

Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities

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BACKGROUND: Fresh-frozen plasma (FFP) is frequently transfused to patients with mild prolongation of coagulation values under the assumption that FFP will correct the coagulopathy. There is little evidence to support this practice, however. To determine the effect of FFP on coagulation variables and correlation with bleeding in patients with mildly prolonged coagulation values, a prospective audit of all FFP transfusions at the Massachusetts General Hospital between September 2, 2004, and September 30, 2005, was performed.

STUDY DESIGN AND METHODS: All patients transfused with FFP for a pretransfusion prothrombin time (PT) between 13.1 and 17 seconds (international normalized ratio [INR], 1.1-1.85) and with a follow-up PT-INR within 8 hours of transfusion were included. Of 1091 units of FFP transfused, follow-up coagulation values within 8 hours were available for 121 patients (324 units).

RESULTS: Transfusion of FFP resulted in normalization of PT-INR values in 0.8 percent of patients (95% confidence interval [CI], 0.0020-0.045) and decreased the PT-INR value halfway to normalization in 15.0 percent of patients (95% CI, 0.097-0.225). Median decrease in PT was 0.20 seconds (median decrease in INR, 0.07). Pretransfusion PT-INR, partial thromboplastin time, platelet count, and creatinine values had no correlation with red blood cell loss.

CONCLUSION: It is concluded that transfusion of FFP for mild abnormalities of coagulation values results in partial normalization of PT in a minority of patients and fails to correct the PT in 99 percent of patients.

Fresh-frozen plasma (FFP) is frequently transfused to patients with mild-to-moderate elevations in prothrombin time (PT) under the twin assumptions that these test results imply a coagulopathy and that FFP transfusion will correct the coagulopathy. The assumption that coagulation test variables predict the risk of bleeding has been challenged.¹⁻³ Numerous studies evaluating bleeding following central venous line placement,^{4,5} liver biopsy,⁶ thoracentesis,⁷ paracentesis,⁷ and lumbar puncture⁸ have all revealed no correlation between the risk of bleeding and mild abnormalities in preprocedure PT, partial thromboplastin time (PTT), or platelet (PLT) values. Despite this, use of FFP before invasive procedures for mildly prolonged PT values is a widespread practice.^{9,10} The persistence of this transfusion practice may relate to the assumption that FFP corrects the abnormal coagulation results.

In contrast to the substantial evidence indicating the poor predictive value of preoperative coagulation screening assays, there have been few studies examining the effect of FFP transfusion on the PT value after transfusion. In 1966 Spector and coworkers¹¹ published the first study of the effect of large volumes of FFP (3-9 units) transfused to 13 patients with liver disease and elevated PT values (17-26 sec).¹¹ The PT failed to normalize in any of these patients and elevation of coagulation factors were short-

ABBREVIATIONS: ICU = intensive care unit; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time.

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lived (declining by 50% within 4 hr after transfusion). Three additional studies of the effect of FFP on patients with elevated PT and liver disease were subsequently published.^{12,13} The most recent study noted a significant decrease in PT after FFP transfusion to 85 patients with a pretransfusion PT ranging from 13.5 to 21.5 seconds.¹³ FFP transfusion, however, rarely resulted in correction of PT to within 3 seconds of control values.

To date, there have been no studies examining the effect of FFP in a large cohort of hospitalized patients with mild elevations of the PT (PT < 17 sec or international normalized ratio [INR] < 2.0). Because such mild abnormalities are common among hospitalized patients, a substantial proportion of FFP is transfused to such individuals.^{9,10} The only published observation of the effect of FFP transfusion on patients with mild prolongations of PT comes from a series of 22 patients with INR values between 1.1 and 1.6.¹⁴ In this group of patients receiving a mean of 1.9 units of FFP, Holland and associates¹⁴ noted no significant change in the INR value. We set out to evaluate prospectively the effect of FFP transfusion on laboratory variables of hemostasis in a large number of patients and to determine whether there is any correlation between the pretransfusion PT-INR range and evidence of bleeding.

