utilized as covariates with explicit exclusion of intraoperative features (ie, surgery length, intraoperative transfusions of platelets and cell-salvaged blood, intraoperative RBC transfusions given before plasma, intraoperative factor concentrate use).

Throughout the study period a well-established transfusion algorithm was used to guide plasma transfusion (and other hemostatic interventions).[6] The indication for algorithm-based plasma transfusion is presence of microvascular bleeding as determined by anesthesiologist and surgeon consensus and prothrombin time >16.6 sec/INR >1.6, and/or activated partial thromboplastin time >57 sec via ACL-IL Top 500 analyzer (Werfen, Bedford, MA). Indication for platelet transfusion is a platelet count $<102 \times 10^9$/L or TEG maximum amplitude <48 mm, and for cryoprecipitate when the fibrinogen is <144 mg/dL (all assuming return of activated clotting time to within 10% baseline). Of note, at the study institution, antithrombin concentrates are used for treatment of antithrombin deficiency with inadequate heparinization, and hence plasma is not utilized for this purpose. Red blood cell transfusion triggers were not standardized in cardiac surgical patients during the study period, however, institutionally endorsed guidelines for RBC transfusion formulated by a multidisciplinary team of anesthesiologists, hematologists, surgeons, pathologists, and transfusion medicine specialists were readily available to all providers (accessed through the internal web server), which included the following indications for RBC transfusion: 1) active bleeding with cardiovascular instability at any hemoglobin; 2) at hemoglobin ≤8 g/dL in the setting of coronary artery disease, signs of end-organ ischemia, acute brain injury, or symptoms related to anemia (eg, unexplained hypotension, tachycardia, chest pain, heart failure); 3) at hemoglobin from 8 to 10 g/dL in the setting of acute coronary syndromes; and 4) at hemoglobin ≤7 g/dL in hemodynamically stable, nonbleeding patients. In cardiac surgery, it is common practice to target a hemoglobin concentration of ≥8.0 g/dL at surgical completion and in the early postoperative period (eg, first 24 hours). Institutional guidelines for RBC transfusion, as described above, were similarly applicable in the postoperative care of these patients.

## Statistical Analysis

The authors followed methods similar to those employed in a study of plasma transfusion in patients across all surgical subspecialties.[7] This current work focuses solely on patients undergoing cardiac surgery, with expanded surgical details extracted from the surgical record and the STS database. Briefly, descriptive statistics, frequencies, and percentages for categorical variables and medians and interquartile ranges for continuous variables were used to summarize baseline demographics and intraoperative characteristics. Differences in the distribution of baseline characteristics across categorized plasma dose per mL/kg (<10 *v* 10+) were compared using $\chi^2$ or Fisher's exact tests for categorical variables (where appropriate) and Wilcoxon rank-sum tests for continuous variables. The outcomes of postoperative RBCs within 24 hours, in-hospital mortality, ICU-, and hospital-free days, RBC transfusion intraoperatively after the first plasma unit transfused, intraoperative EBL, and reoperation for bleeding also were summarized descriptively by plasma dose per mL/kg.

Associations between intraoperative plasma dose (per 1,000 mL) with postoperative INR and R were analyzed using multivariable linear regression. Associations between plasma dose (per 1 unit, defined by a typical unit volume of 300 mL), pretransfusion INR, pre−post transfusion INR, pretransfusion R, and pre−post transfusion R with postoperative and intraoperative outcomes were analyzed using multivariable regression models. Postoperative RBC use (yes/no?), hospital mortality, intraoperative RBC use after initial plasma transfusion (yes/no?), and reoperation for bleeding were analyzed using logistic regression, and ICU-free days, hospital-free days, and EBL were analyzed using linear regression. Each model was adjusted for potentially important confounding variables including demographic features (age, sex, body mass index), preoperative laboratory values (hemoglobin, creatinine, platelet count), intraoperative resuscitation features (platelet transfusion volume, total crystalloid volume, colloid volume, allogeneic RBC volume, cell-salvage volume), severity of comorbid illness (Charlson score, SOFA score, left ventricular ejection fraction), and surgical features (perfusion time, aortic cross-clamp time, surgery type, and redo-sternotomy). When analyzing INR and plasma volumes, and for all outcomes but hospital mortality, the authors had the power to additionally adjust for the effects of preoperative medications (aspirin, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), heparin or low-molecular-weight heparin, vasopressors, inotropes within 24 hours of the procedure), intraoperative factor concentrate administration (including prothrombin complex concentrates and single factor replacements), and additional surgical features (surgery length, emergency surgery, and EBL). Only the preoperative adjustment terms were included for the intraoperative outcomes because inclusion of intraoperative terms in those models would be taking into account future information. Finally, only adjusted models were used (as detailed above) when analyzing relationships between outcomes and pretransfusion R-times and changes in R-times, because TEG data were only available for roughly 20% of the sample.

The authors used a multiple imputation approach with 10 independent imputed data sets to fill in missing values (sex 0.1%, surgery time 1.0%, hemoglobin and ASA physical status

1.6%, creatinine and plasma volume 3.6%, anesthesia type 4.2%, body mass index 5.0%, and EBL 6.2%).[12,13]

Multiple sensitivity analyses were planned a priori, including additionally adjusting for STS prediction score (only applicable for 40% of patients), and repeating the analysis based upon 3 unique categories of pretransfusion INR (≤1.5, between 1.5 and 2, and ≥2) and high or low intraoperative allogeneic RBC requirements (≥3 units for high, <3 units for low). Additionally, multivariable regression analyses to examine the association between plasma dose (mL/kg) and the primary and secondary outcomes were performed. All statistical analyses were performed using computer software (SAS Version 9.4, SAS Institute Inc, Cary, NC). A two-sided p value <0.05 was considered significant.

