ABNORMAL COAGULATION TESTS OBTAINED IN THE EMERGENCY DEPARTMENT ARE ASSOCIATED WITH MORTALITY IN PATIENTS WITH SUSPECTED INFECTION

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Abstract—Background: Early recognition of acute organ dysfunction in emergency department (ED) patients with suspected infection may help select patients at increased risk of mortality. The hematologic system is often overlooked in the evaluation and management of patients with infection because it is poorly circumscribed and serves a multitude of functions. Study Objectives: We examine the hypothesis that abnormalities in commonly and easily obtained markers of coagulation function (international normalized ratio [INR], partial thromboplastin time [PTT], and platelet count [PLT]) are associated with mortality in ED patients admitted to the hospital with suspected infection. Methods: Design: Secondary analysis of a prospective observational cohort study. Setting: Urban tertiary care university hospital with 50,000 annual ED visits. Patients: Included patients: adults (age 18 ≥ years) evaluated in the ED for a suspected infection, had an INR, PTT, and PLT obtained during the ED stay, admitted to the hospital. Excluded patients: on oral anticoagulant therapy, received heparin, or pre-existing severe liver disease. Results: There were 1688 patients included. The in-hospital mortality rate was 5.9%. After adjusting for elderly status, comorbid illness burden, and severity of illness, elevated INR was associated with a 2.9 (95% confidence interval [CI] 1.6–5.2) increased odds of death, and a low platelet count (< 150,000/μL) was associated with 2.0 (95% CI 1.2–3.3) increased odds of death. The C-statistic for the model was 0.80. Conclusion: We found an independent association between abnormalities in the coagulation system and mortality in ED patients with suspected infection. These findings underscore the close interaction between inflammation and coagulation and provide evidence that these simple laboratory tests should be routinely considered during the early evaluation of the infected patient. © 2012 Elsevier Inc.

Keywords—coagulation; hematology; infection

INTRODUCTION

There are an estimated 750,000 cases of severe sepsis and septic shock annually in hospitalized patients in the United States, with an estimated in-hospital mortality rate of over 30% (1). Nearly two-thirds of these patients are initially evaluated in the emergency department (ED) (2). Early identification and treatment of severe sepsis in the ED can improve morbidity and mortality (3,4). Early recognition of acute organ dysfunction in ED patients with suspected infection may help select patients at increased risk of mortality who may benefit most from aggressive treatment strategies (5,6).

The hematologic system is often overlooked in the evaluation and management of patients with sepsis syndromes. Unlike other organ systems, the hematologic system is poorly circumscribed, and serves a multitude of functions (7). Regulation of coagulation occurs through a
balance of anti- and procoagulant proteins, which are synthesized in the liver, endothelium, and circulating cells. Red blood cells, white blood cells, and platelets are involved in both the local and systemic response to invading pathogens, and are widely distributed throughout the body. Together, these different components play an important role in oxygen delivery, hemostasis, and defense against pathogens.

The interactions between the inflammatory and coagulation systems are becoming increasingly understood at the cellular level (8). In vitro and in vivo studies in animals and humans demonstrate that inflammatory responses shift the hemostatic balance to favor a procoagulant state. In extreme cases, this can manifest as disseminated intravascular coagulation (9). Inflammatory mediators have a multiplicity of effects on markers of coagulation, including elevated platelet count, altered platelet reactivity, increased platelet consumption, down-regulation of natural anticoagulant mechanisms, and impaired fibrinolysis. Collectively, these changes lead to initiation and propagation of coagulation (8).

To date, most of the studies examining the relationship between inflammation and coagulation have either examined the development of disseminated intravascular coagulation (DIC), or have assessed the role of biomarkers of coagulation activation that are not commonly assessed in clinical practice (e.g., antithrombin, plasminogen activator inhibitor, protein C) (10–14). To examine the importance of changes in the hemostatic system in ED patients with suspected infection, we undertook the current study to examine the hypothesis that abnormalities in commonly and easily obtained markers of coagulation function (international normalized ratio [INR], partial thromboplastin time [PTT], and platelet count [PLT]) are associated with mortality in ED patients admitted to the hospital with a suspected infection.

**MATERIALS AND METHODS**

**Study Design**

This was a secondary analysis of a prospective observational cohort study. The study was approved by the Institutional Review Board at our institution.

**Study Setting and Population**

Consecutive patients were enrolled at an urban tertiary care university hospital with approximately 50,000 annual ED visits. The study enrollment period was between September 18, 2005 and September 30, 2006. We included all adult patients (age 18 years or older) who were evaluated in the ED for a suspected infection as determined by the treating physician, had an INR, PTT, and PLT obtained during the ED stay, and were subsequently admitted to the hospital. Patients were excluded if they were on oral anticoagulant therapy at the time of ED evaluation, if they received intravenous heparin during their ED stay, or if they had a pre-existing diagnosis of severe liver disease, which was defined a priori as any patient who had a previous diagnosis of decompensated or end-stage liver disease by their primary care physician or hepatologist as determined by medical record review at the time of admission.

