D-dimer Correlates With Proinflammatory Cytokine Levels and Outcomes in Critically Ill Patients*

Andrew F. Shorr, MD, MPH; Stephen J. Thomas, MD; Stephan A. Alkins, MD; Thomas M. Fitzpatrick, MD, PhD; and Geoffrey S. Ling, MD, PhD

Study objectives: To determine the relationship between d-dimer (DD) and both proinflammatory and anti-inflammatory cytokine levels, and to confirm the association between DD status and outcomes in critically ill patients.

Design: Prospective observational study.

Setting: Medical ICU (MICU) of a tertiary care, academic medical center.

Patients: Individuals admitted to the MICU.

Interventions: Within 24 h of MICU admission, patients had DD status determined and interleukin (IL) levels (IL-6, IL-8, and IL-10) and tumor necrosis factor (TNF)-α measured. The strength of the DD level was also noted. Subjects were then monitored prospectively to determine mortality rate and the incidence of organ failure.

Measurement and results: The study cohort included 79 patients (mean age, 65.2 years; 54.5% male patients). DD was present in 53.2% of subjects. The DD reaction was weak (1+) in 15 patients and strong (2+) in 27 patients. The TNF-α, IL-6, and IL-8 levels all increased in parallel with the increasing strength of the DD level. IL-10 levels did not differ based on DD status. Similarly, the severity of illness as measured by the APACHE (acute physiology and chronic health evaluation) II score was highest among those with higher DD levels: 24.7 ± 6.2 for those with 2+ DD vs 17.2 ± 3.1 and 11.5 ± 2.7 for those with 1+ DD and no circulating DD, respectively (p < 0.001). For patients lacking DD, the mortality rate was 8.1%, compared to 13.3% and 55.6% for those with 1+ and 2+ DD levels, respectively (p < 0.001). No patient without DD had multisystem organ failure (MSOF) develop, while the incidence of MSOF also increased with increasing DD levels. As a screening test for mortality, the DD performed as well as the APACHE II system.

Conclusions: The coagulation system is active in critically ill patients, and DD levels correlate with activation of the proinflammatory cytokine cascade. The absence of a relationship between DD and anti-inflammatory cytokines (IL-10) suggests that the presence of DD may reflect the imbalance between proinflammatory and anti-inflammatory cytokines. DD identifies patients at increased risk for both MSOF and death.

Key words: ARDS; critical illness; cytokine; d-dimer; death; outcomes; sepsis

Abbreviations: APACHE = acute physiology and chronic health evaluation; AUC = area under curve; CI = confidence interval; DD = d-dimer; IL = interleukin; MICU = medical ICU; MSOF = multisystem organ failure; TNF = tumor necrosis factor

D-dimer (DD) results from the destruction of cross-linked fibrin and therefore is a measure of clot formation and lysis. In turn, the presence of DD indicates activation of the coagulation system. DD is often measured in the evaluation of patients with suspected disseminated intravascular coagulation, and is emerging as a screening test for venous thromboembolism.1,2 DD has also been shown to correlate with outcomes in a number of diseases, including closed head injury and systemic lupus erythematosus.3,4 More specifically, endothelial injury and dysregulation of coagulation homeostasis have been noted in several diseases that may neces-

*From the Pulmonary and Critical Care Medicine Service, Walter Reed Army Medical Center, Washington, DC.
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Correspondence to: Andrew Shorr, MD, MPH, Pulmonary and Critical Care Medicine, Walter Reed Army Medical Center, 6900 Georgia Ave NW, Washington, DC; e-mail: AFSHORR@DNAMAIL.COM

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sitate treatment in an ICU, including variceal hemorrhage, sepsis, and ARDS.5–7 Investigators hypothe-
size that such diseases result in a microvascular coagulopathy that may lead to the formation of microthrombi.8 These microthrombi occlude the vascular beds of various organs and may contribute to their eventual failure.

In an earlier study,9 we demonstrated that DD correlated with mortality in a diverse group of critically ill medical patients. In a similar, larger trial, Kollef and colleagues10 noted that DD levels were critically ill medical patients. In a similar, larger trial, correlated with mortality in a diverse group of hemorrhage, sepsis, and ARDS.5–7 Investigators hypoth-
ecinated prior to the initiation of the study.