## Results

A total of 1,794 unique patients were included (Fig 1). Table 1 displays the baseline demographic, clinical, and laboratory features for the cohort, categorized into plasma volumes at a threshold of 10 mL/kg. The median (interquartile range [IQR]) pretransfusion and post-transfusion INR values for the cohort were 1.7 (1.6-1.9) and 1.3 (1.2-1.4), respectively. The median time from pretransfusion INR measurement to plasma transfusion was 0.9 (0.7-1.9) hours, and the median time from last intraoperative plasma transfusion end to post-transfusion INR measurement was 1.2 (0.8-1.6) hours. The median (IQR) pretransfusion and post-transfusion R values were 7.3 (6.1, 9.9) and 6.8 (5.7, 8.3) respectively. The median (IQR) number of plasma units transfused was 2 (2-4). Patients with a pretransfusion INR ≥2 tended to receive more plasma units, as 51% of those with INR ≥2.0 received 4+ plasma units, compared with 22% and 38% for those with INR between 1.5 and 1.9 and <1.5, respectively ($p < 0.001$). Thirty-six percent of patients underwent isolated CAB or Valve surgery, followed by 13.4% CAB+Valve, 8.8% CAB+Valve+Other, and 41.5% were "Other." The median CPB perfusion and cross-clamp times were 115 minutes and 80 minutes, respectively. Approximately 39.9% of patients received intraoperative RBCs (median, 1 unit) after the qualifying plasma transfusion, 64% received platelets (median volume 326 mL), and 12% received cryoprecipitate (median volume 208 mL). Unadjusted postoperative outcomes are displayed in Table 2. With regard to postoperative event rates, 250 (18.0%) patients received a postoperative RBC transfusion within 24 hours, 88 (4.9%) died during the hospitalization, and 127 (7.1%) required reoperation for bleeding (Table 2).

The magnitude of INR change (pre−post transfusion) was significantly different between groups with differing pretransfusion INR values (Fig 2). Patients with higher pretransfusion INR values tended to have larger decreases from pre−post INR. There was no

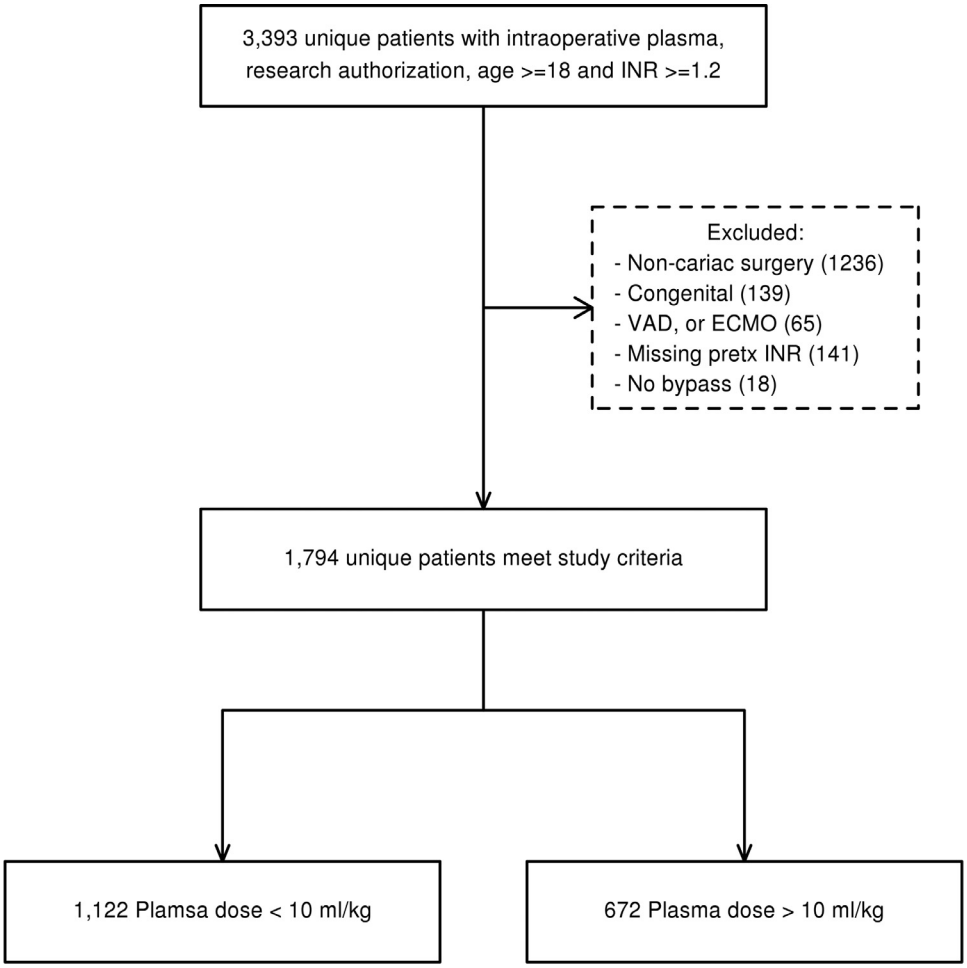


Fig 1. Study population flow diagram. ECMO, extracorporeal membrane oxygenation; INR, international normalized ration; VAD, ventricular assist device.

