Original Contribution

D-dimer is a significant prognostic factor in patients with suspected infection and sepsis☆

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Abstract

Purpose: The aim of the study was to determine whether C-reactive protein (CRP), procalcitonin (PCT), and D-dimer (DD) are markers of mortality in patients admitted to the emergency department (ED) with suspected infection and sepsis.

Basic Procedures: We conducted a prospective cohort in a university hospital in Medellín, Colombia. Patients were admitted between August 1, 2007, and January 30, 2009. Clinical and demographic data and Acute Physiology and Chronic Health Evaluation II and Sepsis Organ Failure Assessment scores as well as blood samples for CRP, PCT, and DD were collected within the first 24 hours of admission. Survival was determined on day 28 to establish its association with the proposed biomarkers using logistic regression and receiver operating characteristic curves.

Main Findings: We analyzed 684 patients. The median Acute Physiology and Chronic Health Evaluation II and Sepsis Organ Failure Assessment scores were 10 (interquartile range [IQR], 6-15) and 2 (IQR, 1-4), respectively. The median CRP was 9.6 mg/dL (IQR, 3.5-20.4 mg/dL); PCT, 0.36 ng/mL (IQR, 0.1-3.7 ng/mL); and DD, 1612 ng/mL (IQR, 986-2801 ng/mL). The median DD in survivors was 1475 ng/mL (IQR, 955-2627 ng/mL) vs 2489 ng/mL (IQR, 1698-4573 ng/mL) in nonsurvivors (P=.0001). The discriminatory ability showed area under the curve–receiver operating characteristic for DD, 0.68; CRP, 0.55; and PCT, 0.59. After multivariate analysis, the only biomarker with a linear relation with mortality was DD, with an odds ratio of 2.07 (95% confidence interval, 0.93-4.62) for values more than 1180 and less than 2409 ng/mL and an odds ratio of 3.03 (95% confidence interval, 1.38-6.62) for values more than 2409 ng/mL.

Principal Conclusions: Our results suggest that high levels of DD are associated with 28-day mortality in patients with infection or sepsis identified in the emergency department.

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1. Introduction

Sepsis is a clinical syndrome that results from the interaction between an infectious agent and the host’s immune, inflammatory, and coagulation responses [1]. Early diagnosis and appropriate treatment of sepsis are very important in reducing mortality because it continues to be extremely high, ranging from 28% to 50% [2]. It is necessary to identify patients at high risk for death, either through readily available laboratory tests or clinical criteria.

Traditionally, scoring systems such as Acute Physiology and Chronic Health Evaluation (APACHE), Sepsis Organ Failure Assessment (SOFA), Multiple Organ Dysfunction Syndrome (MODS), and Simplified Acute Physiology Score (SAPS) have been used to identify patients with increased risk of death and organ dysfunction [3-7]. However, besides their relative complexity, they lack certain biomarkers studied for the diagnosis and specific monitoring of patients with sepsis [5,8,9]. Among these biomarkers, C-reactive protein (CRP) and procalcitonin (PCT) have proven to be useful in the differential diagnosis of infectious vs noninfectious systemic inflammatory response and also in monitoring response to antimicrobials [10,11]. In recent years, the prognostic value of these markers in critically ill patients with or without sepsis has been investigated, showing good correlation between serial measurements and the severity of sepsis and some association with mortality [12-17]. However, their real value as mortality markers has not been established [18]. On the other side, coagulation abnormalities are consistently present in the pathophysiology of the host inflammatory response to bacterial infection [19]. D-dimer (DD) as well as other biomarkers related to coagulation is significantly increased during sepsis and especially when developing disseminated intravascular coagulation (DIC) [19]. D-dimer is a simple, inexpensive, commonly available test that reflects closely the activation of the coagulation system and, in this way, potentially also the severity of the host response. For this reason, DD has been explored as a potential marker for risk stratification in infected patients [20]. However, it is unknown whether DD levels are an independent prognostic mortality marker in patients with infection or sepsis.

Biomarkers associated to outcomes on a population basis are potentially important either for risk stratification or helping to assess severity of illness. The former serves clinical research and quality improvement; the latter mandates a different level of care or leads to applying specific interventions. Our clinical tools are currently limited in predicting which emergency department (ED) patients with an infection, confirmed or suspected, but without overt sepsis or organ dysfunction will progress to severe sepsis or death. A predictive biomarker could be helpful to clinicians to risk-stratify infected patients, earlier in their illness, to an appropriate level of care. Moreover, our findings might offer potential “advantages” into some coagulation-based therapies for sepsis that appeared promising in animal models but were unsuccessful in clinical trials. Future trials in this area might benefit from targeting therapy based on specific biomarkers of the coagulation activation as the underlying problem of interest.

Our goal was to determine the potential usefulness of CRP, PCT, and DD levels obtained from patients admitted to the ED with suspicion of infection as early markers of 28-day mortality.

