Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units*

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**LEARNING OBJECTIVES**

After participating in this educational activity, the participant should be better able to:

1. Assess risk factors for the development of international normalized ratio abnormalities in patients with coagulopathy.
2. Examine implications of abnormal international normalized ratio values in the administration of fresh frozen plasma.
3. Evaluate incidence of abnormal international normalized ratio values in critically ill patients.

Unless otherwise noted, the faculty’s, staff’s, and authors’ spouse(s)/life partner(s) (if any) have nothing to disclose.

The authors have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

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**Objective:** Coagulopathy occurs frequently in critically ill patients, but its epidemiology, current treatment, and relation to patient outcome are poorly understood. We described the prevalence, risk factors, and treatment of prolongation of the prothrombin time in critically ill patients using the international normalized ratio to standardize data and explored its association with intensive care unit survival.

**Design:** Prospective multiple center observational cohort study.

**Setting:** Twenty-nine adult intensive care units in the United Kingdom.

**Patients:** All sequentially admitted patients over an 8-wk period.

**Interventions:** None.

**Measurements and Main Results:** Prospective daily data were collected concerning prevalence, predefined risk factors, and treatment of coagulopathy throughout intensive care unit admission. Of 1923 intensive care unit admissions, 30% developed abnormal international normalized ratio values (defined as an international normalized ratio >1.5). Most international normalized ratio abnormalities were minor and short-lived (73% of worst international normalized ratio values 1.6–2.5). Male sex, chronic liver disease, sepsis, warfarin therapy, increments in Acute Physiology and Chronic Health Evaluation II score, severity of renal and hepatic dysfunction, and red cell transfusions were all independent risk factors for international normalized ratio abnormalities (all \( p < .001 \)). In all regression models, there was a strong independent association between abnormal international normalized ratio values and greater intensive care unit mortality (\( p < .0001 \)), particularly when international normalized ratio increased after intensive care unit admission. Among patients with abnormal international normalized ratios, 33% received fresh-frozen plasma transfusions during their intensive care unit stay, but the pretransfusion international normalized ratio value varied widely. Fifty-one percent of fresh-frozen plasma treatments were to nonbleeding patients and 40% to nonbleeding patients whose international normalized ratio was normal or only modestly deranged (≤2.5). The dose of fresh-frozen plasma administered was highly variable (median dose 10.8 mL/kg\(^{-1}\) (first, third quartile 7.2, 14.4; range, 2.4–41.1 mL/kg\(^{-1}\)).

**Conclusions:** Prothrombin time prolongation is prevalent in critically ill patients and is independently associated with greater intensive care unit mortality. Wide variation in fresh-frozen plasma treatment exists suggesting clinical uncertainty regarding best practice, particularly as a prophylactic treatment. (Crit Care Med 2010; 38:1939–1946)

**Key Words:** transfusion; critical illness; coagulation; prothrombin time; coagulopathy; fresh-frozen plasma

*See also p. 2065.

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The disease processes that cause critical illness can impair blood coagulation, increasing the risk of bleeding (1). In addition, excessive activation of coagulation pathways may result in microvascular thrombosis resulting in organ dysfunction as a result of inflammation and impaired tissue oxygen supply. Studying the epidemiology and clinical importance of coagulopathy is challenging as a result of the complex interaction between these physiological systems and the assays used to assess them. The most widely used laboratory assay of coagulation factor activity, particularly in relation to acquired disease-related defects, is the prothrombin time (PT), and this may be standardized against control tests either to calculate a prothrombin ratio or, in many hospitals, using the international normalized ratio (INR). Fresh-frozen plasma (FFP) is a common treatment for coagulopathy, but current clinical guidelines concerning its use are based largely on expert opinion or data from relatively poor-quality studies (2–5). Several studies have examined the use of FFP in various patient populations (6–13), but the prevalence, severity, and risk factors for coagulopathy during an episode of critical illness are poorly described. In addition, the association between coagulopathy disturbances and patient outcome is unknown. This information is needed to design high-quality trials of FFP treatment and make clinical practice more evidence-based. We carried out a multicentered study to describe the epidemiology of a key marker of coagulopathy, prolongation of the PT, in critically ill patients and its association with patient survival. Participants in this CME activity should be better able to assess the risk factors for coagulopathy in critically ill patients, and evaluate the incidence and appropriate management and administration of FFP to these patients.