Table 1
Demographic and Clinical Characteristics of Patients Receiving Intraoperative Plasma Transfusion by Categorized Plasma mL/kg

| Characteristic | <10 N = 1,122 | 10+ N = 672 | Total N = 1,794 | p Value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age (y) | 73 (64, 80) | 72 (63, 80) | 73 (63, 80) | 0.44† |
| Male sex | 794 (71.8%) | 418 (62.2%) | 1212 (68.2%) | <0.001‡ |
| BMI (kg/m$^2$) | 29.1 (25.9, 33.4) | 26.9 (23.5, 30.8) | 28.3 (24.9, 32.5) | <0.001† |
| **Patient comorbidities** | | | | |
| Preoperative Charlson score | 5 (4, 7) | 5 (4, 7) | 5 (4, 7) | 0.83† |
| Preoperative SOFA score | 4 (2, 5) | 5 (4, 6) | 4 (3, 6) | <0.001† |
| STS Predicted Mortality Applicable | 560 (49.9%) | 185 (27.5%) | 745 (41.5%) | <0.001‡ |
| STS Predicted Mortality (%) | 2.2 (1.1, 4.4) | 3.8 (1.6, 7.1) | 2.4 (1.2, 5.1) | <0.001† |
| **Laboratory values** | | | | |
| Preoperative INR | 1.7 (1.6, 1.8) | 1.8 (1.6, 2.1) | 1.7 (1.6, 1.9) | <0.001† |
| Preoperative INR | | | | <0.001‡ |
| <1.5 | 75 (6.7%) | 55 (8.2%) | 130 (7.2%) | |
| 1.5-1.9 | 882 (78.6%) | 383 (57.0%) | 1265 (70.5%) | |
| ≥2 | 165 (14.7%) | 234 (34.8%) | 399 (22.2%) | |
| Postoperative INR* | 1.3 (1.2, 1.4) | 1.3 (1.2, 1.4) | 1.3 (1.2, 1.4) | 0.13† |
| INR decrease (pre−post) | 0.4 (0.3, 0.5) | 0.5 (0.3, 0.7) | 0.4 (0.3, 0.6) | <0.001† |
| N with TEG R time values | 204 (18.2%) | 170 (25.3%) | 374 (20.8%) | <0.001‡ |
| Preoperative R time | 7.3 (5.9, 9.2) | 7.6 (6.3, 10.9) | 7.3 (6.1, 9.9) | 0.08† |
| Postoperative R time | 6.5 (5.7, 8.1) | 7.2 (5.7, 8.7) | 6.8 (5.7, 8.3) | 0.03† |
| R time decrease (pre−post) | 0.6 (−0.9, 2.5) | 0.7 (−1.5, 3.4) | 0.6 (−1.0, 2.9) | 0.70† |
| Preoperative hemoglobin | 13.2 (11.6, 14.4) | 12.3 (10.7, 13.7) | 12.9 (11.1, 14.2) | <0.001† |
| Preoperative creatinine | 1.1 (0.9, 1.3) | 1.1 (0.9, 1.4) | 1.1 (0.9, 1.3) | 0.50† |
| Preoperative platelet count | 191 (160, 232) | 185.0 (142.5, 234.5) | 188 (156, 232) | 0.01† |
| **Preoperative medications** | | | | |
| Clopidogrel within 14 days | 184 (16.6%) | 82 (12.2%) | 266 (14.9%) | 0.01‡ |
| Aspirin within 7 days | 761 (68.7%) | 446 (66.4%) | 1207 (67.8%) | 0.31‡ |
| NSAIDs within 7 days | 94 (8.5%) | 45 (6.7%) | 139 (7.8%) | 0.17 ‡ |
| Warfarin within 5 days | 331 (29.9%) | 257 (38.2%) | 588 (33.0%) | <0.001‡ |
| Factor Xa inhibitor within 5 days | 23 (2.1%) | 8 (1.2%) | 31 (1.7%) | 0.17‡ |
| Direct thrombin inhibitor within 5 days | 22 (2.0%) | 13 (1.9%) | 35 (2.0%) | 0.94‡ |
| Therapeutic heparin infusion within 1 day | 8 (0.7%) | 4 (0.6%) | 12 (0.7%) | 1.00§ |
| Therapeutic LMW heparin within 1 day | 25 (2.3%) | 22 (3.3%) | 47 (2.6%) | 0.19‡ |
| Vitamin K within 1 day | 11 (1.0%) | 12 (1.8%) | 23 (1.3%) | 0.15‡ |
| Vasopressors or inotropes within 24 hours | 33 (3.0%) | 50 (7.4%) | 83 (4.7%) | <0.001‡ |
| **Surgical characteristics** | | | | |
| Operation category | | | | <0.001‡ |
| CAB or Valve only | 467 (41.6%) | 185 (27.5%) | 652 (36.3%) | |
| CAB+Valve | 164 (14.6%) | 77 (11.5%) | 241 (13.4%) | |
| CAB+Valve+Other | 100 (8.9%) | 57 (8.5%) | 157 (8.8%) | |
| Other | 391 (34.8%) | 353 (52.5%) | 744 (41.5%) | |
| Redo-sternotomy | 186 (16.6%) | 187 (27.8%) | 373 (20.8%) | <0.001‡ |
| Ejection fraction | 60 (52, 65) | 58 (45, 65) | 60 (50, 65) | <0.001† |
| Perfusion time | 104 (73, 145) | 137 (96, 202) | 115 (79, 166) | <0.001† |
| Cross-clamp time | 75.5 (51.5, 105.0) | 90 (56, 131) | 80.0 (53.5, 112.0) | <0.001† |
| ASA PS | 3 (3, 3) | 3 (3, 4) | 3 (3, 4) | <0.001† |
| Emergency procedure | 22 (2.0%) | 41 (6.1%) | 63 (3.5%) | <0.001‡ |
| **Intraoperative transfusion characteristics** | | | | |
| Intraoperative EBL (mL) | 1313 (904, 1758) | 1654 (1,131, 2,769) | 1423 (972, 1994) | <0.001† |
| Number of plasma units given | 2 (2, 2) | 4 (2, 4) | 2 (2, 3) | <0.001† |
| Number of plasma units given | | | | <0.001‡ |
| Missing | 4 | 0 | 4 | |
| 1 | 111 (9.9%) | 0 (0.0%) | 111 (6.2%) | |
| 2 | 819 (73.3%) | 57 (8.5%) | 876 (48.9%) | |
| 3 | 151 (13.5%) | 117 (17.4%) | 268 (15.0%) | |
| 4+ | 37 (3.3%) | 498 (74.1%) | 535 (29.9%) | |
| Plasma volume (mL) | 560 (537, 595) | 1,142.5 (932.5, 1885.5) | 599 (551, 1095) | <0.001† |
| Plasma dose (mL/kg) | 6.7 (5.5, 8.0) | 15.2 (12.1, 22.9) | 8.3 (6.2, 13.0) | <0.001† |
| RBCs transfused intraop after primary FFP | 280 (25.0%) | 435 (64.7%) | 715 (39.9%) | <0.001‡ |
| RBC units after FFP (if any) | 1 (1, 2) | 2 (1, 3) | 1 (1, 2) | <0.001† |
| Platelets | 602 (53.7%) | 554 (82.4%) | 1,156 (64.4%) | <0.001‡ |
| Platelet volume (mL) | 290 (252, 393) | 534 (293, 810) | 326 (278, 580) | <0.001† |
| Cryoprecipitate | 46 (4.1%) | 166 (24.7%) | 212 (11.8%) | <0.001‡ |