MATERIALS AND METHODS

Participants

We conducted a prospective audit of all transfusions of FFP from September 2, 2004, to June 30, 2005, at the Massachusetts General Hospital (Boston, MA). The study was reviewed by the Partners Institutional Review and Ethics Board and permission for the study was granted. Any patient who received FFP with a pretransfusion PT of 13.1 to 17 seconds (INR range, 1.1-1.85) was recorded. Because the duration of effect of FFP lasts approximately 6 to 8 hours, only those patients who had a follow-up PT-INR value within 8 hours of transfusion were included in the study. From this set of patients we excluded 1) patients receiving FFP for therapeutic plasma exchange and 2) patients whose pretransfusion PT-INR value was recorded more than 48 hours before the FFP transfusion. In cases where patients had received transfusions on more than one occasion during the prospective audit, we only included data from the patient's earliest transfusion episode. This ensured that every patient was only represented once in the data set.

Measurements

We recorded patient age, sex, date of FFP transfusion, and hospital location at time of FFP transfusion, roughly organized as medical floor (including neurology floor and cardiac step-down unit), medical intensive care unit (ICU) (including cardiac care ICU and neurologic ICU), surgical

ICU (including cardiac surgical ICU), surgical floor (including obstetrics and gynecology), pediatric inpatients, and outpatient clinics.

The requesting physician's indication for FFP transfusion was also recorded. Physicians ordering transfusions must select from a list of common indications for FFP transfusion listed on the physician order entry form. Alternatively, they could describe indications for FFP transfusions not listed on the physician order entry form. FFP requests from the operating room or emergency department did not require an indication for FFP transfusion.

We retrospectively reviewed each patient's medical record and recorded the following laboratory values when available: pretransfusion creatinine and PLT values as well as the pre- and posttransfusion PT, INR, PTT, and hematocrit (Hct) values. We recorded the number of all other blood products given around the time of FFP transfusion (defined as 4 hr before or after FFP transfusion). Finally, we recorded the type, dosages, and routes of all hemostatic drugs (vitamin K, protamine, DDAVP, antifibrinolytic drugs, factor concentrates) given within 24 hours of FFP transfusion. Patients who were receiving therapeutic doses of anticoagulation medications within 24 hours of FFP transfusion (warfarin, heparin, low-molecular-weight heparin, anti-factor Xa medications, and direct thrombin inhibitors) were counted, as was the type of anticoagulant medication. Finally, all suspected transfusion reactions due to FFP or other blood products transfused in conjunction with FFP were recorded.

PT was determined with a standard method of determination of the time necessary to coagulate 0.2 mL of plasma at 37°C after addition of 0.2 mL of thromboplastin (Simplastin L, bioMérieux, Durham, NC), which has an ISI of 2.0. The INR was calculated by raising the PT ratio to the power of the recipient ISI. The times of measurement of the pre- and posttransfusion PT-INR, PTT, Hct, and PLT values were recorded in minutes relative to the time that FFP was released from the blood transfusion service.

Estimated red blood cell (RBC) loss was calculated by the formula:

$$\text{RBC loss} = ((\text{Hct}_{\text{pre-FFP transfusion}} - \text{Hct}_{\text{post-FFP transfusion}}) / 3) + \text{number of units of RBCs transfused.}$$

Thus, the units of RBC loss are noted as RBC equivalent units. A negative value for RBC loss denotes an increase in RBC content whereas a positive value indicates a loss of RBC content.

Statistical analysis

The proportion of patients who attained a normal posttransfusion PT (≤ 13 sec; $\text{INR} \leq 1.1$), the proportion who achieved at least 50 percent correction of the pretransfusion PT, and the median decrease in PT were calculated with 95 percent confidence intervals (CIs). All statistical

analyses were completed with statistical software (Stata, Version 8.0, Stata Corp., College Station, TX).

Several groups were compared based on the proportion of patients whose PT values decreased at least halfway to normal. To explore whether there was a dose-response effect of FFP on the PT, patients who received 1 unit were compared to patients who received 2 units. To determine whether the time of measurement of PT after FFP transfusion affected the posttransfusion PT value, the proportion of patients who achieved greater than 50 percent correction of PT with a posttransfusion measurement of less than 4 hours was compared to the proportion who achieved 50 percent correction based on a PT measurement at least 4 hours after FFP transfusion. To determine whether there was a relationship between pretransfusion PT and likelihood of correction of PT, the number of patients achieving at least 50 percent correction of PT with a pretransfusion PT of 13 to 14 seconds (INR, 1.1-1.25) was compared with those with a pretransfusion PT of greater than 14 to 17 seconds (INR, 1.25-1.85). All analyses were completed with Fisher's exact test. Similar analyses were planned for patients who fully corrected, but the number of patients who fully corrected was too small to make comparisons meaningful.