METHODS

Participating Centers. Twenty-nine intensive care units (ICUs) in the United Kingdom participated comprising a total of 301 critical care beds. The ICUs were in 19 tertiary hospitals and 10 regional hospitals and included two ICUs with specialist liver units and five ICUs admitting patients requiring neurointensive care. All ICUs recruited admissions over a 4- to 8-wk period during which clinical care of all patients remained the responsibility of attending clinicians to reflect "usual practice."

The Multicentered Research Ethics Committee waived the need for patient consent.

Study Subjects. All patients admitted to general adult ICUs were screened. The only predefined exclusions were ICU readmissions during the same hospital stay, transfers from other ICUs, and admissions where life expectancy was considered <4 hrs. Specialist medical and surgical cardiac ICUs were excluded. Screening logs captured all admissions to ensure accurate denominator data.

Data Collection. Data collection included age, sex, source of admission, primary reason for ICU admission, Acute Physiology and Chronic Health Evaluation II score, estimated dry weight, medical history, and details of hematology blood results and blood components used in the 24 hrs before admission. Daily data collection included routine laboratory tests, all procedures, and the occurrence of clinically significant hemorrhage (defined a priori as estimated total cumulative blood loss >300 mL or 1 U of red cells and/or bleeding from a critical site such as intracranial). The timing of all blood component transfusions was recorded. For all FFP transfusions, clinicians recorded the clinical indication as "coagulopathy with bleeding," "coagulopathy with no bleeding," or "coagulopathy with no bleeding before an invasive procedure."

Existing local practices for reporting of coagulation tests were used, which comprised either INR or PT. For comparative analysis between hospital laboratories, PT values were converted to INR (INR = [PT/MNPT]181, in which MNPT and ISI were the laboratory-specific mean normal PT and international specificity index (the mean ISI for these hospitals was 1.06, close to 1), respectively. We chose this approach a priori as the best method of adjusting for interinstitutional differences in thromboplastin sensitivities, because standardization of PT assays was not feasible, and 10 of 29 hospitals reported only INR data. For our primary analysis, we defined PT prolongation as an INR >1.5. We chose this cutoff because many clinicians base transfusion decisions on this value, and we aimed to generate pragmatic clinically relevant estimates for the epidemiology of coagulation disturbances. We recognized that this cutoff was semiarbitrary and also calculated prevalence data for patients in whom a worst INR >1.2 and >2 were reported as a sensitivity analysis.

If a patient developed PT prolongation equivalent to an INR >1.5, an additional data collection form was completed, including the presence of systemic inflammatory response syndrome, infection, hemorrhage, red cell transfusions, and organ dysfunction during the 24 hrs before onset of the PT abnormality.

Data collection was continued from the period of admission to ICU death, discharge, or 30 continuous days in the ICU. All data forms underwent quality control and query resolution followed by computer-based data verification and validation before analysis of the final data set.

Analysis. Preagreed definitions were used (see supplementary data, Supplemental Digital Content 1, http://links.lww.com/CCM/A162). The severity of PT prolongation used the worst recorded INR during the ICU stay. Duration of PT prolongation episodes was described using Kaplan-Meier methods to allow for censored patients who did not complete an episode as a result of death or discharge before resolution of PT abnormality.

A range of predefined factors at ICU admission were agreed by consensus a priori as potential risk factors for PT prolongation and were compared between patients with and without PT prolongation during their ICU stay. We developed a regression model exploring the relation between patient characteristics at ICU admission and the presence of PT prolongation during admission. We also calculated the prevalence of systemic inflammatory response syndrome, infection, circulatory shock, acute lung injury, acute renal failure, hepatic dysfunction, moderate hemorrhage, and major hemorrhage during the 24 hrs before onset of PT prolongation.

Management of PT Prolongation With FFP. We calculated the proportion of patients with PT prolongation who received FFP during ICU admission, the indications for FFP transfusion, and the volume of FFP received per transfusion episode. For these calculations, the estimated patient dry weight at ICU admission was used to estimate dose in mL/kg. The INR values preceding FFP transfusion episodes were used as measures of transfusion triggers.

