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Prophylactic Plasma Transfusion is Not Associated with Decreased Red Blood Cell Requirements in Critically Ill Patients

Matthew A Warner, MD¹, Arun Chandran, MBBS^{2,3}, Gregory Jenkins, MS⁴, and Daryl J Kor, MD⁵

¹Resident, Department of Anesthesiology, Mayo Clinic, Rochester, MN

²Resident, Internal Medicine, Mount Auburn Hospital, Harvard Medical School, Cambridge, MA

³Research Fellow, Department of Anesthesiology, Mayo Clinic, Rochester, MN

⁴Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

⁵Associate Professor, Department of Anesthesiology, Division of Critical Care Medicine, Mayo Clinic, Rochester, MN

Abstract

Background—Critically ill patients frequently receive plasma transfusion under the assumptions that abnormal coagulation test results confer increased risk of bleeding and that plasma transfusion will decrease this risk. However, the impact of prophylactic plasma transfusion remains poorly understood. The objective of this study was to determine the relationship between prophylactic plasma transfusion and bleeding complications in critically ill patients.

Methods—This is a retrospective cohort study of adults admitted to the ICU at a single academic institution between January 1, 2009 and December 31, 2013. Inclusion criteria included age ≥ 18 years and an International Normalized Ratio (INR) measured during ICU admission. Multivariable propensity-matched analyses were used to evaluate associations between prophylactic plasma transfusion and outcomes of interest with a primary outcome of red blood cell (RBC) transfusion in the ensuing 24 hours and secondary outcomes of hospital and ICU free days and mortality within 30 days of ICU discharge.

Results—A total of 27,561 patients were included in the investigation with 2,472 (9.0%) receiving plasma therapy and 1,105 (44.7%) for which plasma transfusion was prophylactic in nature. In multivariable propensity-matched analyses, patients receiving plasma had higher rates of RBC transfusion [OR: 4.3 (95% CI: 3.3 – 5.7), $p < 0.001$] and fewer hospital free days [estimated % increase: –11.0% (95% CI: –11.4, –10.6%), $p < 0.001$]. There were no significant differences in

Corresponding Author & Reprint Requests: Daryl J. Kor, MD, MSc, Department of Anesthesiology, Division of Critical Care Medicine, Mayo Clinic, Rochester, MN, 200 1st Street S.W., Rochester, MN 55905, kor.daryl@mayo.edu.

IRB Information: This study was approved by the IRB at the Mayo Clinic in Rochester, MN. Contact: IRB specialist; Pamela Jones, Phone: 507-266-4000; irbservicecenter@mayo.edu, Address: 200 1st Street SW, Rochester, MN 55905

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ICU free days or mortality. These findings appeared robust, persisting in multiple predefined sensitivity analyses.

Conclusions—Prophylactic administration of plasma in the critically ill was not associated with improved clinical outcomes. Further investigation examining the utility of plasma transfusion in this population is warranted.

Keywords

plasma; intensive care; bleeding; transfusion; red blood cell; prophylaxis

Introduction

The decision to administer plasma to the critically ill patient with abnormal coagulation parameters in the absence of active bleeding remains controversial. Although it is widely accepted that the bleeding patient with coagulopathy may require plasma administration, the utility of prophylactic transfusion for the prevention of bleeding complications remains unknown. To date, few investigations have specifically addressed this topic, most finding no hemostatic benefit in critically ill patients transfused with plasma.^{1,2} However, as bleeding episodes may be devastating in this population and data remains scarce, further investigation is warranted.

The most common reason for plasma transfusion is the correction of an elevated International Normalized Ratio (INR) despite a lack of evidence to support such a practice.^{3,4} In the United Kingdom, more than 10% of patients admitted to the intensive care unit (ICU) receive plasma with the majority of transfusions occurring in the absence of active bleeding.⁵ Moreover, nearly 80% of plasma administered to non-bleeding patients occurs at mild-to-moderate levels of INR elevation (i.e. $\text{INR} < 2.5$). While plasma administration may lead to a fall in markedly elevated INRs, there is only a modest associated rise in actual coagulation factor levels due in large part to the nonlinear relationship between factor levels and INR.^{3,6,7} In addition, plasma does not reliably correct mild-to-moderate elevations in INR or induce a more procoagulant state.^{5,8–10} Perhaps most importantly, the assumption that mild-to-moderate elevations of INR confer increased bleeding risk lacks the support of robust experimental evidence.^{3,11,12} Notably, plasma transfusion is not without risk. Specifically in the critically ill population, plasma administration has been associated with a myriad of complications, including transfusion-related acute lung injury^{1,13–16}, circulatory overload^{17,18}, multi-organ failure^{15,19}, and infectious complications.²⁰ Therefore, it is essential that any discussion of presumed benefits of transfusion therapies be balanced with thorough assessment of patient risk.