**Study Protocol**

Patients were identified prospectively and their ED charts were reviewed and abstracted without knowledge of the patient’s hospital course using a previously described methodology that has been shown to exhibit a high degree of inter-rater reliability in identifying patients with suspected infection (15). In brief, we reviewed the daily list of ED admissions to screen for patients with an admission diagnosis consistent with infection (e.g., pneumonia) or possibly consistent with infection (e.g., shortness of breath). Trained research assistants reviewed and abstracted the ED medical records of eligible patients to confirm that the ED clinicians had a clinical suspicion of infection at the time of admission. This was determined by reviewing the medical decision-making portion of the emergency physician’s notes and by the decision to give antibiotics. Only information that was available during the ED course (i.e., before admission) was abstracted. Outcome data were not available during this phase of data collection. Pertinent demographic data and components of history, physical examination, and vital sign information were recorded using a structured data collection instrument. Laboratory values were collected, and the suspected source of infection was derived from the medical decision-making portion of the chart. To limit the possibility of bias, outcome data were collected separately using the hospital’s information systems.

Comorbidity status was assessed using the Charlson comorbidity index (16). The Charlson index has been shown to be associated with 1-year mortality in ED patients with suspected infection (17). Severity of illness was determined using the Mortality in Emergency Department Sepsis (MEDS) score (15). The MEDS score has been shown to be associated with both in-hospital and 1-year mortality in ED patients with suspected infection, and externally validated in a multi-center study (15,18,19). To avoid collinearity in the regression model, the platelet count and age components of the MEDS score were excluded, resulting in a modified MEDS score (mMEDS). The end-stage liver disease component of the Charlson score was excluded, resulting in a modified Charlson score. The mMEDS and modified Charlson scores were reported as continuous variables. The primary outcome of interest was in-hospital mortality rate.
Laboratory test results were classified as normal or abnormal using clinically relevant thresholds determined a priori: INR $\geq 1.5$, PTT $\geq 35$ s, PLT $\geq 150,000$/uL. The INR and PLT thresholds were chosen due to their clinical use and their use as thresholds in other studies (15). The PTT threshold was chosen because it is the upper limit of normal in our clinical laboratory. We built a multiple logistic regression model to adjust for potential confounders, including elderly status (age $\geq 65$ years), severity of illness (modified MEDS score), and comorbid burden (modified Charlson score) to assess whether coagulation parameters were, in fact, independent predictors of mortality in sepsis. The C-statistic was reported as a measure of model performance. All statistics were analyzed using JMP 7.0 (SAS Institute, Cary, NC).

**RESULTS**

There were a total of 1688 patients who met the inclusion criteria. During the time of enrollment, there were 5638 patients evaluated in the ED with suspected infection, of which 4151 patients were admitted to the hospital. There were 1765 patients excluded because they did not have all three laboratory tests obtained during their ED stay. Patients had a mean age of 63.8 ($\pm$ SD 19) years, and 48% were male (Table 1). The most commonly identified suspected sources of infection were lung (21%), skin and soft tissue (14%), and urinary tract (13%). The mean modified Charlson score was 1.6 ($\pm$ 1.9), and the mean mMEDS score was 2.8 ($\pm$ 2.7). The in-hospital mortality rate was 5.9%.

The mean INR was 1.25 ($\pm$ 0.5), and 8.1% (136/1552) of all patients had an INR $\geq 1.5$. The mean PTT was 27.9 s ($\pm$ 11.7), and 7.2% (121/1688) of all patients had a PTT $\geq 35$ s. The mean platelet count was 272,000/uL ($\pm$ 138,000/uL), and 14.7% (249/1688) of all patients had a platelet count $\geq 150,000$/uL.

After adjusting for elderly status (age $\geq 65$ years), comorbid illness burden (Charlson score), and severity of illness (mMEDS score), elevated INR ($\geq 1.5$) was associated with a 2.9 (95% confidence interval [CI] 1.6–5.2) increased odds of death, and a low platelet count ($\geq 150,000$/uL) was associated with 2.0 (95% CI 1.2–3.3) increased odds of death (Table 2). The PTT was not independently associated with increased mortality in this model. The C-statistic for the model was 0.80.

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<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
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<tr>
<td>Intercept</td>
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<td>INR $&gt;$ 1.5</td>
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<td>1.6–5.2</td>
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<td>Platelets $&lt;$ 150,000/uL</td>
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The C-statistic representing the area under the curve for model accuracy was 0.80. CI = confidence interval; INR = international normalized ratio.