Relationship Between PT Prolongation and ICU Outcome. We developed logistic regression models to explore the association between PT prolongation during ICU stay and mortality during admission. First, we included all measured baseline characteristics at ICU admission and then entered the first INR value into the model to explore the importance of PT prolongation at ICU admission. In further models, we explored differences between patients whose severity of PT prolongation worsened from those in whom it resolved or remained unaltered. In these models, we used both absolute INR values and changes in INR from the first recorded INR (delta INR).

RESULTS

There were 2386 admissions during the study period to the 29 adult ICUs (14 in England, 12 in Scotland, two in Northern Ireland, one in Wales). Of these, 1990 admissions were eligible for data collection. The 396 exclusions comprised 138 readmissions, 96 locally agreed exclusions, 83 transfers from other ICUs, 70 patients where admission was expected to be <4 hrs, and nine others. Of 1990 eligible ad-
mission, 67 did not have adequately complete data for analysis. The final total of 1923 admissions (96.6% of all eligible admissions) used 11,075 ICU days, of which data were complete for 11,014 days (99.4%). Demographic and diagnostic characteristics of the cohort are shown in Table 1. A total of 11,153 INR and/or PT coagulation tests were undertaken, which equated to 5.8 tests per admission and 1.01 tests per ICU day. For 1882 (17%) of these tests, INR was equated to 5.8 tests per admission and 1.01 tests per ICU day. For 1882 (17%) of these tests, INR was equated to 5.8 tests per admission and 1.01 tests per ICU day.

Prevalence, Severity, and Duration of PT Prolongation. A flow diagram showing the pattern of PT prolongation in relation to ICU admission is shown in Figure 1. PT prolongation was documented in 12.9% of patients during the 24 hrs before admission and was present at ICU admission in 22.8% of patients. Combining these periods gave a prevalence of 25.2%. Only 9.6% of the 1438 patients without PT prolongation at ICU admission subsequently developed it during ICU stay, and the overall prevalence of PT prolongation at some time during ICU stay was 30.0% (32.4% if the pre-ICU period was also included). For the sensitivity analysis, 59.9% of patients had a worst INR of >1.2 and 13.6% of patients had a worst INR of >2.

Most (n = 526 [91%]) of the patients with INR >1.5 had a single episode of PT prolongation, but 40 (7%) had two episodes, five (1%) had three episodes, four (1%) had four episodes, and one patient had five episodes. Many patients had short-lived minor derangements of the PT and in 158 (27%) of patients, a single INR result in the range of 1.6–2.0 was recorded. The worst recorded INR value was ≥2.5 for 421 patients (73% of cases); for more severe derangements, the worst value was 2.6–3.5 for 79 (14%) of cases, 3.6–5.0 for 46 (8%) of cases, and >5.0 in 30 (5%) of cases. A paired activated partial PT value was available for 549 (95%) of the episodes of PT prolongation (mean value 53.2 secs; sd 29.8 secs).

The median (first, third quartile) duration of PT prolongation was 2.9 days (1.9, 5.5 days) and the episode had resolved at the time of ICU discharge in 215 (37%) cases. For unresolved episodes, 198 (34%) patients were discharged alive from the ICU with ongoing PT prolongation, and 160 (28%) died in the ICU before the episode resolved. Three patients had ongoing PT prolongation after 30 days in the ICU when data collection stopped.

Characteristics of Patients With PT Prolongation. Admission characteristics for patients with and without PT prolongation are compared in Table 1. Patients with PT prolongation were more likely to be older, female, have higher Acute Physiology and Chronic Health Evaluation II scores, have chronic liver disease and dial-

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Table 1. Characteristics of the study cohort at admission to the ICU and of the subgroups with or without PT prolongation during the ICU stay