Correlation between estimated RBC loss and pretransfusion PT-INR, PTT, PLT value, and creatinine was determined with Spearman's correlation coefficient. This nonparametric method of correlation was used because there were several outlier values in each group. Transformations of the pretransfusion values were also tested for correlation when necessary from inspection of the graphs. Because multiple comparisons were made between four variables and estimated RBC loss, the Bonferroni correction was used to adjust the p value of significance from not greater than 0.05 to not greater than 0.0125.

RESULTS

Characteristic of patients

Between September 2, 2004, and June 30, 2005, a total of 1091 units of FFP were transfused to patients with a pretransfusion PT of 13.1 to 17 seconds (INR range, 1.1-1.85) at Massachusetts General Hospital. Of these 1091 units, 471 were associated with a follow-up PT measurement within 8 hours of transfusion. These 471 units were transfused to 121 different patients. Of these 471 units, 324 units were transfused during the first transfusion episode in these 121 patients and were included in this study.

The characteristics of the 121 patients included in this study are listed in Table 1. Although the median age was 50 years, the range of ages was wide. The majority of patients had normal renal function as evidenced by a median creatinine value well within the range of normal. Because our patients represented those in surgery, intensive care, and general medical care, there was a wide range

TABLE 1. Characteristics of 121 patients receiving FFP with a PT of 13.1 to 17 sec (INR, 1.1-1.85)

Median age (range)	50 years (6-69)
Sex (%)	75 male, 46 female (62%, 38%)
Median creatinine at time of FFP transfusion (range)	1 mg/dL (0.2-13.4)
Median PLT count before FFP transfusion (range)	$98 \times 10^9/L$ (18-802)
Median estimated RBC loss (range)†	2.4 RBC unit equivalents (-1.1 to +25.6)
Median number of units RBCs transfused (range)	2 (1-24)
Median number of units FFP transfused (range)	2 (1-20)
Median number of units PLTs transfused	0 (0-30)
Number of patients on therapeutic anticoagulation just before FFP transfusion (%)	
Warfarin	10 (8.3)
Heparin/low-molecular-weight heparin	2 (1.7)/1 (0.8)

* A positive value indicates a loss of RBC unit equivalents whereas a negative value indicates an increase in RBC unit equivalents.

† Estimated RBC loss was calculated according to the formula: Estimated RBC loss = $((\text{Hct}_{\text{pre-FFP transfusion}} - \text{Hct}_{\text{post-FFP transfusion}})/3) +$ number of units of RBCs transfused.

in the estimated RBC loss occurring around the time of FFP transfusion. Some patients lost as much as the equivalent of 25 units of RBCs whereas transfusion in others resulted in a net increase of approximately 1 RBC unit. This diversity in bleeding was also evident in the units of actual RBCs transfused, which ranged from 0 to 24 units. Although the median PLT count was below the range of normal limits, most patients did not have a clinically significant thrombocytopenia requiring PLT transfusion. Finally, approximately 8.3 percent of patients had been on warfarin within 24 hours of FFP transfusion. The distribution of FFP is shown in Table 2, and the stated indications for transfusion of FFP are shown in Table 3.

Effect of FFP on the PT

Figure 2 shows the effect of FFP transfusion on the INR value for patients with mild elevation of the PT-INR. The effect of different doses of FFP on the INR is shown in Fig. 1. After 324 transfusion events, the median decrease in PT was 0.20 seconds (95% CI, 0.1-0.4) and the median decrease in INR was 0.07 (Fig. 2). The proportion of patients achieving normalization of PT after FFP transfusion (i.e., posttransfusion PT < 13.1 sec; INR < 1.1) was 0.0083 (95% CI, 0.002-0.045). Furthermore, only in 15.0 percent of patients did the PT-INR correct at least halfway to normal (95% CI, 9.7%-22.5%). Among these cases, there was no significant relationship between pretransfusion PT and likelihood of achieving 50 percent correction of the PT after FFP transfusion ($p > 0.5$, Fisher's exact test). This fact is also reflected in Fig. 2, which

TABLE 2. Distribution of FFP transfusion for a PT of 13.1 to 17 seconds (INR, 1.1-1.85) by hospital location