Severity of illness was measured via the APACHE (acute physiology and chronic health evaluation) II score.17 Severe sepsis and septic shock were defined in accordance with the conclusions of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.18 Consistent with the report of the American-European Consensus Conference Committee, ARDS was considered to be present if the subject had bilateral infiltrates acutely develop on chest radiograph in the absence of either a pulmonary capillary wedge pressure of > 18 mm Hg or clinical evidence of left atrial hypertension and had a PaO2/fraction of inspired oxygen ratio of ≤ 200. MSOF required severe dysfunction of at least two organs.19 For definitions of organ dysfunction, we employed those proposed by Hebert et al20 and Rubin et al21 with modifications. Specifically, organ failures were defined as follows: (1) renal, serum creatinine level > 2 mg/dL or a twofold rise in the creatinine level from baseline value; (2) hepatic, bilirubin level > 2.0 mg/dL or an alkaline phosphatase level > 350 U/L; (3) pulmonary, requirement for mechanical ventilation or a PaO2 < 60 mm Hg while breathing an fraction of inspired oxygen > 0.5 or the use of > 10 cm H2O of positive end-expiratory pressure; (4) cardiovascular, systolic BP ≤ 90 mm Hg or need for treatment with any vasopressor; (5) hematologic failure, WBC count < 2,000/μL or a platelet count < 75,000/μL, and/or an international normalized ratio of > 2.0; (6) neurologic, Glasgow Coma Scale score < 10 or a decrease in the Glasgow Coma Scale score by 3 if a primary CNS injury is present; and (7) GI, fresh blood from a nasogastric or orogastric tube and/or melaena or fresh blood from the rectum accompanied by a fall in hemoglobin > 20 g/L requiring at least 2 U of packed RBCs in 24 h.

Assays

At the time of study enrollment, DD was measured on whole blood with a rapid, semiquantitative system (SimpliRed; AGEN Biomedical Limited; Brisbane, Australia). In the presence of DD, this assay leads to RBC agglutination. For each sample, at least 10 μL of blood was placed in a test well and mixed with reagent for 2 min. In accordance with the instructions of the manufacturer, if there was no agglutination, we confirmed the absence of DD by performing a negative control. This was completed with a different reagent in another reaction well adjacent to the test well. If agglutination indicating the presence of DD was noted, its

Materials and Methods

Subjects and Setting

The study population included patients admitted to the medical ICU (MICU) at our institution between October 1999 and December 1999. Patients admitted to the MICU were eligible to participate if they were expected to remain in the MICU for > 24 h. Our institution is a tertiary-care, academic medical center, and the MICU contains eight beds. The study was approved by the Human Use Committee at Walter Reed Army Medical Center. Informed consent for participation was obtained from either the patient directly or his or her surrogate. If it was not possible to obtain consent within 24 h of hospital admission, the patient was not eligible to enroll into the study. For patients admitted more than once to the MICU, only data from the initial admission was analyzed.

End Points

Eligible patients were identified, and after consent was ob-
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intensity was graded as either weak (1+) or strong (2+) as outlined by the manufacturer. The stronger intensity of the reaction corresponds to higher levels of DD. The lower limit of detection of DD for the Simplified assay is 200 ng/mL. This level is in accordance with the upper limit of normal for DD. All DD assays were interpreted by one of two investigators (A.F.S. or S.J.T.). In other studies, the interobserver variability for this system has been minimal.  

Plasma samples for cytokine analysis were drawn contemporaneously with DD measurement. After immediate centrifugation, these were stored at −70°C until cytokine levels were determined. Thus, the number of freeze-thaw cycles was minimized. The cytokine analysis was performed so that the technician performing the assays was blinded to the patients’ DD status and to their clinical outcomes. Concentrations of TNF-α, IL-6, and IL-8 were measured by electroilluminescence. The sensitivity of this assay for each of these cytokines is 4.0 pg/mL, 5.0 pg/mL, and 5.0 pg/mL, respectively. IL-10 was measured by a electroilluminescence system. The sensitivity of this approach is 5.0 pg/mL.

Statistics

Continuous data are reported as mean ± SD. All comparisons were unpaired and two tailed. Normally distributed continuous variables were analyzed with the Student’s t test or analysis of variance. For continuous data that demonstrated a nonparametric distribution, we relied on the Wilcoxon rank sum test or the Kruskal-Wallis test. A χ² test was performed to compare categorical variables unless the expected size of any one cell was small. In those instances we used the Fisher’s Exact Test. To determine the screening characteristics of the various biochemical markers (eg, cytokines, DD) at predicting study end points (eg, mortality), we constructed standard two-by-two tables. Similarly, we created receiver operating curves to facilitate comparisons of the various biochemical tests. We analyzed the area under curves (AUCs) to identify if any particular biochemical marker was superior at predicting the clinical end points of interest. Statistical analysis was completed using software (SPSS 9.0; SPSS, Chicago, IL). All p values ≤ 0.05 were assumed to indicate statistical significance.