Given the uncertainty surrounding the efficacy of plasma transfusion for non-bleeding ICU patients, the aim of this investigation was to assess the relationships between prophylactic plasma administration and bleeding complications, with a primary outcome of red blood cell (RBC) transfusion. We hypothesized that prophylactic plasma transfusion would not be associated with reduced rates of subsequent RBC transfusion episodes.

Materials and Methods

This is a retrospective cohort study conducted under the approval of the Mayo Clinic (Rochester, Minnesota) Institutional Review Board with a waived requirement for written informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the design and conduct of the study.²¹

The study population includes adult patients admitted to two medical, three surgical, and one combined medical-surgical ICU at a tertiary care academic medical center. Basic ICU characteristics are provided in Supplemental Table 1. Inclusion criteria included age ≥ 18 years, ICU admission between January 1st 2009 and December 31st 2013, and the presence of an INR measured during ICU admission. For patients with multiple ICU admissions during the study period, only the first admission with an INR value was included. For patients with multiple INR values who did not receive plasma, the highest INR value during that encounter was utilized as the qualifying INR value. In patients with multiple INR values who did receive plasma during their first ICU admission, the INR immediately preceding plasma transfusion was utilized. Exclusion criteria included lack of research authorization and prior inclusion in the study. Patients receiving an RBC transfusion in the 24 hours before measurement of the qualifying INR were also excluded in order to minimize the risk of including those with active bleeding. Similarly, patients receiving RBC transfusion in the interval between INR measurement and plasma transfusion were excluded.

The primary exposure variable for this investigation was the presence or absence of prophylactic plasma transfusion within 24 hours of the qualifying INR value. Prophylactic plasma transfusion was defined as the first episode of plasma administration during the qualifying ICU admission, excluding those patients that had received RBC transfusion in the 24 hours before INR measurement or plasma administration. The presence and timing of all transfusion episodes were extracted from the electronic health record, with the timing of transfusion defined as the actual transfusion initiation time rather than the time of component issue from the blood bank.

The primary outcome for this investigation was RBC transfusion within 24 hours of the qualifying INR value for non-plasma transfused patients and within 24 hours of plasma transfusion for plasma-transfused patients. Secondary outcome measures included ICU and hospital free days (defined as 28 minus the ICU or hospital length of stay in days, with patients dying prior to discharge and those with ICU or hospital durations greater than 28 days receiving a score of zero), and all-cause mortality within 30 days of ICU discharge.

Relevant information for study participants was extracted using the Perioperative Datamart, an institutional resource that contains clinical, demographic, transfusion, and laboratory data for patients admitted to acute care environments.²² Additional baseline characteristics were obtained from the Mayo Clinic Life Sciences System (MCLSS), a second institutional database.²³ Extensive validation has been performed on these databases, and the accuracy of extracted data is superior to that collected by manual methods.²⁴

Statistical Analysis

Given the need to account for confounding and selection bias in this retrospective investigation, individuals were matched with and without plasma transfusions using 1:1 propensity score matching based on INR, platelet count, aspirin, clopidogrel, warfarin, therapeutic unfractionated heparin, low molecular weight heparin, and direct thrombin inhibitor therapy. To account for missing platelet count values (7.1% missing), predicted probabilities of qualifying plasma transfusion were constructed employing random forest with 400 trees and imputation of missing values using the `rfsrc` function in the `randomForestSRC` R package.²⁵ These predicted probabilities were then used to propensity score match subjects 1:1 using the `Matching` v4.8-3.4 R package²⁶ with a caliper of 0.25. Imbalance in covariates was quantified using % absolute difference (figure 2) and p-values from the test assessing imbalance; Kolmogorov-Smirnov test for continuous covariates and Fisher's exact test for categorical data. Differences greater than 10% were considered to show residual imbalance. While gender and race showed imbalance, there was no evidence of a clinical effect of these factors on outcome, so no further action was taken. Therapeutic heparin and INR were also found to be imbalanced and were subsequently used as covariates.

The binary end points of qualifying RBC transfusion (primary outcome) and 30-day mortality (secondary outcome) were modeled using logistic regression adjusting for confounding variables through propensity-matching as described above, while secondary outcomes ICU and hospital free days were modeled using negative binomial generalized linear models. The effect of plasma transfusion was tested using a likelihood ratio test. An analysis of the matched pairs was conducted adjusting for therapeutic heparin and INR while an analysis of the entire cohort was unadjusted. To further assess the robustness of study findings, multiple sensitivity analyses were planned *a priori* including restriction to 1) medical ICU patients; 2) surgical ICU patients; and 3) patients with INR ≤ 1.5 . To address the multiple tests conducted in tables 2–4, the p-value threshold for significance of a single test was set at 0.003125 using a Bonferroni correction (i.e. $0.05 \div 16$ tests), to ensure a study-wise cut-off of 0.05. All analyses were performed using R v3.1.1.