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Admissions (n = 1923)</th>
<th>Admissions With INR &gt;1.5 (n = 576)</th>
<th>Admissions With Normal INR Test (n = 1347)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (sd; minimum–maximum)</td>
<td>58.3 (18.8; 9–100)</td>
<td>60.8 (18.0; 9–100)</td>
<td>57.8 (19.1; 10–97)</td>
<td>.0002</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>1087 (57)</td>
<td>295 (51.2)</td>
<td>792 (58.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Mean APACHE II score (sd)</td>
<td>18.4 (8.3)</td>
<td>21.4 (17.1)</td>
<td>17.1 (7.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Source of admission, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>479 (25)</td>
<td>110 (19.3)</td>
<td>369 (27.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Operating room</td>
<td>801 (42)</td>
<td>222 (38.9)</td>
<td>579 (43.2)</td>
<td></td>
</tr>
<tr>
<td>Transfer from ward</td>
<td>522 (27)</td>
<td>203 (35.6)</td>
<td>319 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Transfer from other hospital</td>
<td>110 (6)</td>
<td>36 (6.3)</td>
<td>74 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Type of admission, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>875 (46)</td>
<td>273 (47.5)</td>
<td>602 (44.7)</td>
<td>.007</td>
</tr>
<tr>
<td>Surgical</td>
<td>908 (47)</td>
<td>277 (48.2)</td>
<td>631 (46.9)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>130 (7)</td>
<td>25 (4.4)</td>
<td>113 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Risk factors for coagulopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic coagulation disorder, no. (%)</td>
<td>7 (&lt;0.1)</td>
<td>1 (0.2)</td>
<td>6 (0.5)</td>
<td>.66</td>
</tr>
<tr>
<td>Chronic liver disease, no. (%)</td>
<td>119 (6)</td>
<td>83 (14.4)</td>
<td>36 (2.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Chronic renal failure with dialysis, no. (%)</td>
<td>54 (3)</td>
<td>26 (4.5)</td>
<td>28 (2.1)</td>
<td>.005</td>
</tr>
<tr>
<td>Warfarin therapy before ICU admission, no. (%)</td>
<td>47 (2)</td>
<td>41 (7.1)</td>
<td>6 (0.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sepsis at admission</td>
<td>499 (26)</td>
<td>206 (35.8)</td>
<td>293 (21.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Highest recorded creatinine concentration during 24 hrs before ICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>1047</td>
<td>292 (63.1)</td>
<td>755 (78.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>151–300</td>
<td>242</td>
<td>111 (24.0)</td>
<td>131 (13.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;300 μmol/L</td>
<td>140</td>
<td>60 (13.0)</td>
<td>80 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Highest bilirubin recorded during 24 hrs before ICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>847</td>
<td>215 (59.6)</td>
<td>632 (83.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>20–100</td>
<td>230</td>
<td>114 (31.6)</td>
<td>116 (15.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;100 μmol/L</td>
<td>42</td>
<td>32 (8.9)</td>
<td>10 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion during initial treatment period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 units</td>
<td>1378</td>
<td>351 (60.9)</td>
<td>1027 (76.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1–4 units</td>
<td>332</td>
<td>128 (22.2)</td>
<td>204 (15.1)</td>
<td></td>
</tr>
<tr>
<td>5–8 units</td>
<td>113</td>
<td>50 (8.7)</td>
<td>63 (4.7)</td>
<td></td>
</tr>
<tr>
<td>≥8 units</td>
<td>100</td>
<td>47 (8.2)</td>
<td>53 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Median length of ICU stay (Q1, Q3)</td>
<td>2.0 (0.8, 5.5)</td>
<td>3.0 (1.1, 8.1)</td>
<td>1.8 (0.8, 4.3)</td>
<td></td>
</tr>
<tr>
<td>Outcome, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from ICU</td>
<td>1521 (79)</td>
<td>355 (62)</td>
<td>1166 (87)</td>
<td></td>
</tr>
<tr>
<td>Still in ICU after 30 days</td>
<td>38 (2)</td>
<td>18 (3)</td>
<td>20 (1)</td>
<td></td>
</tr>
<tr>
<td>Died in ICU within 30 days</td>
<td>364 (19)</td>
<td>203 (35)</td>
<td>161 (12)</td>
<td></td>
</tr>
</tbody>
</table>

ICU, intensive care unit; PT, prothrombin time; INR, international normalized ratio; APACHE, Acute Physiology and Chronic Health Evaluation.