(*continued*)

**Table 1** (*continued*)

| Characteristic | <10 N = 1,122 | 10+ N = 672 | Total N = 1,794 | p Value |
|---|---|---|---|---|
| Cryoprecipitate volume (mL) | 203 (189, 214) | 210 (196, 387) | 208.0 (194.0, 267.5) | 0.002† |
| Cell saver volume (mL) | 661.5 (457.0, 882.0) | 831 (571, 1,388) | 713 (492, 998) | <0.001† |
| Total IV crystalloid volume (mL) | 1678 (1,100, 2,300) | 1800 (1,234, 2,640) | 1,730 (1,171, 2,430) | <0.001† |
| Intraop CPB crystalloid (mL) | 2923 (2,222, 3,753) | 3140 (2,350, 4,348) | 3,000 (2,264, 3,945) | <0.001† |
| Colloid volume (mL) | 2279.9 (1,633.7, 3,121.3) | 4079.3 (2,817.7, 6,264.0) | 2,785.0 (1,910.7, 3,966.6) | <0.001† |
| Prothrombin complex concentrates | 4 (0.4%) | 25 (3.7%) | 29 (1.6%) | <0.001§ |

NOTE. Numbers indicate N (%) and median (Q1, Q3).
Abbreviations: ASA PS, American Society of Anesthesiologists Physical Status classification score; CAB, coronary artery bypass; CPB, cardiopulmonary bypass; EBL, estimated blood loss; FFP, fresh frozen plasma; INR, international normalized ratio; Intraop, intraoperative; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; R time, thromboelastography R time; RBC, red blood cells; SOFA, sequential organ failure assessment; STS, Society of Thoracic Surgeons; TEG, thromboelastography.
*Total plasma units was unavailable for 4 patients (all in the <10 ml/kg group), though total plasma volume was available
† Wilcoxon.
‡ $\chi^2$.
§ Fisher's exact.

Table 2
Outcomes of Patients Receiving Intraoperative Plasma Transfusion by Plasma Volume (mL/kg)

| Characteristic | <10 N = 1,122 | 10+ N = 672 | Total N = 1,794 |
|---|---|---|---|
| **Early postoperative RBCs** | 150 (19.4%) | 100 (16.2%) | 250 (18.0%) |
| **In-hospital mortality** | 32 (2.9%) | 56 (8.3%) | 88 (4.9%) |
| **ICU-free days** | 26.9 (25.4, 27.1) | 25.2 (20.3, 27.0) | 26.3 (24.1, 27.1) |
| **Hospital-free days** | 20.7 (16.6, 22.6) | 16.7 (1.3, 20.7) | 19.7 (13.3, 21.8) |
| **Intraoperative RBCs after plasma** | 280 (25.0%) | 435 (64.7%) | 715 (39.9%) |
| **Intraoperative RBC volume (units)** | 0 (0, 0) | 1 (0, 3) | 0 (0, 1) |
| **Intraoperative EBL (mL)** | 1,313 (904, 1,758) | 1,654 (1,131, 2,769) | 1,423 (972, 1,994) |
| **Re-surgery for bleeding** | 42 (3.8%) | 85 (12.7%) | 127 (7.1%) |

NOTE. Numbers indicate N (%) and median (Q1, Q3).
Abbreviations: EBL, estimated blood loss; ICU, intensive care unit; RBC, red blood cells.

significant association between increased plasma volume (per 1,000 mL) and change in post-transfusion R times [mean decrease = 0.51 seconds; 95% confidence interval (−1.70 to 2.71); p = 0.65].

### *Plasma Transfusion Volume and Clinical Outcomes (aim 1)*

Intraoperative plasma dose (per unit) was significantly associated with multiple outcomes (Table 3) even after multivariable adjustment. Each additional plasma unit was associated with increased odds of RBC transfusion in the 24 hours after surgery [odds ratio (OR) 1.12 (1.04, 1.20); p = 0.002], increased odds of intraoperative RBCs after the first unit of plasma [OR 1.85 (1.69, 2.03); p < 0.001], and decreased hospital-free days [mean −0.20 (−0.39, −0.01); p = 0.04]. When analyzed by increases in plasma dose per mL/kg, the findings assimilated the primary analysis with the addition of less ICU-free days (data not shown).