The sample size was estimated at 2,038 total study participants (two-sided alpha of 0.05, beta = 0.20) by assuming an RBC transfusion rate of 10% in ICU patients with INR ≤ 1.5 (estimated to be 10% of the total ICU population based on historical data) and a plasma transfusion rate of 20% in this population to identify an odds ratio of 0.5 for RBC transfusion in those who receive prophylactic plasma compared to those who do not. This number was increased by 50% to facilitate *a priori* sensitivity analyses. To achieve this number of patients with elevated INRs, we conservatively estimated the need to evaluate 31,000 ICU admissions.

Results

A total of 45,785 patients were admitted to an eligible ICU during the study period with 27,561 (60.2%) meeting inclusion criteria (Figure 1). Of the 25,089 patients not receiving plasma therapy, 3,009 were excluded having received an RBC transfusion in the 24 hours preceding INR measurement. Of the 2,472 patients receiving plasma, 1,367 patients were

excluded due to receiving RBC transfusion in the 24 hours preceding INR measurement or in the period between INR measurement and plasma transfusion. In total, 1,105 patients received a prophylactic plasma transfusion (44.7% of plasma-transfused subjects) with a median (interquartile range) volume of 2 (1 – 2) units. The median time between INR measurement and plasma transfusion was 2.6 (1.2 – 4.9) hours.

Comparison of baseline clinical, demographic, and laboratory characteristics between plasma-transfused and non-plasma transfused subjects are shown in Table 1. Briefly, patients receiving plasma were older with a higher burden of comorbid disease and coagulation abnormalities and were more likely to be receiving warfarin anticoagulation. After propensity-matching, between group differences were significantly reduced (Table 1, Figure 2).

A total of 2,588 patients (9.3%) received a qualifying RBC transfusion in the 24 hours following INR measurement or plasma transfusion, including 2,170 patients (9.8%) in the non-plasma group and 367 (33.2%) in the plasma-transfused group ($p < 0.001$). The median time to RBC transfusion from INR measurement was 5.4 (2.2 – 12.3) hours for the non-plasma transfused group and 6.5 (3.8 – 12.3) hours for the plasma-transfused group, with a median time from plasma to RBC transfusion of 3.6 (1.9 – 7.4) hours. Results of univariate analyses in the non-matched cohort are displayed in Supplemental Table 2. Briefly, those receiving plasma had higher rates of RBC transfusion, increased mortality, and fewer hospital free days. The median RBC transfusion volume was statistically greater in those who received plasma than in those who did not [2 (2 – 2) units versus 2 (1 – 2) units, $p = 0.003$].

In total, 978 patients receiving prophylactic plasma were propensity-matched 1:1 with a patient not receiving plasma. Of note, 127 patients receiving plasma were removed from propensity-matched analyses due to the lack of a suitable non-transfused subject. Propensity-matching significantly reduced between group differences (Table 1, Figure 2), however certain variables remained with absolute standardized differences greater than 10.0, including INR with a median (interquartile range) of 1.6 (1.2, 2.2) in the plasma-transfused group and 1.8 (1.5, 2.4) in the non-plasma transfused group and therapeutic heparin rates of 6.1% in the plasma-transfused group and 2.5% in the non-plasma transfused group. Given these differences, all subsequent outcome modeling in the propensity-matched cohort contained adjustments for INR and heparin use.

The results of adjusted multivariable propensity-matched analyses for the full matched cohort are displayed in Table 2. Patients receiving plasma had higher RBC transfusion rates [OR 4.3 (95% CI: 3.3 – 5.7), $p < 0.001$] and fewer hospital free days [Estimated decrease 11.0% (95% CI: 10.6% – 11.4%), $p < 0.001$] when compared to non-plasma transfused subjects. There were no significant differences in mortality or ICU free days.

Regarding the subgroup of patients with abnormal coagulation test results, 5,038 patients (18.3%) had a qualifying INR value ≥ 1.5 , of which 787 (15.6%) received prophylactic plasma. In total, 618 patients with INR ≥ 1.5 who were transfused plasma were propensity-matched 1:1 with a non-transfused counterpart. When restricting analyses to these patients,

plasma administration was associated with increased RBC transfusion rates and fewer hospital free days, but no significant difference in mortality (Table 3). Results of propensity-matched sensitivity analyses restricting the analysis to medical or surgical ICU patients are displayed in Table 4. Briefly, plasma administration was associated with increased RBC requirements and fewer hospital free days in both subpopulations. There was no significant difference in mortality in either group.