Number (%) of patients transfused by hospital location (n = 121)	
Operating room	31 (25.6)
Surgical floor (includes surgical subspecialties and gynecology)	42 (34.7)
Medical ICU (includes cardiac care ICU)	14 (11.6)
Medical floor (includes step-down unit, medical neurology)	17 (14.0)
Surgical ICU (includes burn unit)	9 (7.4)
Emergency department	8 (6.6)
Number (%) of units transfused by hospital location (n = 324)	
Operating room	119 (36.7)
Surgical floor (includes all surgical subspecialties and gynecology)	95 (29.3)
Medical ICU (includes cardiac care ICU)	31 (9.6)
Medical floor (includes step-down unit)	25 (7.7)
Surgical ICU (includes burn unit)	26 (8.0)
Emergency department	28 (8.6)

TABLE 3. Indication for FFP transfusion stated by ordering physician

Indication	Number (%) of patients transfused for this indication (n = 121)	Number (%) of FFP units transfused for this indication (n = 324)
Before procedure with elevated INR	18 (14.9)	33 (10.1)
Bleeding and elevated INR	23 (19.0)	67 (20.7)
Coumadin before procedure	1 (0.8)	1 (0.3)
Factor deficiency (including liver disease)	6 (5.0)	15 (4.6)
Coumadin and bleeding	7 (5.8)	13 (4.0)
Prophylaxis (nonbleed)	1 (0.8)	0 (0)
None given (patient in emergency department or operating room)*	35 (28.9)	132 (40.7)
Other (free text indication)	30 (24.8)	63 (19.4)

* No indication for FFP transfusion was required when FFP was requested from the operating room or emergency department.

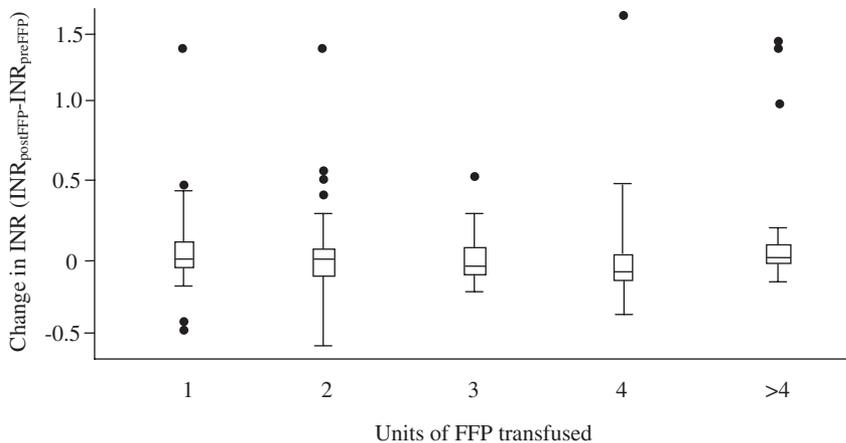


Fig. 1. Box-and-whiskers plot of the effect of FFP transfusion (n = 324 units) on the change in INR based on number of units of FFP transfused per patient among patients (n = 121) with mild abnormalities of coagulation.

depicts a histogram of the change in INR for patients with a pretransfusion INR of 1 to 1.5 and another separate histogram of the change in INR for patients with a higher pretransfusion INR (>1.5; Fig. 2).

From the box-and-whiskers plot illustrated in Fig. 1, there did not appear to be a significant dose-response effect, and increasing amounts of FFP did not appear to result in larger decrements in PT. Indeed, when the likelihood of achieving at least 50 percent correction of the PT was compared in patients receiving 1 versus 2 units of FFP, no significant association was noted ($p > 0.5$, Fisher's exact test).

To demonstrate that the effect of FFP transfusion on coagulation variables was similar in patients who were actively bleeding as well as in more stable patients, we calculated the proportion of patients achieving a 50 percent correction of PT-INR value in those patients receiving not more than 1 RBC units and those receiving more than 1 RBC units. The proportion of patients achieving 50 percent correction of PT-INR value was 15.9 percent (95% CI, 0.083-0.261) among patients who received not more than 1 RBC units and 15.7 percent among those receiving more than 1 RBC units (95% CI, 0.101-0.227).

The effect of FFP on the PT value measured at different time intervals after FFP transfusion is illustrated in Table 4. The mean time of measurement of posttransfusion PT was 3.4 hours \pm 24.6 minutes after FFP transfusion (mean \pm SEM). Although this study included patients with a follow-up PT value up to 8 hours after transfusion and attempts to identify patients with consumptive coagulopathies were not made, there was no relation of posttransfusion PT values and time after FFP transfusion. There was no significant difference in the likelihood of achieving 50 percent normalization of PT-INR based on measurement of posttransfusion PT of less than 4 hours or at least 4 hours from FFP transfusion ($p = 0.392$, Fisher's exact test).