2. Methods

2.1. Study design

This was an observational, prospective study of adult ED patients screened for sepsis and admitted to the hospital with a diagnosis of suspected or confirmed infection from July 1, 2007, to January 31, 2009. All data were collected prospectively by medical record review. The local ethics committee approved the collection of samples for the analysis of biomarkers after receiving oral informed consent. Nonstandardized treatments for sepsis such as early goal-directed therapy or activated protein C (Xigris, Eli Lilly, IN, USA) were used at our institution during the study period.

2.2. Setting

This was a single-center study at the Hospital Universitario San Vicente de Paul (Medellin, Colombia), which is a fourth-level care university hospital with 550 beds and 3 intensive care units (ICUs) (surgical, medical, and cardiovascular), with an admission rate of approximately 1800 patients per month through the ED, and is a referral center for a region with a population of approximately 3 million people. Patients in this study are part of the population of the study “Toward an operative diagnosis in sepsis: a latent class approach” [21]. In addition, another prespecified nested subsample was analyzed to evaluate some biomarkers as potential diagnostic tests, and the corresponding article was recently published [22].

2.3. Selecting of participants

All patients were 18 years or older and were recruited to the study within 24 hours of ED admission. According to the study protocol [21], patients were considered eligible if they had at least one of the following criteria as the admission diagnosis to the hospital: (1) suspected or confirmed infection, (2) fever of unknown origin, (3) delirium or any type of encephalopathy of unknown origin, or (4) acute hypotension not explained by hemorrhage, myocardial infarction, stroke, or heart failure. The study population for the current analysis comprises those patients admitted to the hospital with a confirmed or suspected infection. Their final diagnoses were defined by the clinical consensus between 3 researchers with training and experience in internal
2.4. Methods of measurement

2.4.1. Biomarkers

Serum samples for PCT and CRP were collected in a dry tube with gel separator and centrifuged within the first 2 hours. Procalcitonin concentrations were measured by an immunoluminometric assay (VIDAS B•R•A•H•M•S PCT; Biomerieux, Lyon, France). Detection limit was less than 0.05 ng/mL, and according to manufacturer’s calculations, the variation coefficients for intraseries, interseries, and total precision reproducibility were 1.93%, 3.63%, and 6.18%, respectively. C-reactive protein was measured quantitatively by an immunoturbidimetric assay using an ARCHITECT c-System (Abbott Laboratories, IL, USA). Detection limit was 0.5 mg/dL, and the imprecision of the assay was 5% or less of the total coefficient of variation, as reported by the manufacturer. Samples for DD were collected in a tube containing citrate as anticoagulant and were processed within 2 hours. d-dimer was measured by a turbidimetric immunoassay in an ACL Elite coagulometer (Barcelona, Spain) using a Hemosil kit (Instrumentation Laboratory, Boston, MA). Results were reported in nanogram per milliliter, and values below 500 ng/mL were considered normal. Coefficients of variation reported by the manufacturer were of 6.8%, 4.6%, and 2.5% for intraseries variation of the normal plasma pool, DD low control, and DD high control, respectively, and of 9.0%, 7.7%, and 4.5% as the total coefficient of variation, respectively. All previous assays were conducted at the hospital laboratory by trained personnel under the institution technical standards and who had no knowledge of the clinical status of the patients nor the study objectives.

2.5. Data collection and processing

A research physician (FJ, GDLR, or MLV) and trained nurses recruited the patients by reviewing admission lists and medical records at the ED from Monday to Saturday. The general protocol for each patient immediately after enrollment included collection of baseline clinical and demographic characteristics, calculation of APACHE II [8] and SOFA [9] scores at admission, and collection of blood samples to determine CRP, PCT, and DD levels. Treating physicians were in charge of the overall management of patients and the ordering of relevant microbiological studies, according to the protocols of the institution. A standard case report form was used to record daily progression of patients by reviewing medical and nursing records until the time of discharge or death. In the patients who left the hospital alive, the vital status was verified at day 28 by outpatient control or telephone calls to each patient or their first relatives. The outpatient control was defined for some patients according to their clinical condition at discharge. In those patients, either the attending physician or one of the physician investigators did a common clinical interview and a physical examination. For the rest of the participants, telephone calls were made by research nurses assigned to the study, asking to talk with each patient to ask about his or her general health condition. When they were not available, the nurses asked other family members about the patient’s health status and vital condition.

2.6. Outcome measures

The primary end point was 28-day mortality. The secondary outcomes were ICU admission and length of stay among survivors.