Discussion

Plasma transfusion for the prevention of bleeding complications is common in the critically ill despite a lack of supporting evidence. In this investigation, prophylactic plasma transfusion was not associated with decreased RBC requirements. To the contrary, patients receiving plasma had higher rates of RBC transfusion in the subsequent 24 hours, a relationship which persisted in multiple predefined sensitivity analyses including limitation to those in either the medical or surgical ICU. In addition, patients transfused with plasma had fewer hospital free days.

Approximately 4 million units of plasma are transfused each year in the United States, with the majority of transfusions occurring outside of published guidelines.^{4,27} In fact, there are few evidence-based indications for plasma transfusion. These include replacement of single coagulation factor or protein deficiencies for which no safe fractionated product exists,^{28,29} replacement of multiple factor deficiencies associated with severe bleeding and/or disseminated intravascular coagulation,²⁸ prevention of dilutional coagulopathy in the setting of massive hemorrhage and/or major trauma,³⁰ plasma exchange in thrombotic thrombocytopenic purpura,²⁸ and reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrates are not available.²⁸

In contrast, there is a paucity of evidence regarding the prophylactic use of plasma for the prevention of bleeding complications in the critically ill. Dara and colleagues retrospectively analyzed the effects of plasma transfusion in 115 patients with non-bleeding coagulopathy, finding no difference in bleeding episodes in transfused versus non-transfused patients.¹ More recently, Müller and colleagues designed a randomized controlled trial of plasma transfusion in critically ill patients prior to invasive procedures, but this study was stopped before obtaining predefined target enrollment due to slow inclusion². In the 81 randomized patients, the incidence of bleeding did not differ between transfused and non-transfused subjects, although the study was underpowered for the outcome measure. In addition, plasma transfusion (12 ml/kg) successfully reduced INR to less than 1.5 in only half of transfused patients. Furthermore, evidence suggests that even when plasma is successful in decreasing mild-to-moderately elevated INR values, the overall effects on thrombin generation are limited and normalization of coagulation status does not occur.¹⁰ While the precise mechanisms underlying this observation remain incompletely defined, it should be noted that plasma also contains anticoagulant and fibrinolytic proteins, and *in vivo* changes in anticoagulant-procoagulant balance are not adequately reflected in the INR.

Interestingly, in the current investigation patients transfused with plasma had higher RBC requirements than those not receiving plasma, even when limiting analyses to those with

elevated INR. While the retrospective design of this investigation precludes determination of the precise mechanisms associating plasma with higher RBC requirements, there are several theoretical explanations. First, transfusion practices differ by provider, and it is possible that providers inclined to transfuse plasma prophylactically would also be more likely to transfuse RBCs. Hence, the relationship between plasma and RBC transfusion may be a reflection of provider-specific transfusion practices. Second, patients who received plasma may have been inherently different (e.g. more acutely ill or at greater risk of bleeding) than those who did not receive plasma despite attempts to balance baseline risk in adjusted analyses. Third, plasma is a high volume product which may result in significant hemodilution; in some patients reducing hemoglobin values beyond RBC transfusion thresholds. In addition, plasma-associated volume expansion may potentially increase intravascular pressures and have the paradoxical effect of disrupting newly formed hemostatic plugs, analogous to the presumed benefit of maintaining permissive hypotension in major trauma³¹ or utilizing restrictive transfusion strategies in acute gastrointestinal hemorrhage.³² Finally, plasma may induce a change in the hemostatic balance of anticoagulant and procoagulant proteins, and there is evidence to suggest that similar to non-bleeding patients with liver disease^{33,34} and severe sepsis,³⁵ non-bleeding critically ill patients with mild-to-moderate elevations in INR may maintain normal in vivo hemostatic balance.¹⁰