### *Coagulation Test Values and Clinical Outcomes (aim 2)*

After adjustment for potential confounders, pretransfusion INR values and the magnitude of change in INR after transfusion were associated with multiple outcomes (Table 3). Higher pretransfusion INR values (per 0.1 increase) were associated with increased odds of postoperative RBCs [1.25 (1.17, 1.34); p < 0.001] and intraoperative RBCs [1.12 (1.04, 1.21); p = 0.002], fewer mean ICU-[−0.33 (−0.50, −0.16); p < 0.001] and hospital-free days [−0.25 (−0.43, −0.07; p = 0.006], and increased odds of re-operation for bleeding [1.15 (1.03, 1.27); p = 0.01]. Each 0.1 decrease from pre- to post-transfusion INR was significantly associated with decreased odds of postoperative RBCs [0.78 (0.73, 0.85); p < 0.001], intraoperative RBCs [0.88 (0.81, 0.96); p = 0.003], more ICU-free days [0.36 (0.17, 0.55); p < 0.001], and decreased odds of reoperation for bleeding [0.88 (0.78, 0.99); p = 0.01]. For given plasma volumes, patients achieving greater reduction in elevated pretransfusion INR values experienced more favorable outcomes. Pretransfusion R times and changes in R times after plasma transfusion were not significantly associated with any of the outcomes.

### *Sensitivity Analyses*

Only 41% of cardiac surgeries had an applicable STS risk score. When the authors subset their analyses to this group and additionally adjusted for STS score, the authors observed similar findings as in the primary analysis, with the exception that the association between plasma dose (per

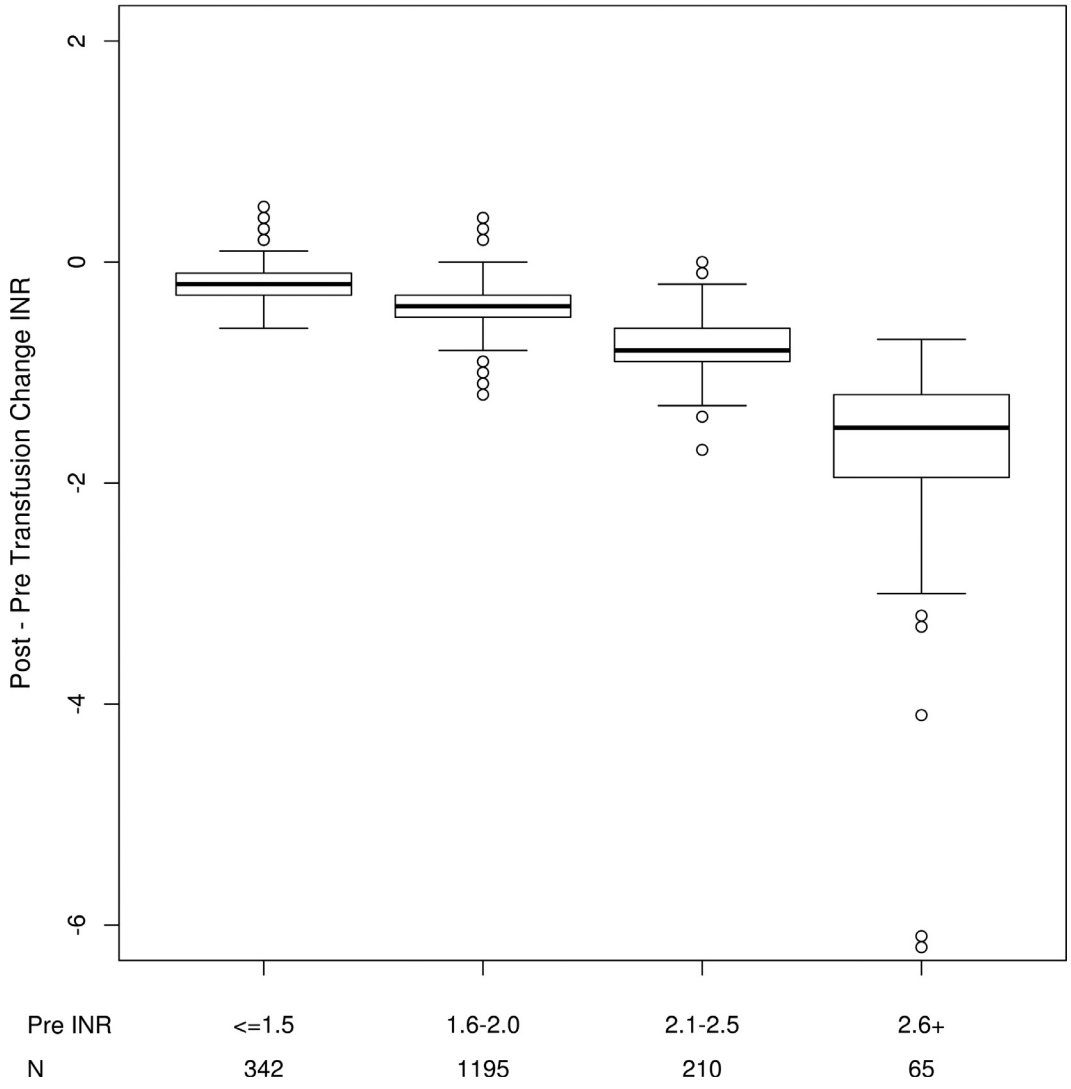


Fig 2. Change in INR by severity of pretransfusion INR. INR, international normalized ratio.