*See regression analysis for ICU outcome.
ysis-dependent renal failure, have sepsis, and be receiving warfarin therapy. More patients with PT prolongation were admitted from the general hospital wards rather than the operating room or emergency department. They were more likely to have elevated plasma bilirubin and creatinine concentrations and to have received blood transfusions before ICU admission.

During the 24 hrs before onset of PT prolongation, there was a high prevalence of documented systemic inflammatory response syndrome (61.4%) and proven or clinically suspected infection (46.8%). Considering specific organ dysfunction, the prevalence of circulatory shock was 69.4%, acute lung injury 51.9%, acute renal failure 13.9%, and liver dysfunction 7.4%. The prevalence of moderate and major hemorrhage was 6.9% and 2.3%, respectively.

In a multivariate logistic regression model, the factors found to have independent associations with PT prolongation are shown in Table 2. In the final model, the probability of PT prolongation in ICU was markedly increased by male sex, warfarin therapy at ICU admission, greater Acute Physiology and Chronic Health Evaluation II score, the presence of chronic liver disease, and elevated plasma bilirubin, sepsis, and blood transfusions during the 24 hrs before onset. Associations were similar when the model included a worst INR of >1.5 or >2.0, with the exception of an
association with nonoperating room admissions in the model using INR >2.0.

Use of FFP. In total, 215 patients (11.2%) received FFP during the study, which was administered during 159 of 642 episodes of PT prolongation (24.8%). For the majority (94) of PT prolongation episodes, one FFP transfusion treatment occurred; two treatments occurred in 38, the majority (94) of PT prolongation episodes in the study population. The numbers and proportions of all episodes are broken down for FFP transfusions that were and were not associated with hemorrhage.

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Figure 2. International normalized ratio (INR) values preceding fresh-frozen plasma (FFP) transfusion for all the FFP transfusion episodes documented in the study population. The numbers and proportions of all episodes are broken down for FFP transfusions that were and were not associated with hemorrhage.

 though this difference was clinically small (median 2.1 [first, third quartile 1.9, 2.6] vs. 1.9 [1.7, 2.4]; p < .0001). Confirmed infection was less prevalent for episodes treated with FFP (40.7% vs. 51.4%, p = .04), but there was no difference in the prevalence of preexisting chronic liver disease, warfarin therapy, systemic inflammatory response syndrome, shock, acute lung injury, or renal or liver dysfunction.

The reasons given for FFP administration were bleeding (n = 124 [45.9%]), prophylaxis for a procedure (n = 45 [16.7%]), and in 100 cases (37.0%), no procedure was planned and no bleeding was present. There was wide variation in the dose of FFP used; the median (first, third quartile; range) volume of FFP transfused per treatment was 803 mL (541, 1093; 220 –2775 mL), which equated to a median (first, third quartile; range) dose of 10.8 mL/kg (7.2, 14.4; 2.4 – 41.1 mL/kg). Considering all 404 FFP transfusion treatments, 51.3% were to patients in whom no hemorrhage was present. The INR values preceding FFP transfusion varied widely and were often only mildly increased (Fig. 2). Notably, for 40.4% of all FFP treatments, there was no hemorrhage and the preceding INR was <2.5 and for 13.9% of all treatments there was no hemorrhage and the preceding INR was <1.5.

Mortality. In unadjusted analysis, the ICU mortality was higher for patients with PT prolongation than those without (35% vs. 12%). In the regression model incorporating all factors listed in Table 1, greater age, Acute Physiology and Chronic Health Evaluation II score, bilirubin concentration, transfusion of >8 units of red blood cells, and admissions that were not from the operating room were all independently associated with greater ICU mortality. No statistically significant associations were found with sepsis (p = .06), sex, admitting specialty, chronic ischemic heart disease, chronic liver disease, chronic renal failure, warfarin therapy at ICU admission, or plasma creatinine (all p > .3). When the admission INR was introduced into the model, admission INR was strongly associated with ICU mortality after adjusting for the other factors (Table 3; the 47 patients receiving warfarin therapy were excluded from this model). In all of the models exploring the importance of the highest INR after ICU admission, there was a strong association between a higher or increasing INR value and greater ICU mortality, even after allowing for the initial INR (all p < .0001). The differences in absolute risk for ICU death are illustrated in Table 4. An increase in the INR of >1 during the ICU stay was associated with an approximately 40% absolute increase in ICU death rate in patients with and without PT prolongation at ICU admission.