Though the large sample size, validated electronic data extraction techniques, and rigorous statistical adjustments are strengths of this investigation, there are significant limitations that must be mentioned. First, the retrospective nature of this study introduces the potential for confounding and bias despite attempts to mitigate these effects in the study design and analytical approach. We do note that propensity-matched analyses largely mitigated baseline differences in measured variables. Additionally, residual imbalances in a small number of variables were further addressed in adjusted analyses. Nonetheless, the potential for unmeasured confounding persists and cannot be understated. Hence, the non-plasma transfused group may have been sicker despite propensity-matching, and this may have been reflected by increased rates of RBC transfusion. It should also be emphasized that the clinical motivation influencing transfusion decisions could not be standardized as this can only be accomplished with prospective investigation. Hence, this retrospective study can only identify associations between plasma transfusion and bleeding complications. The assessment of cause-effect relationships will require a robust clinical trial design. Secondly, it is possible that not all plasma transfusions were prophylactic in nature, as non-bleeding ICU patients may be transfused for other reasons including plasma exchange and the correction of antithrombin deficiency. In attempt to reduce this potential bias, we limited our analyses to a restricted population with abnormal INR values, assuming that abnormal results would be rare in the aforementioned clinical circumstances. The results of these sensitivity analyses were similar to the primary analyses. In addition, the exclusion of patients receiving RBCs in the 24 hours prior to INR measurement or plasma transfusion may have inadvertently removed some non-bleeding patients from further analysis; however this exclusion was predefined in order to minimize the risk of including therapeutic plasma transfusion episodes occurring in the setting of resuscitation from active hemorrhage. It would have been possible to extend this time period of exclusion to patients receiving red

blood cells in the 48 or 72 hours before INR measurement or plasma transfusion, potentially excluding additional patients that had recently suffered hemorrhage. However, as red blood cell transfusion is common in the ICU and is often triggered by anemia without signs of active bleeding, this would also have resulted in a greater likelihood of inappropriate exclusion of non-bleeding patients. In addition, it is unlikely that a patient with no RBC transfusion requirements over a 24-hour interval has continued to experience significant active bleeding. Another limitation of this investigation is the relatively low-dose of plasma utilized with a median volume of 2 units, which corresponds to approximately 7 ml/kg for the average adult patient. Previous studies have consistently noted that plasma volumes less than 10 ml/kg are unlikely to correct an abnormal INR; hence the lack of perceived benefit may have been attributable, in part, to inadequate plasma dosing. Finally, this study reflects the experience of a single academic medical center and will require validation to ensure external validity and generalizability.

In conclusion, prophylactic administration of plasma was not associated with reduced bleeding complications or improved outcomes in a large population of critically ill patients. In light of these findings, more conservative management of coagulation abnormalities in non-bleeding ICU patients may be warranted, though further research is necessary to better understand the relationship between prophylactic plasma and subsequent RBC transfusion episodes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. *Crit Care Med*. 2005; 33:2667–71. [PubMed: 16276195]
2. Muller MC, Arbous MS, Spoelstra-de Man AM, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial (CME). *Transfusion*. 2015; 55:26–35. quiz 25. [PubMed: 24912653]
3. Dzik WH. Predicting hemorrhage using preoperative coagulation screening assays. *Curr Hematol Rep*. 2004; 3:324–30. [PubMed: 15341698]
4. Vlaar AP, in der Maur AL, Binnekade JM, Schultz MJ, Juffermans NP. A survey of physicians' reasons to transfuse plasma and platelets in the critically ill: a prospective single-centre cohort study. *Transfus Med*. 2009; 19:207–12. [PubMed: 19706138]
5. Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll D. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Critical care*. 2011; 15:R108. [PubMed: 21466676]

6. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost.* 1997; 77:477–80. [PubMed: 9065997]
7. Kor DJ, Gajic O. Blood product transfusion in the critical care setting. *Current opinion in critical care.* 2010; 16:309–16. [PubMed: 20543684]
8. Holland LL, Foster TM, Marlar RA, Brooks JP. Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios. *Transfusion.* 2005; 45:1234–5. [PubMed: 15987373]
9. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion.* 2006; 46:1279–85. [PubMed: 16934060]
10. Muller MC, Straat M, Meijers JC, et al. Fresh frozen plasma transfusion fails to influence the hemostatic balance in critically ill patients with a coagulopathy. *J Thromb Haemost.* 2015
11. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? *Crit Care Med.* 2006; 34:S170–3. [PubMed: 16617262]
12. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion.* 2005; 45:1413–25. [PubMed: 16131373]
13. Vlaar AP, Binnekade JM, Prins D, et al. Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study. *Crit Care Med.* 2010; 38:771–8. [PubMed: 20035217]
14. Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. *Transfusion.* 2004; 44:1468–74. [PubMed: 15383020]
15. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. *J Trauma.* 2009; 67:221–7. discussion 8–30. [PubMed: 19667872]
16. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest.* 2007; 131:1308–14. [PubMed: 17400669]
17. Li G, Rachmale S, Kojicic M, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion.* 2011; 51:338–43. [PubMed: 20723173]
18. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion.* 2012; 52:160–5. [PubMed: 21762464]
19. Johnson JL, Moore EE, Kashuk JL, et al. Effect of blood products transfusion on the development of postinjury multiple organ failure. *Arch Surg.* 2010; 145:973–7. [PubMed: 20956766]
20. Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. *Crit Care Med.* 2008; 36:1114–8. [PubMed: 18379235]
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007; 370:1453–7. [PubMed: 18064739]
22. Herasevich V, Kor DJ, Li M, Pickering BW. ICU data mart: a non-iT approach. A team of clinicians, researchers and informatics personnel at the Mayo Clinic have taken a homegrown approach to building an ICU data mart. *Healthc Inform.* 2011; 28:42, 4–5.
23. Chute CG, Beck SA, Fisk TB, Mohr DN. The Enterprise Data Trust at Mayo Clinic: a semantically integrated warehouse of biomedical data. *J Am Med Inform Assoc.* 2010; 17:131–5. [PubMed: 20190054]
24. Singh B, Singh A, Ahmed A, et al. Derivation and validation of automated electronic search strategies to extract Charlson comorbidities from electronic medical records. *Mayo Clin Proc.* 2012; 87:817–24. [PubMed: 22958988]
25. Ishwaran, H., Kogalur, UB. R package version 2.2.0. 2016. Random forests for survival, regression, and classification (RF-SRC).