unit) and postoperative RBCs was no longer significant, and pretransfusion INR was associated with increased hospital mortality [1.45 (1.08, 1.96); p = 0.02], whereas greater decreases in pre–post transfusion INR were associated with decreased hospital mortality [0.67 (0.49, 0.93); p = 0.02] (Supplemental Table 1). Analyses by pretransfusion INR categories are displayed in Supplemental Table 2. In the INR ≥2 group, plasma dose was not significantly associated with need for postoperative RBCs. However, plasma dose was associated with a higher rate of intraoperative RBC transfusion and a lower rate of reoperation for bleeding. In those with INR values from 1.5 to 2.0, the same trends in the primary analysis between plasma dose and outcomes were observed with the exception of hospital-free days. In those with INR <1.5, plasma dose was associated with increased odds for intraoperative RBCs. Analyses subset by high or low intraoperative RBC transfusion volumes are displayed in Supplemental Table 3, with 66.0% of the cohort receiving <3 RBC units. The outcomes were generally consistent across groups.

## Discussion

The primary aim of this study was to evaluate the effect of plasma transfusion volumes on clinical outcomes in nearly 2,000 patients undergoing cardiac surgery. To that end, the authors found that increasing plasma transfusion volumes were associated with inferior clinical outcomes. Specifically, after adjustment for potentially confounding variables, increasing plasma transfusion volumes were associated with increased odds for postoperative RBC transfusion, intraoperative RBC transfusion (analyses limited to RBCs administered after first plasma unit), and fewer hospital-free days. However, higher pretransfusion INR values were strongly associated with increased risk for postoperative and intraoperative RBC transfusion, fewer ICU- and hospital-free days, and increased reoperation for bleeding. Moreover, patients who experienced a greater degree of INR correction after plasma transfusion had more favorable clinical outcomes, including lower odds of postoperative/intraoperative RBC transfusion, and more ICU-free days. The optimal endpoint for plasma-mediated INR

Table 3
Multivariable Regression Models Examining Associations With Outcomes

| Outcome | Postoperative RBCs[†] Odds Ratio (95% CI) | Hospital Mortality[†,¶] Odds Ratio (95% CI) | ICU-Free Days[‡] Mean Estimate (95% CI) | Hospital-Free Days[‡] Mean Estimate (95% CI) | Intraop RBCs[†,§] Odds Ratio (95% CI) | EBL (per 100 mL)[‡,§] Mean Estimate (95% CI) | Reoperation for Bleed[†] Odds Ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| **Plasma dose (per unit)**[††] | 1.12 (1.04-1.20)** | 0.94 (0.84-1.05) | −0.01 (−0.19 to 0.18) | −0.20 (−0.39 to −0.01)* | 1.85 (1.69-2.03)*** | 28.55 (−144.09 to 201.20) | 0.97 (0.87-1.09) |
| **Pretransfusion INR (per 0.1)**[††] | 1.25 (1.17-1.34)*** | 1.12 (1.00-1.26) | −0.33 (−0.50 to −0.16)*** | −0.25 (−0.43 to −0.07)** | 1.12 (1.04-1.21)** | 7.73 (−41.91 to 57.38) | 1.15 (1.03-1.27)* |
| **Pre−post INR (per 0.1)**[††] | 0.78 (0.73-0.85)*** | 0.90 (0.79-1.02) | 0.36 (0.17 to 0.55)*** | 0.19 (−0.00 to 0.39) | 0.88 (0.81-0.96)** | −9.63 (−71.87 to 52.60) | 0.88 (0.78-0.99)* |
| **Pretransfusion R time (per 0.1)**[§§] | 1.00 (1.00-1.01) | 1.00 (0.97-1.02) | −0.01 (−0.02 to 0.01) | −0.02 (−0.03 to 0.00) | 1.00 (0.99-1.00) | −0.17 (−1.56 to 1.22) | 1.00 (0.99-1.01) |
| **Pre−post R time (per 0.1)**[§§] | 1.00 (0.99-1.00) | 1.00 (0.98-1.03) | −0.01 (−0.02 to 0.01) | 0.00 (−0.01 to 0.02) | 1.00 (1.00-1.01) | 0.17 (−1.10 to 1.45) | 1.00 (0.99-1.01) |

Abbreviations: CI, confidence interval; EBL, estimated blood loss; ICU, intensive care unit; INR, international normalized ratio; Intraop, intraoperative; R time, thromboelastography R time; RBC, red blood cells.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† Analyzed using multivariable logistic regression.

‡ Analyzed using multivariable linear regression.

§ Only preoperative characteristics were included as adjustment terms when analyzing the outcomes of RBC units and estimated blood loss.

†† Regression models included plasma units (per 300 mL), pretransfusion INR, and decrease in INR plus preoperative demographics (age, sex, body mass index); preoperative laboratory values (creatinine, hemoglobin, platelet count); preoperative medications (aspirin, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, heparin or low−molecular−weight heparin, vasopressors, inotropes within 24 hours of the procedure); preoperative PLT, plasma, and RBC transfusions; intraoperative transfusion volumes (plasma, platelets, allogeneic RBCs, cell−salvaged blood); total intraoperative crystalloid and colloid volumes; intraoperative factor concentrate administration (including prothrombin complex concentrates and single factor replacements); surgical features (surgery type, surgery length, redo-sternotomy, ejection fraction, perfusion time, cross-clamp time, emergency surgery, and estimated blood loss); and patient comorbidities (preoperative Charlson score, preoperative SOFA scores).