Correlation of hemostasis variables with estimated RBC loss

The graphs of correlation between estimated RBC loss and pretransfusion PT-INR, PTT, creatinine, and PLT value are shown in Fig. 3. The Spearman rank order correlation

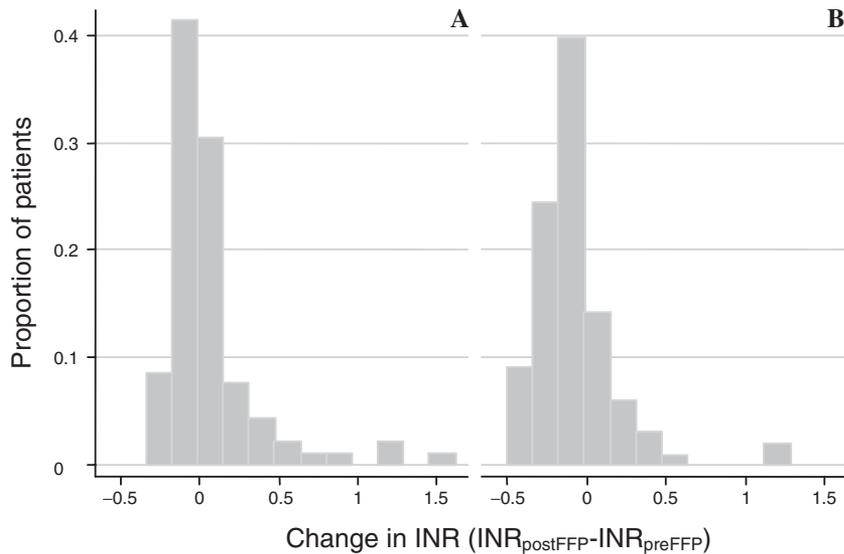


Fig. 2. Effect of FFP transfusion on PT-INR value in 121 patients with mild elevation of PT-INR. (A) Histogram of the change in INR in those patients with a pre-FFP transfusion INR of 1.1-1.5. (B) Histogram of the change in INR in those patients with a pre-transfusion INR of 1.5 to 1.85.

TABLE 4. Effect of FFP transfusion on the PT-INR value based on number of hours after FFP transfusion in patients (n = 121) with mild abnormalities of coagulation

Hours after FFP transfusion	Median change in INR*	Number of patients	Proportion (95% CI) achieving 50% correction of PT-INR
0-2	0.009	68	0.103 (0.046-0.189)
2-4	-0.057	66	0.242 (0.151-0.353)
4-6	-0.068	40	0.15 (0.063-0.279)
6-8	-0.073	16	0.063 (0.0034-0.252)

* Change in INR = $INR_{post-FFP} - INR_{pre-FFP}$.

coefficient is shown on each graph. There was no significant correlation between estimated RBC loss and pre-transfusion PT-INR ($p = 0.047$), PTT ($p = 0.29$), PLT ($p = 0.82$), or creatinine value ($p = 0.36$). Although the correlation between pretransfusion PT-INR and estimated RBC loss was associated with a p value that approached significance ($p = 0.047$), this association was not significant after correcting for multiple comparisons. Furthermore, the correlation coefficient describing the association between PT-INR value and estimated RBC loss was -0.182 indicating that as the pretransfusion PT increased, the observed estimated RBC loss tended to decrease. Thus, there was neither a clinically meaningful nor a significant association between the pretransfusion PT value and estimated RBC loss.

Transfusion reactions

There were 6 reported suspected transfusion reactions of 191 transfusion episodes. All transfusion reactions were

reviewed by blood transfusion service physicians at the Massachusetts General Hospital. Of the 6 suspected transfusion reactions, 2 were deemed to be unrelated to the transfusion of any blood products, 3 were classified as febrile nonhemolytic transfusion reactions due to RBC transfusion, and 1 was an urticarial transfusion reaction due to FFP transfusion.