26. Sekhon JS. Multivariate and Propensity Score Matching Software with Automated Balance Optimization: The Matching package for R. *Journal of Statistical Software*. 2011; 42:1–52.
27. Lauzier F, Cook D, Griffith L, Upton J, Crowther M. Fresh frozen plasma transfusion in critically ill patients. *Crit Care Med*. 2007; 35:1655–9. [PubMed: 17522577]
28. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol*. 2004; 126:11–28. [PubMed: 15198728]
29. Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2007; 98:383–8. [PubMed: 17458436]
30. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma*. 2009; 66:693–7. [PubMed: 19276739]
31. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma*. 2011; 70:652–63. [PubMed: 21610356]
32. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013; 368:11–21. [PubMed: 23281973]
33. Lisman T, Bakhtiari K, Pereboom IT, Hendriks HG, Meijers JC, Porte RJ. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. *J Hepatol*. 2010; 52:355–61. [PubMed: 20132999]
34. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood*. 2010; 116:878–85. [PubMed: 20400681]
35. Collins PW, Macchiavello LI, Lewis SJ, et al. Global tests of haemostasis in critically ill patients with severe sepsis syndrome compared to controls. *Br J Haematol*. 2006; 135:220–7. [PubMed: 17010048]

Figure 1.
Study population flow diagram.

Figure 2.

Standardized mean differences between groups for matched (●) and unmatched (◇) samples. Points to the right of the vertical reference line represent a standardized difference greater than 10.0 between those who received prophylactic preoperative plasma transfusion versus those who did not.

Table 1

Baseline demographic, laboratory, and clinical characteristics for the study cohort.

Variable ^a	Unadjusted		p-value	Propensity Score Matched		p-value
	Plasma Transfusion (N=1105)	No Plasma Transfusion (N=22080)		Plasma Transfusion (N=978)	No Plasma Transfusion (N=978)	
<u>Demographics</u>						
Age	69.6 (57.7, 79.6)	65.6 (53.2, 76.0)	< 0.001	69.3 (58.1, 79.7)	68.5 (56.6, 78.6)	0.418
Male	701 (63.4%)	13416 (60.8%)	0.077	632 (64.6%)	572 (58.5%)	0.006
Race: White	1013 (91.7%)	19849 (90.1%)	0.057	900 (92.0%)	867 (88.7%)	0.014
<u>Comorbidities</u>						
Charlson Score	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	< 0.001	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	0.783
CHF	296 (26.8%)	3687 (16.7%)	< 0.001	261 (26.7%)	268 (27.4%)	0.760
Cancer	132 (11.9%)	2443 (11.1%)	0.352	116 (11.9%)	127 (13.0%)	0.493
Chronic Renal Failure	307 (27.8%)	4158 (18.8%)	< 0.001	263 (26.9%)	245 (25.1%)	0.381
Metastasis	35 (3.2%)	603 (2.7%)	0.395	31 (3.2%)	36 (3.7%)	0.619
AIDS	0 (0.00%)	16 (0.07%)	1.00	0 (0.00%)	0 (0.00%)	-
Dementia	32 (2.9%)	492 (2.2%)	0.146	31 (3.2%)	39 (4.0%)	0.394
DM	211 (19.1%)	3782 (17.1%)	0.094	177 (18.1%)	179 (18.3%)	0.953
DM w/Complications	123 (11.1%)	2251 (10.2%)	0.309	114 (11.7%)	113 (11.6%)	1.00
Peptic Ulcer Disease	4 (0.4%)	15 (0.1%)	0.011	3 (0.3%)	1 (0.1%)	0.625
Peripheral Vascular Disease	93 (8.4%)	1390 (6.3%)	0.007	83 (8.5%)	62 (6.3%)	0.084
Liver Disease	80 (7.2%)	844 (3.8%)	< 0.001	64 (6.5%)	82 (8.4%)	0.143
Moderate-Severe Liver Disease	42 (3.8%)	401 (1.8%)	< 0.001	34 (3.5%)	53 (5.4%)	0.048
Myocardial infraction	174 (15.7%)	3102 (14.0%)	0.121	157 (16.1%)	149 (15.2%)	0.663
Hemiplegia	13 (1.2%)	192 (0.9%)	0.319	9 (0.9%)	10 (1.0%)	1.00
Connective Tissue Disease	55 (5.0%)	889 (4.0%)	0.119	48 (4.9%)	55 (5.6%)	0.544
Leukemia	14 (1.3%)	259 (1.2%)	0.774	12 (1.2%)	16 (1.6%)	0.569
Lymphoma	44 (4.0%)	648 (2.9%)	0.056	40 (4.1%)	41 (4.2%)	1.00
Pulmonary Disease	189 (17.1%)	3360 (15.2%)	0.095	169 (17.3%)	162 (16.6%)	0.718
<u>Labs & Medications</u>						