§§ Regression models included plasma dose (per mL/kg), pretransfusion R, and decrease in R plus age, sex, body mass index, preoperative hemoglobin, creatinine, platelet count, crystalloid, colloid, RBC, Charlson, SOFA, ejection fraction, perfusion time, cross-clamp time, and operation type.

correction remains unknown. Intuitively, the cessation of microvascular bleeding may serve as a suitable endpoint, and it is possible that additional plasma administration beyond this may contribute to worse outcomes. However, the precise time for which cessation of microvascular bleeding is achieved can be difficult to reliably ascertain in real-time as this is a clinical diagnosis that requires assessment of the surgical field from both surgeons and anesthesiologists.

Perioperative coagulopathy and bleeding in patients undergoing cardiac surgery is common with some studies reporting overall transfusion rates in excess of 50%.[1] Transfusion rates for non-RBC hemostatic products (eg, plasma, platelets, cryoprecipitate) have been reported from 11% to greater than 20% in this population.[1,2,6] It is well accepted that perioperative bleeding increases risk for major morbidity and mortality in patients undergoing cardiac surgery.[14] Bleeding in this cohort is multifactorial and partially owing to a complex coagulopathy induced by blood contact with the CPB circuit. Specifically, a coagulation factor mediated coagulopathy is common in this population for which historically, allogeneic plasma transfusion has been the therapy of choice. Unfortunately, little is known regarding the optimal plasma transfusion practice in this surgical setting.

Algorithm-driven transfusion practices have become increasingly common in most cardiac surgical practices in recent years, and the use of such pathways has been shown to reduce transfusion rates.[6] Transfusion algorithms commonly contain laboratory-based cutoffs for which transfusions are suggested in the presence of ongoing microvascular bleeding. There is certainly a debate as to the best perioperative tests of coagulation, much of which is far beyond the scope of this manuscript. Despite a national trend toward use of viscoelastic assays (eg, TEG, rotational thromboelastometry) in the perioperative period, many centers still utilize standard coagulation testing (eg, INR, activated partial thromboplastin time, platelet count, and fibrinogen) to guide perioperative transfusion. The INR test has several shortcomings when used as a predictor for bleeding in the acute operative setting.[15-17] Furthermore, the INR threshold for plasma transfusion is debatable. Although the ASA supports plasma transfusion when the INR is >2.0 in the presence of microvascular bleeding,[5] other cardiac surgery specific algorithms use an INR >1.6 as the cutoff for plasma transfusion.[6] As mentioned above, the coagulopathy induced by utilization of CPB is complex and causes alterations in nearly every aspect of the coagulation cascade. Thus, in instances of ongoing microvascular bleeding, plasma transfusion in patients whose INR falls in an intermediate zone (INR 1.6-2.0) is common, and often occurs simultaneously with the correction of other hemostatic laboratory abnormalities. While comprehensive discussion of various coagulation testing modalities and management approaches for coagulopathy in cardiac surgery is beyond the scope of this investigation, it is important to note that there is likely substantial heterogeneity in laboratory test utilization and provider-specific practice patterns. With regard to INR values and outcomes in this study, overall, elevation in INR was associated with worse clinical outcomes including higher rates of intraoperative and postoperative RBC transfusion, fewer ICU- and hospital-free days, and higher rates of re-operation for bleeding. On the other hand, TEG R-times were not significantly associated with any of these outcomes, though values were only available for 20% of the study cohort and therefore may have been underpowered to detect outcome differences.

When considering the use of plasma transfusion to combat intraoperative bleeding and coagulation factor derangements, providers are faced with the dilemma regarding optimal plasma transfusion volumes. Prior studies have shown a greater improvement in coagulation test values with larger plasma transfusion volumes; however, this does not necessarily translate to improvements in clinical outcomes. Furthermore, there is little known about clinical outcomes associated with plasma transfusion volumes in patients undergoing cardiac surgery.[18,19] The goal of plasma transfusion in these circumstances is to increase coagulation factor activity levels to an acceptable range to assist hemostasis. The ideal coagulation factor activity level in bleeding cardiac surgical patients is unknown; however, an arbitrary individual coagulation factor level of 30 IU/dL has been thought to be sufficient for hemostasis.[18] Prior studies have shown a direct correlation between INR and factor activity levels.[20] This theoretical 30% factor activity target correlates roughly with an INR value near 2.0.[21] Larger plasma transfusion volumes (30 mL/kg *v* 10-15 mL/kg) have been demonstrated to improve coagulation factor concentration levels to a greater extent, yet how this correlates with bleeding and other more important clinical outcomes is poorly defined.[18] The ASA Practice Guidelines for Blood Component Therapy recommended a plasma transfusion dose of 10 to 15 mL/kg, which aligns with common practice in most centers, though the median plasma dose in this investigation was slightly lower at 8.3 mL/kg.[22] In a study by Mazzeffi et al, patients undergoing cardiac surgery who required massive transfusion (>8 units RBCs) and received plasma transfusion ratios >1:1 (plasma:RBC) had improved survival rates, lower re-operation rates, and less acute kidney injury, yet had prolonged mechanical ventilation and higher rates of atrial fibrillation.[23] In the current study only 39.9% received intraoperative RBC transfusions (median 1 unit), with plasma transfusion volumes across the entire cohort exceeding RBC transfusion volumes, hence also a plasma:RBC ratio of >1:1.