**DISCUSSION**

We found that abnormalities in coagulation markers occurred in 7–15% of patients in our cohort, and that abnormalities in INR and platelet count were significantly associated with mortality in ED patients with suspected infection. These findings underscore the close interaction between inflammation and coagulation and the importance of the coagulation cascade in sepsis. Furthermore, this study provides evidence that these simple laboratory tests should be routinely considered during the early evaluation of the infected patient. Prior studies, most notably the Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, have demonstrated that in patients with severe sepsis and septic shock, activation of coagulation and inflammatory pathways are virtually universal phenomena (13,20). In patients who do not fulfill the criteria for overt DIC, many have been shown to have an evolving coagulopathy, as demonstrated by worsening coagulation tests (10). The current criteria for non-overt DIC assess the pattern of change in coagulation tests such as the PLT, prothrombin time (PT), and D-dimer, along with additional specialized tests such as protein C and antithrombin levels. Our study is different from these prior studies because it includes all ED patients with suspected infection, and includes only coagulation tests commonly and easily obtained in the ED.

Systemic inflammation, as a result of infection, is associated with activation of primary and secondary hemostasis. Activation of primary hemostasis is manifested by thrombocytopenia in 35–59% of patients (7). Activation of secondary hemostasis is manifested by increased circulating levels of D-dimers in virtually all patients with severe sepsis, decreased protein C levels in up to 90% of such patients, and reduced antithrombin III (ATIII) levels in more than half of patients (11,13,14,21). Marked activation of coagulation and secondary consumption of clotting factors may lead to the clinical syndrome of DIC, characterized by widespread fibrin deposition and thrombosis of small and midsize vessels, along with uncontrolled bleeding resulting from consumption of platelets and coagulation proteins. However, in contrast to the universal finding of coagulation activation in patients with severe sepsis, DIC is estimated to occur in only 15–30% of these individuals (22,23).

Several mechanisms have been implicated in the development of thrombocytopenia in sepsis, including de novo ethylenediaminetetraacetic acid-dependent antibodies and secondary pseudthrombocytopenia, immune mechanisms, hematophagocytosis, platelet sequestration on activated endothelium, and consumption in DIC (7,24–27). Activation of the blood clotting mechanism in sepsis is initiated by tissue factor expression on the surface of circulating monocytes, tissue macrophages, and, possibly, subsets of endothelial cells (28). Sepsis is also associated with an attenuation of anticoagulant mechanisms, including protein C and ATIII levels, and the fibrinolytic pathway (29,30). Moreover, sepsis-mediated downregulation of thrombomodulin and endothelial protein C receptor on the endothelial cell surface may impair activation of protein C (31).

The above changes may have prognostic implications. For example, thrombocytopenia is associated with higher mortality in patients with severe sepsis (32). The degree and duration of thrombocytopenia, as well as the net change in the platelet count, are important determinants of survival (33). Low levels of circulating ATIII and protein C are predictive of poor survival (14,34). In clinical studies of multiple organ dysfunction, maximum PT and PTT were shown to be longer in non-survivors than in survivors (35). Other studies have reported that DIC is an independent predictor for mortality in patients with sepsis (36). However, DIC is often a late complication of overwhelming infection, rather than a presenting symptom. This study represents an attempt to understand the importance of coagulation dysfunction early in the examination of patients with suspected infection.

**Limitations**

This study has a number of limitations. We used the inclusion criteria of all ED patients who were admitted to the hospital and had INR, PT, and PLT obtained in the ED. There are certainly patients with potential infection who did not have all three laboratory tests obtained in the ED, which could have led to a selection bias. Although platelet counts are nearly universally obtained on all patients admitted with a suspected infection, it is possible that clinicians obtained INR and PT on patients who were suspected to be more ill, and therefore more likely to die during their hospitalization. Coagulation abnormalities may be confounded by other covariates that were not measured, and the increased risk of mortality that we found may not represent the true association between these parameters and mortality. Additionally, we used the outcome of death by any cause due to its robust nature, but patients may have had deaths not attributable to infection. The covariates that we used were obtained from the ED chart, which may be incomplete or inaccurate, leading to a misclassification bias. This was a single-center study, and prospective validation on a different patient population is required to assess the generalizability of our findings.

**CONCLUSION**

We found a statistically significant, independent association between abnormalities in the coagulation system...
(INR and PLT) and mortality in ED patients with suspected infection. These findings are potentially useful when identifying which patients require admission to the hospital, higher levels of care (e.g., step-down or intensive care unit), and when selecting patients for more aggressive sepsis therapies.

REFERENCES


ARTICLE SUMMARY

1. Why is this topic important?
Recognition of acute organ dysfunction in emergency department (ED) patients with suspected infection may help select patients at increased risk of mortality.

2. What does this study attempt to show?
This study examines the hypothesis that abnormalities in commonly and easily obtained markers of coagulation function (international normalized ratio [INR], partial thromboplastin time, and platelet count) are associated with mortality in ED patients admitted to the hospital with suspected infection.

3. What are the key findings?
After adjusting for elderly status, comorbid illness burden, and severity of illness, elevated INR or low platelet count was associated with an increased odds of death.

4. How is patient care impacted?
These findings underscore the close interaction between inflammation and coagulation, and provide evidence that these simple laboratory tests should be routinely considered during the early evaluation of the infected patient.