RESULTS

The study cohort included 79 patients. As shown in Table 1, the mean age of the subjects was 65.2 ± 14.7 years and 54.4% were male patients. The most frequent reasons for admission to the MICU were GI bleeding (25.3%), followed by respiratory failure (16.5%) and severe sepsis/septic shock (13.9%). The overall incidence of MSOF was 11.4%, while the in-hospital mortality rate for the entire cohort was 25.3%. DD was present in slightly more than half of the patients. Fifteen patients (35.7%) with circulating DD had a weak agglutination reaction; for the remainder (64.3%), the intensity of the reaction was graded as strong.

There was a significant association between DD status and proinflammatory cytokine levels (Table 2). For patients lacking DD, the mean TNF-α level measured 45.71 ± 36.16 pg/mL, as compared to 82.20 ± 15.10 pg/mL in patients with weak agglutination reactions and 104.96 ± 50.67 pg/mL in those with strong reactions (p < 0.001). Similarly, IL-6 levels increased significantly with the increasing presence of DD. IL-6 was barely detectable in those without DD. In patients with mild DD reactions, the mean IL-6 level was 27.00 ± 53.99 pg/mL, while it was more elevated at 99.91 ± 30.31 pg/mL in patients with strong DD reactions (p = 0.019). A similar pattern was also observed with respect to IL-8 (Table 2). There was no correlation, however, between the anti-inflammatory cytokine we studied, IL-10, and DD status. IL-10 levels were equivalent across the spectrum of DD results. Since cytokine levels have been shown to be associated with survival in critically ill patients, we performed a logistic regression to control for baseline cytokine concentrations. After adjusting for hospital admission concentrations of TNF-α, IL-6, IL-8, and IL-10, the odds ratio for in-hospital mortality for patients with the highest DD levels was 10.44 (95% confidence interval [CI], 1.40 to 78.15).

For the clinical end points, severity of illness was strongly correlated with the intensity of the DD reaction. In those without detectable DD, the APACHE II score was 11.5 ± 2.7, as compared to 17.2 ± 3.1 and 24.7 ± 6.2 for patients with 1+ and 2+ DD levels, respectively (p < 0.001). As a corollary, no patient lacking DD had either severe sepsis, septic shock, or ARDS develop. For those with DD, irrespective of the level, the incidence of severe sepsis or septic shock was significantly higher (54.8%, p < 0.001). Similarly, ARDS occurred more frequently among those with DD as compared to those without DD (0% vs 14.3%, p = 0.027). There was also a parallel step-up in the incidence of ARDS with increasing DD levels. For example, ARDS was 2.6 times more likely to occur among individuals with the strongest DD reactions as compared to those with mild elevations in DD (eg, 1+ reactions).

We noted like relationships between DD and both

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Table 1—Baseline Patient Characteristics (n = 79)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65.2 ± 14.7</td>
</tr>
<tr>
<td>Male</td>
<td>54.4</td>
</tr>
<tr>
<td>White race</td>
<td>70.9</td>
</tr>
<tr>
<td>Admitting diagnoses</td>
<td></td>
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<tr>
<td>GI hemorrhage</td>
<td>25.3</td>
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<tr>
<td>Acute respiratory failure</td>
<td>16.5</td>
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<tr>
<td>Sepsis</td>
<td>13.9</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11.4</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>10.1</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>8.9</td>
</tr>
<tr>
<td>MSOF</td>
<td>11.4</td>
</tr>
<tr>
<td>In-hospital mortality rate</td>
<td>25.3</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or %.
MSOF and mortality (Fig 1). No patient in whom DD was absent had MSOF develop. For those with mild DD elevations, one subject (6.7%) had MSOF; for those with higher DD levels, 29.6% had MSOF (p < 0.001). The median number of failing organs also correlated with DD: no organs failed in the DD-negative patients, one organ failed in those with weak DD, and three organs failed in those with high DD levels (p < 0.001). The in-hospital mortality rate was also significantly higher for patients with greater elevations in circulating DD: 55.6% of patients with high DD levels died as opposed to 13.3% of those with moderate DD elevations and 8.1% of subjects lacking DD (p < 0.001). The relative risk for mortality in patients with any detectable DD was 7.71 (95% CI, 2.03 to 29.19).