Variable ^d	Unadjusted		p-value	Propensity Score Matched		
	Plasma Transfusion (N=1105)	No Plasma Transfusion (N=22080)		Plasma Transfusion (N=978)	No Plasma Transfusion (N=978)	p-value
APTT (seconds)	36.0 (31.0, 42.0)	32.0 (28.0, 36.0)	< 0.001	35.0 (31.0, 41.8)	35.0 (31.0, 42.0)	0.489
Albumin (g/dL)	3.4 (2.8, 4.0)	3.7 (3.0, 4.2)	< 0.001	3.4 (2.8, 4.0)	3.4 (2.8, 4.0)	0.934
INR	1.7 (1.4, 2.2)	1.2 (1.0, 1.4)	< 0.001	1.6 (1.4, 2.2)	1.8 (1.5, 2.4)	< 0.001
Creatinine (mg/dL)	1.1 (0.8, 1.7)	0.9 (0.7, 1.2)	< 0.001	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)	0.391
Platelet count (x 10 ⁹ /L)	147 (105, 208)	159 (118, 218)	< 0.001	145 (104, 204)	149 (1.8, 215)	0.274
Hemoglobin (g/dL)	10.3 (9.3, 11.7)	10.8 (9.6, 12.3)	< 0.001	10.3 (9.3, 11.7)	10.4 (9.1, 11.9)	0.181
Aspirin or Clopidogrel (7 days)	531 (48.1%)	7721 (35.0%)	< 0.001	466 (47.6%)	475 (48.6%)	0.717
Direct Thrombin Inhibitor (7 days)	13 (1.2%)	168 (0.8%)	0.156	13 (1.3%)	14 (1.4%)	1.00
Warfarin (7 days)	478 (43.3%)	5246 (23.8%)	< 0.001	418 (42.7%)	443 (45.3%)	0.274
Factors Xa Inhibitor (7 days)	1 (0.1%)	40 (0.2%)	0.722	1 (0.1%)	0 (0.0%)	1.00
LMW Heparin (24 hrs)	108 (9.8%)	1764 (8.0%)	0.0362	97 (9.9%)	90 (9.2%)	0.645
Therapeutic Heparin (24 hrs)	60 (5.4%)	2181 (9.9%)	< 0.001	60 (6.1%)	24 (2.5%)	< 0.001
Procedural Characteristics						
ICU type			0.105			< 0.001
. Medical	399 (36.1%)	7755 (35.1%)		335 (34.3%)	468 (47.9%)	
. Surgical	535 (48.4%)	11313 (51.2%)		489 (50.0%)	373 (38.1%)	
. Mixed	171 (15.5%)	3012 (13.6%)		154 (15.7%)	137 (14.0%)	

^aContinuous variables are summarized as median (Q1, Q3). Categorical variables are summarized as n (%).

CHF = congestive heart failure; DM = diabetes mellitus; DM with complications = diabetes mellitus with end-organ dysfunction; AIDS = acquired immunodeficiency syndrome; LMW heparin = low-molecular weight heparin; INR = international normalized ratio; APTT = activated partial thromboplastin time.