Patients receiving plasma transfusion in this study had inferior outcomes with increasing transfusion volumes despite controlling for potentially confounding variables. Approximately 75% of patients had a pretransfusion INR value <2, with the majority falling between 1.5 and 1.9. While the exact context for each transfusion episode is not known, perhaps this intermediate group (INR 1.5-1.9) with some preservation of coagulation factor activity is not receiving the intended hemostatic benefit but rather is simply exposed to the risks of transfusion. It is well appreciated that transfusion of allogeneic blood products is associated with various complications that may impact patient outcomes, including excessively positive postoperative fluid balances, transfusion-related acute lung injury, transfusion associated circulatory overload, febrile, and allergic reactions, infection, and multiorgan failure.[21,24-27] Additionally, risk for these complications escalates with increasing plasma transfusion volumes.[27] Interestingly, in patients with pretransfusion INR values

≥2, higher plasma doses were no longer associated with some of the unfavorable outcomes seen in the intermediate INR group (ie, postoperative RBCs) and was actually protective with regard to re-operation for bleeding. Hence, this may support an INR threshold ≥2 as a potential cutoff for less restricted plasma transfusion (ie, 10-15 mL/kg), as this group may be most likely to benefit from such therapy. Conversely, plasma transfusion for patients with more modest elevations in INR (ie, INR <2), when deemed clinically necessary, should perhaps be limited to low volumes with incremental reassessment of bleeding and coagulation testing. There is no evidence to support routine plasma transfusion for INR values <1.5, which represented only a fraction of the study cohort (7%).

In addition to analyses by pretransfusion INR, the authors analyzed outcomes by the magnitude of intraoperative allogeneic RBC transfusion, which may serve as a surrogate for the severity of the surgical bleeding insult. Outcomes related to plasma transfusion volume were similar regardless of intraoperative RBC transfusion volume, with increased plasma volumes associated with more postoperative RBCs, fewer ICU- and hospital-free days, and increased reoperation for bleeding.

Another potential explanation for the observed association between higher plasma transfusion volumes and inferior clinical outcomes in the overall study cohort might relate to transfusion-mediated hypervolemia. In the absence of ongoing large-volume hemorrhage, it is possible that increasing transfusion volumes may cause an appreciable rise in circulating blood volume, which may result in increased intravascular pressures and downstream disruption of newly formed hemostatic plugs, leading to further microvascular blood loss. This theoretical mechanism has been proposed when considering superior outcomes observed with more restrictive transfusion strategies for those with acute upper gastrointestinal bleeding.[28] Similar benefits have been described with hypotensive resuscitation strategies for patients with acute hemorrhage, though research is limited almost exclusively to trauma. In that setting, this strategy has shown promise with regard to reductions in bleeding, mortality, acute respiratory dysfunction, and organ dysfunction.[29] Furthermore, low central venous pressure strategies have shown hemostatic benefit in those undergoing liver resection.[30] Current adoption of similar practices to cardiac surgery is premature; however, an appreciation for the potential relationship between hypervolemia, elevated vascular pressures, and bleeding may have important implications for cardiac surgical patients. Moreover, the potential consequences on important downstream clinical outcomes, such as acute kidney injury, are unknown.

Beyond the observed relationships between plasma transfusion volumes and clinical outcomes, it is important to note that elevated pretransfusion INR values were associated with unfavorable outcomes and that a greater degree of INR correction after plasma transfusion was associated with more favorable outcomes. Paradoxically, increasing plasma transfusion volumes, for any degree of INR correction, was associated with inferior outcomes. Given that a majority of patients in this study had pretransfusion INR values <2, the margin for INR correction was quite small given that the intrinsic INR of the plasma unit itself may be as high as 1.5.[21] Thus, many of these patients may not have experienced hemostatic or INR-correction benefits from increasing doses of plasma, but would have been subjected to potential unfavorable transfusion associated outcomes, as described previously. Certainly, there also may be patients who received plasma and experienced no correction or even worsening of INR values in the setting of ongoing surgical bleeding. While this latter subset is likely small, it is well established that ongoing surgical bleeding is associated with unfavorable outcomes.

### *Limitations*

The limitations of this study include those inherent to all retrospective analyses, including charting omissions and inaccuracies. The exact circumstances associated with each plasma transfusion event are unknown (eg, severity of microvascular bleeding, decision to administer a given transfusion volume), though the timings for all transfusions are precise. Additionally, the primary endpoint of postoperative RBC transfusion was used as a surrogate for ongoing blood loss, though decisions to transfuse may have deviated from standardized institutional guidelines. While the common practice is to target a hemoglobin ≥8.0 g/dL in the immediate postcardiac surgical period, the exact circumstances surrounding each RBC transfusion event are unknown. This study included only patients receiving plasma transfusion, so comparing outcomes to similar patients not receiving plasma transfusion did not occur. Additionally, data related to appropriate transfusion algorithm adherence for other hemostatic products (ie, platelets and cryoprecipitate) was not explored, hence uncorrected abnormalities related to such may have contributed to bleeding, transfusion, and outcomes. While the authors have attempted to carefully control for confounding, the potential exists that those receiving higher plasma transfusion volumes represent a more chronically complex cohort or more complicated operative subset beyond what could be captured with adjustment. This study also represents a single center experience and the results may not be generalizable to all practice settings.

## Conclusion

Overall, higher pretransfusion INR values and higher plasma transfusion volumes were associated with unfavorable clinical outcomes. Those with pretransfusion INR values ≥2 may benefit from higher plasma transfusion volumes than other patient groups; however, optimal transfusion volumes are not known. Ultimately, large prospective studies are needed to define optimal plasma transfusion triggers, targets, and volumes in patients undergoing cardiac surgery. Moreover, future studies should be designed to compare clinical outcomes between plasma-based versus factor-based coagulopathy correction (eg, prothrombin complex concentrates) in cardiac surgery.

## Conflict of Interest

The authors have no conflicts of interests to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2019.12.049.

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