As a screening test for mortality, the DD performed comparably to the APACHE II score. (Fig 2). The AUC for the APACHE II score was 0.86; the AUC for the DD assays was 0.81 (p = not significant). The DD assay also functioned as well as either the TNF-α or IL-6 level at predicting MSOF. The AUC for the DD as a screening tool for MSOF was 0.87, while it was 0.88 for TNF-α and 0.83 for IL-6 (p = not significant).

### Discussion

This prospective study demonstrates that the results of a simple DD assay are predictive of multiple clinical outcomes in critically ill medical patients. The presence of circulating DD correlated not only with mortality but also with the incidence of sepsis, ARDS, and MSOF. As a screening test for mortality, the DD performed as well as the APACHE II score. On a biochemical level, we noted a close relationship between DD titers and proinflammatory cytokines. This finding is in contrast to the observation that anti-inflammatory cytokine levels (IL-10) did not vary based on DD status.

Two earlier studies have addressed the relationship between DD and clinical outcomes in the ICU. In a smaller study using a different assay system, we noted that 43% of patients had circulating DD. We also observed a significant correlation between mortality and DD status. Unlike the SimpliRed system, for the earlier study we employed a latex agglutination assay. Although inexpensive and able to provide results rapidly, latex agglutination tests are prone to more interobserver variability. This present study builds on the initial effort, in that we focused on

<table>
<thead>
<tr>
<th>Variables</th>
<th>DD− (n = 37)</th>
<th>DD 1+ (n = 15)</th>
<th>DD 2+ (n = 27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL</td>
<td>45.74 ± 36.16</td>
<td>82.20 ± 15.10</td>
<td>104.96 ± 50.670</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>0.97 ± 5.29</td>
<td>27.00 ± 23.99</td>
<td>99.91 ± 30.31</td>
<td>0.019</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>11.71 ± 33.68</td>
<td>10.2 ± 21.76</td>
<td>75.43 ± 130.72</td>
<td>0.016</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>1,918.71 ± 1,544.67</td>
<td>1,947.89 ± 1,897.11</td>
<td>1,897.11 ± 1,869.65</td>
<td>0.998</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>11.5 ± 2.7</td>
<td>17.2 ± 3.1</td>
<td>24.7 ± 6.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.

**Figure 1. DD and outcomes.** Note that the difference for incidence of both MSOF and mortality was statistically different based on DD status (p < 0.001).
multiple clinically important end points rather than simply mortality. In a larger trial of 321 subjects, Kollef et al\textsuperscript{10} found that DD measured with the SimpliRed system not only correlated with mortality but also with the development of MOF, sepsis, and vascular thromboses. In general, our findings confirm these earlier studies. Unlike Kollef et al\textsuperscript{10} who relied on a complex 4-point scale to interpret the DD assay, we interpreted the DD as being either negative, weakly positive, or strongly positive. This manufacturer recommends this approach. Thus, our results add to the efforts of Kollef et al\textsuperscript{10} by showing that the relationship between clinical outcomes and DD status still holds when the DD is interpreted with a simpler, less complex scale. Additionally, one strength of our study is that despite using a simpler grading system for the intensity of agglutination, we nonetheless noted a step-up in both severity of illness and mortality with increasing DD levels. This confirms the significance of DD in critical illness by suggesting a possible dose-response relationship between the degree to which the coagulation system is activated as manifest by the DD level and multiple, distinct clinical outcomes.