Table 2

Adjusted analyses for primary and secondary outcomes in the propensity-matched cohort.

Outcome^a	Prophylactic plasma (n=978)	No therapy (n=978)	P Value[*]	OR (95% CI)[*]
RBC transfusion within 24 hours	325 (33.2)	137 (14.0)	< 0.001	4.3 (3.3, 5.7)
Mortality	150 (15.3)	177 (18.1)	0.940	1.0 (0.8, 1.3)
Outcome^a	Prophylactic plasma (n=978)	No therapy (n=978)	P Value[*]	Estimated % increase (95% CI)[*]
ICU free days	25.0 (22.4, 26.8)	24.5 (21.6, 26.5)	0.270	1.3 (−1.0, 3.7)
Hospital free days	19.8 (11.8, 22.8)	20.9 (16.3, 23.6)	< 0.001	−11.0 (−10.6, −11.4)

^aNumbers are n (%) for categorical outcomes and median (Q1,Q3) for continuous outcomes.

^{*}Estimates and p-values are from logistic regression for categorical outcomes and negative binomial regression for length of stay. Model was adjusted using INR and therapeutic heparin. Odds ratios > 1 imply increased odds for the outcome in those receiving plasma. Estimated % increase < 0 imply fewer free days in those receiving plasma.

OR = odds ratio; CI = confidence interval; RBC = red blood cell transfusion; ICU = intensive care unit.

Table 3

Adjusted analyses for primary and secondary outcomes in the propensity-matched cohort in those with INR 1.5.

Outcome^a	Prophylactic plasma (n=618)	No therapy (n=618)	P Value*	OR (95% CI)*
RBC transfusion within 24 hours	176 (28.5)	94 (15.2)	< 0.001	3.4 (2.4, 4.8)
Mortality	120 (19.4)	118 (19.1)	0.400	1.1 (0.8, 1.5)
Outcome^a	Prophylactic plasma (n=618)	No therapy (n=618)	P Value*	Estimated % increase (95% CI)*
ICU free days	25.8 (22.9, 27.1)	24.9 (21.7, 26.5)	< 0.001	2.3 (1.8, 2.8)
Hospital free days	18.9 (10.7, 22.7)	20.6 (15.4, 23.6)	< 0.001	-13.0 (-12.5, -13.5)

^aNumbers are n (%) for categorical outcomes and median (Q1,Q3) for continuous outcomes.

[†]Estimates and p-values are from logistic regression for categorical outcomes and negative binomial regression for length of stay. Model was adjusted using INR and therapeutic heparin. Odds ratios > 1 imply increased odds for the outcome in those receiving plasma. Estimated % increase < 0 imply fewer free days in those receiving plasma.

CI = confidence interval; RBC = red blood cell transfusion; ICU = intensive care unit.

Table 4

Adjusted analyses in the propensity-matched cohort for medical and surgical ICU patients

Outcome ^a	Medical ICU				Surgical ICU			
	Prophylactic plasma (n=313)	No therapy (n=313)	P Value [*]	Estimate (95% CI) [*]	Prophylactic plasma (n=341)	No therapy (n=341)	P Value [*]	Estimate (95% CI) [*]
RBC transfusion within 24 hours	85 (21.7)	41 (13.1)	< 0.001	3.2 (2.0, 5.4)	121 (35.5)	43 (12.6)	< 0.001	5.5 (3.4, 8.9)
Mortality	68 (21.7)	63 (20.1)	0.150	1.3 (0.9, 2.0)	29 (8.5)	39 (11.4)	0.790	0.9 (0.5, 1.6)
Outcome ^a	Prophylactic plasma (n=313)		No therapy (n=313)	Estimate % increase [*]	Prophylactic plasma (n=341)		No therapy (n=341)	Estimated % increase [*]
ICU free days	25.7 (23.2, 26.9)		25.4 (22.9, 26.6)	0.003	24.5 (22.5, 26.8)		23.4 (21.4, 26.4)	0.028
Hospital free days	18.1 (8.2, 22.4)		20.7 (15.4, 23.8)	< 0.001	20.8 (13.9, 22.8)		20.9 (15.8, 23.3)	< 0.001

^aNumbers are n (%) for categorical outcomes and median (Q1,Q3) for continuous outcomes.

^{*}Estimates and p-values are from logistic regression for categorical outcomes and negative binomial regression for length of stay. Model was adjusted using INR and therapeutic heparin. Odds ratios > 1 imply increased odds for the outcome in those receiving plasma. Estimated % increase < 0 imply fewer free days in those receiving plasma.

OR = odds ratio; CI = confidence interval; RBC = red blood cell transfusion; ICU = intensive care unit.