**DISCUSSION**

We have shown that 30% of admissions to general ICUs in the United Kingdom develop prolongation of the PT during the ICU period of their critical illness (using an INR cutoff value of >1.5 to define PT prolongation). In most cases, derangement of PT was mild (75% INR < 2.5) and short-lived (27% had a single INR value of 1.6 -2.0). Despite this, patients with PT prolongation were at significantly increased risk of death compared with patients without PT prolongation, even after adjusting for illness severity at
admission and a range of potentially important patient comorbidities and acute illness characteristics. Worsening PT prolongation was strongly associated with a greater chance of dying in the ICU.

Our large overall sample size (representing approximately 12% of all admissions to ICUs in the United Kingdom during the period of the study) and the number, characteristics, and geographic dispersion of participating ICUs suggest our population was representative of adult general ICUs in the United Kingdom. We included a relatively high number of teaching hospital ICUs, which may have a more complex case mix than smaller ICUs, but despite this, our study provides a detailed prospective description of coagulation disturbances in an unselected population of critically ill patients. The definition of abnormal PT was based on a laboratory threshold INR value >1.5, which is commonly used by clinicians. A more inclusive (INR >1.2) and exclusive (INR >2.0) cutoff revealed a prevalence range of 14–60%, although the inclusive extreme almost certainly included many patients without clinically important coagulation factor abnormalities. We believe a prevalence of 30% is an accurate pragmatic estimate of prevalence for this population given that detailed quantitative correlations with individual coagulation factor levels is not feasible for such a large cohort. Although the INR was developed to standardize assessment of the response to vitamin K antagonists, it does provide a means of comparing data between laboratories by adjusting for the use of different thromboplastins between laboratories, which we considered important in the study.

There was wide variation in the management of PT prolongation with FFP in terms of dose, the indication for correcting PT prolongation, and the pretransfusion INR. Of note, 40% of all FFP treatments were administered to patients without hemorrhage in whom preceding coagulation tests were normal or only modestly deranged (INR ≤2.5). FFP was the standard blood product for managing PT prolongation at the time of the study and administration of other products such as prothrombin complex and factor concentrates are very unlikely to have confounded our data because they were not provided by the blood services and no clinicians reported using them. Our data confirm the high levels of clinical uncertainty in current clinical practice (14–16). Mildly deranged INR values may be associated with near normal coagulation factor levels (17), and the doses of FFP required to achieve clinically meaningful changes in coagulation factor content are difficult to predict (18–21). Abnormalities of PT/INR are also poor predictors of procedure-related bleeding risk (22–26), and the quality of evidence supporting prophylactic FFP transfusion is poor (27, 28). Our data support the need for high-quality clinical evidence to guide management decisions and create greater consistency in clinical practice.

PT prolongation, especially worsening PT, had a strong independent association with a greater chance of dying in ICU. This relationship has several possible explanations and despite our inclusion of a range of predefined factors is potentially subject to residual confounding by factors that we did not adequately adjust for in our regression models, but our data support the hypothesis that coagulopathy, or treatments such as FFP that are associated with it, contribute directly to adverse outcomes during critical illness. For example, many patients with PT prolongation who received FFP had infection, systemic inflammatory response syndrome, or circulatory shock. The risk–benefit balance of correcting coagulopathy in these patients is uncertain and it is noteworthy that sepsis therapies showing most promise in recent years have had anticoagulant rather than procoagulant properties (29–31). FFP transfusions have well-recognized risks, including transfusion-related acute lung injury and transfusion-associated circulatory overload (6, 8, 10, 32, 33), and it is relevant that 52% of patients with PT prolongation fulfilled diagnostic criteria for acute lung injury. These observations provide further justification for the need for adequately powered studies addressing the risk–benefit profile of FFP transfusions.

CONCLUSION

Our large epidemiologic study has shown that PT prolongation is prevalent in critically ill patients and is strongly associated with a greater risk of death. PT
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