More generally, our findings add to the growing evidence underscoring the importance of the coagulation system in critical illness. For example, Rubin and colleagues\textsuperscript{21} demonstrated that elevated levels of von Willebrand antigen, a coagulation system marker of endothelial injury, were predictive of the development of ARDS in patients with nonpulmonary sepsis. Unlike this study, we focused on a more diverse group of patients, and assessed end points other than only ARDS. Similarly, Idell and colleagues\textsuperscript{22} reported enhanced levels of tissue-associated factor VII in BAL fluid from patients with ARDS. Bredbacka et al\textsuperscript{23} postulated that patients with signs of early hypercoagulation, as measured by elevated soluble fibrin levels, would progress to have more organ failures develop and have worse outcomes than patients with normal fibrin levels. Subjects with high fibrin levels had an in-hospital mortality rate of 46% compared to 14% in those with normal fibrin levels. Although our findings are in overall agreement with their results, the studies are not directly comparable. Our study population included only medical patients, while 40% of the study cohort evaluated by Bredbacka et al\textsuperscript{23} were either postoperative or obstetrical patients. Highlighting the importance of the other aspects of the coagulation in critical illness, Boldt et al\textsuperscript{24} noted that serial measurement of protein C may be an important biomarker for distinguishing sepsis from other causes of critical illness, while Hartman and coworkers\textsuperscript{25} reported that 85% of patients with severe sepsis had acquired protein C deficiency. Finally, and most importantly, efforts to restore coagulation homeostasis with infusions of protein C improve survival in select patients with severe sepsis and organ failure.\textsuperscript{12} Further studies are therefore warranted to correlate the relationship with DD status and protein C levels in hopes of developing a rapid, bedside test that will identify patients most likely to benefit from therapies directed at the coagulation system. At present, though, DD status alone should not be used to determine whether to offer treatments directed at the coagulation abnormalities common in critically patients.

The involvement of both proinflammatory and anti-inflammatory cytokines in critical illness is now

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{dd_vs_apache_ii.png}
\caption{DD vs APACHE II as a screening test for mortality. NS = not significant.}
\end{figure}

\[\text{Area Under the Curve}
D Dimer \quad 0.802
\ APACHE II \quad 0.858
\ p value for difference = NS\]
widely appreciated. Levels of certain proinflammatory cytokines have been shown to correlate with severity of illness and to be predictive of mortality for critically ill patients. Presterel et al reported that daily alterations in the APACHE III score and the mortality probability model score paralleled changes in both TNF-α and IL-6 levels. Additionally, TNF-α levels at admission to the ICU in patients with sepsis are predictive of survival. Few studies, however, have expressly examined the relationship between DD and cytokine levels. Pape and coworkers demonstrated a correlation between markers of coagulation including DD and IL-6 in trauma patients, while Lopez-Aguirre et al confirmed a relationship between multiple markers of coagulation system activation and cytokines. However, our finding that proinflammatory cytokine levels are greater in those with higher DD levels shows the potential interrelationships between the coagulation system and inflammation. The absence of a relationship between IL-10 and DD suggests that DD does not reflect changes in the anti-inflammatory cascade that may also be active in critical illness.

For outcome prediction purposes, a number of scoring systems exist to aid clinicians, and include the APACHE score, the mortality probability model score, the multiple organ dysfunction score, and the sequential organ failure assessment score. Only some of these scoring systems incorporate measures of the coagulation system. Those that do address coagulation focus only on the platelet count. Despite this, we observed that the DD levels performed as well as the APACHE II score as a screening test for mortality. In light of the potential predictive power of DD, future efforts to develop organ-failure indexes and severity-of-illness scores should formally include measures of DD. This would hopefully aid in further refining the accuracy of these systems.

Our study has several limitations. First, it was restricted to one center and to only medically ill subjects. Although the relationship between DD and outcomes has been shown now in several studies, little data exist about DD in critically ill surgical patients. Surgery of and within itself will likely lead to the presence of DD in the circulation, and therefore the utility of DD in surgical patients may be less. Second, our study had a limited sample size. The impact of this on our observations can be seen in the range of the 95% CI surrounding the relative risk for mortality. Third, we measured DD only at hospital admission. Sequential assessments of DD status correlated with outcome would provide stronger evidence of a causal relationship between coagulation dysregulation, cytokine levels, and outcomes. In other words, the study design allows us to note an association but does not prove the existence of a causal relationship. Fourth, we used a semiquantitative DD assay system. If we had employed a purely quantitative system, the relationships we noted may have been less apparent. In other words, the cut points in the SimpliRed system could theoretically be ideal for the discriminating among the outcomes we measured or these thresholds could be the rather insensitive. Only a simultaneous comparison with a continuous, quantitative system would allow one to address this uncertainty. Finally, we did not rely on enzyme-linked immunosorbent assays for the measurement of cytokines. Chemiluminescence and electrochemiluminescence are thought to be comparable to traditional enzyme-linked immunosorbent assay systems.

In summary, we observed that DD status on admission to the ICU correlated with multiple clinical end points to include severity of illness, organ failure, and mortality. The presence of DD was also associated with proinflammatory cytokine levels. DD performed as well as the APACHE II score at predicting mortality.

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