DISCUSSION

In this study we examined the effect of FFP transfusion on the PT and evidence of bleeding in patients with mild elevations of the PT (13.1-17 sec; INR, 1.1-1.85). We found that regardless of the number of units of FFP transfused or the number of hours after FFP transfusion, FFP resulted in only trivial decrements of the PT. Despite commonly held views, we found that mild-to-moderate elevation of the PT was "corrected" by FFP in almost no patients. Only a small number of patients achieved even a 50 percent normalization of pretransfusion PT. There was no relationship between extent of PT prolongation within this mildly elevated range and likelihood of achieving at least 50 percent correction of the PT.

In previous studies that were restricted to patients with chronic liver disease, Spector,¹¹ Mannucci,¹⁵ and Youssef¹³ and colleagues reported that FFP transfusion rarely resulted in correction of the PT, and Holland and coworkers¹⁴ reported similar findings in 22 patients. More specifically, when Youssef and colleagues¹³ examined the effect of FFP transfusion to 80 patients with liver disease and an elevated PT, they found that the PT corrected to within 3 seconds of the control value in 10 percent of patients. Our study differs from prior reports as we included a greater number of patients with a wide range of medical and surgical conditions, and we restricted our analysis to patients with a PT of fewer than 17 seconds ($INR < 1.85$). Indeed, because the relationship between coagulation factor levels and PT is exponential, transfusion of 1 to 4 units of FFP would be predicted to be unlikely to create a 50 percent drop in PT values for patients with a pretransfusion PT of 13.1 to 17 seconds.¹⁶ Thus, our results are consistent with the known in vitro relationship between the level of coagulation factors and the PT assay. Transfusion of a greater number of units of FFP might be expected to have a greater effect on correct-

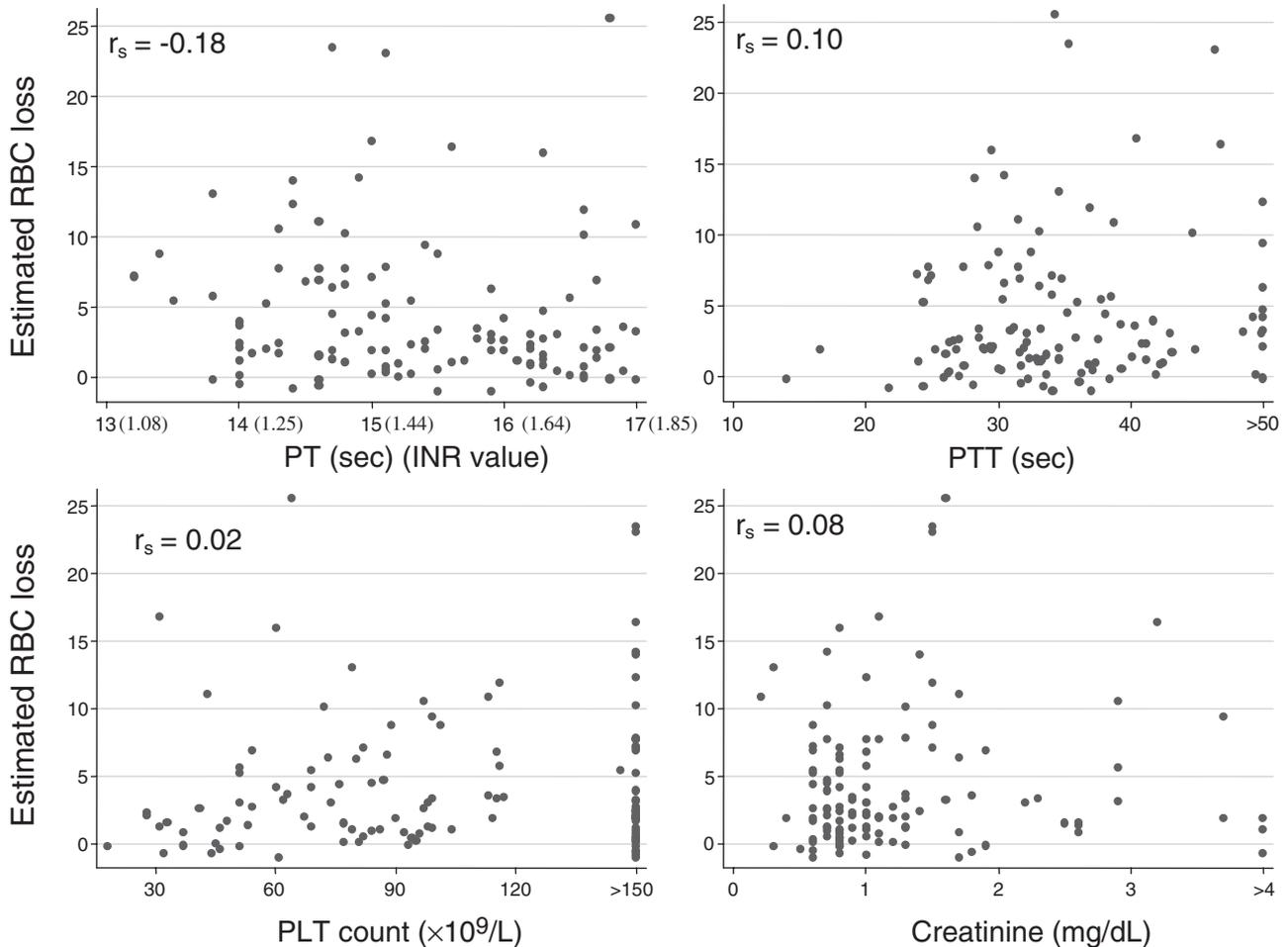


Fig. 3. Lack of correlation between estimated RBC loss* and pretransfusion PT/INR, PTT, creatinine, and PLT values in patients with mild abnormalities of coagulation. *Estimated RBC loss was calculated according to the formula: $RBC\ loss = ((Hct_{pre-FFP\ transfusion} - Hct_{post-FFP\ transfusion})/3) + \text{number of units of RBCs transfused}$. r_s = Spearman rank sum correlation coefficient.

ing PT values after FFP transfusion. A greater decrease in PT value would not necessarily result in decreased estimated RBC loss, however, because there is a poor correlation between laboratory variables of coagulation and risk of bleeding.^{7,16}

We found no significant correlation between the pretransfusion PT-INR value and the estimated extent of bleeding. This result is consistent with the notion that mild-to-moderately abnormal PT test results do not predict or correlate with the extent of blood loss and has been previously reported in multiple prior studies.^{4,5,7,17} We acknowledge, however, that rather than directly measuring blood loss we used hemoglobin (Hb) concentration corrected for RBC administration as a rough indication of blood loss. Because Hb changes are also affected by crystalloid and colloid administration, as well as by diuresis and hemoconcentration, Hb changes do not necessarily accurately represent blood loss.

Our study has limitations. We report findings on a heterogeneous group of patients and cannot completely eliminate the possibility that FFP would have a more substantial effect on the PT value for specific patient subgroups, although none were seen in our data. Furthermore, some of our patients received concurrent therapies, such as intravenous fluid therapy, at the time of the FFP transfusion that would have affected both the post-FFP PT value and the estimated RBC loss. Interestingly, the effect of FFP transfusion on the PT of healthy, nonbleeding volunteers has been previously studied.¹⁸ Hambleton and associates¹⁸ studied the effect of transfusion of 1 L of FFP on the PT of 27 healthy volunteers anticoagulated with coumadin to a mildly elevated INR of 1.5 to 2.0. Although they found a much higher percentage of patients with 50 percent correction of the PT, none of the patients experienced full correction of the PT.¹⁸

Another limitation of our study is that patients with a pretransfusion PT between 13.1 and 17 seconds (INR, 1.1-

1.85) who did not receive FFP were not studied. Therefore, no comparison can be made regarding the extent of blood loss with and without FFP for patients with mild elevations in PT.

The data presented here reveal a trivial effect of FFP transfusion on the PT in patients with mild elevations of pretransfusion PT. These results call to question the practice of FFP transfusion given to patients with mild to moderate prolongation of the PT and suggest that there is no relationship between mild elevations in the PT and extent of estimated blood loss. Given the absence of evidence of benefit coupled with the known risks of transfusion of FFP, FFP transfusion to nonbleeding patients in response to a mild to moderately prolonged PT value cannot be supported. Of note, the incidence of transfusion reactions observed in this study was consistent with the known incidence of transfusion complications reported elsewhere.¹⁹

The role of FFP transfusion to bleeding patients with a PT of 13.1 to 17 seconds (INR, 1.1-1.85) is not entirely clear but results from this study question both goals and assumptions surrounding the PT as a guide to therapy. The true value of FFP transfusion administered to patients with surgical bleeding or transfused before procedures will be best answered in future prospective controlled trials where patients with abnormal coagulation values are randomized to receive FFP versus placebo.

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