2.7. Primary data analysis

Continuous variables are expressed as medians with interquartile ranges (IQRs) or as means with SDs, according to their distributions, and categorical variables are presented with absolute and relative frequencies. Statistically significant differences between groups were explored using parametric (t-test) or nonparametric test (Mann-Whitney U, Kruskal-Wallis, or χ²) according to the type of comparisons. We excluded patients with missing values of the corresponding analyses. To explore the prognostic value of the biomarkers in mortality, we performed receiver operating characteristic (ROC) curves with their respective areas under the curve (AUCs) as equivalent to the C-statistic and the quantification of the discriminative ability of each test. To determine the differences between ROC curves of the different biomarkers, we used the method developed by Hanley and McNeil [25], in which a z more than 1.96 indicates an α error less than 5%. Then, we performed a logistic regression analysis including variables of interest in accordance to those previously defined in the literature (see below “Confounding and sensitivity analysis”). The linear relation between continuous independent variables and the outcome was explored by graphical representations of locally weighted ("lowess") nonparametric regression models [26]. Biomarkers were also explored in different ways: (1) as
continuous variables, (2) through their transformation into dummy variables based on their classification in tertiles with the first tertile as reference, and (3) according to categories defined by the manufacturer or clinical practice. There are no clear and reproducible cutoff points for categories of clinical or laboratory relevance in DD or CRP, as there is for PCT. Therefore, to improve the interpretability, comparability, and the clinical relevance of the results, we derived tertiles from the values of biomarkers and generated dummy variables for the multivariable analysis. Multicollinearity was assessed by measuring the variance inflation factor and verifying that its value for each variable was less than 10 [27]. We evaluated the possible interaction between the biomarkers and sex as well as with the severity of sepsis measured by SOFA [4] through the analysis of the interaction terms in the logistic model by means of the likelihood ratio test, comparing the full and the nested model and considering as significant $P < .1$ [28]. Given the obtained sample size, we tried to follow the rule of at least 10 outcomes per independent variable in the logistic regression analysis, when possible [29]. Results are presented as odds ratio (OR) with their 95% confidence intervals (CIs). All tests were performed using STATA SE statistical software (version 10; College Station, TX).

2.8. Confounding and sensitivity analysis

According to the available literature and the established biologic basis of sepsis, we considered as potential confounders age, sex, presence or absence of bacteremia, the APACHE II and SOFA scores [3,4], and comorbidities including diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, use of steroids or chemotherapy in the previous 3 months, history of cancer in the previous year, human immunodeficiency virus/acquired immunodeficiency syndrome, solid organ transplantation, cirrhosis, and trauma [2,24,30-39]. Comorbidity data were obtained from

*The study population for the current analysis

**Fig. 1** Flowchart with details of patient enrollment and classification.
medical records of each patient, and a *dichotomous variable* was defined as the presence of at least one of the aforementioned variable. Because DD may have a special association with certain conditions such as trauma and cancer, we reanalyzed the data using a new variable with 3 categories: history of cancer or trauma, other comorbidities, or none.

As a sensitivity analysis, in addition to the analysis in the original cohort with suspected infection, we also fitted models in subgroups defined according to the expert committee: infection—with and without sepsis—(n=560) and sepsis (n=454).

### 3. Results

#### 3.1. Characteristics of study subjects

During the study period, 1755 eligible patients were admitted to the ED, and 990 were excluded for various reasons. Of the 765 patients included in the cohort, 684 had infection as the main admission diagnosis, and they represent the population for the current analysis (Fig. 1). The complete analysis was performed in 681 patients because 3 patients had unknown vital status at day 28.

The mean age was 51.2±20 years, and 50.3% (n=344) were women. A total of 306 patients (45%) had no comorbidity. In those patients with comorbidity, the most frequent conditions were diabetes mellitus in 135 (20%), chronic obstructive pulmonary disease in 86 (13%), chronic kidney disease in 76 (11%), use of steroids or chemotherapy in the previous 3 months in 55 (8%), and history of cancer during the previous year in 56 patients (8%).

#### 3.2. Main results

The median APACHE II score on admission was 10 (IQR, 6-15), and the median SOFA score was 2 (IQR, 1-4). The median CRP was 9.6 mg/dL (IQR, 3.5-20.4 mg/dL); PCT, 0.36 ng/mL (IQR, 0.1-3.7 ng/mL); and DD, 1612 ng/mL (IQR, 986-2801 ng/mL). The median hospital stay was 10 days (IQR, 6-19 days); 85 patients (12%) were treated since hospitalization in ICU, and overall mortality at day 28 was 11% (n=75). The main clinical and laboratory characteristics according to the final diagnosis defined by the expert committee and vital status during follow-up are presented in Tables 1 and 2, respectively.

The primary diagnosis of infection at the time of admission was community-acquired pneumonia in 19% (n=129) patients, followed by urinary tract infection in 17% (n=113), soft tissue infection in 16% (n=112), clinical sepsis according to Centers for Disease Control and Prevention definition (“patient has at least one of the following clinical signs or symptoms with no other recognized cause: fever [>38°C], hypotension [systolic pressure <90 mmHg], or oliguria [<20 cm³/h] and blood culture not done or no organisms or antigen detected in blood and no apparent infection at another site and physician institutes treatment for sepsis”[23]) in 11% (n=76), and intra-abdominal infection in 8% (n=55).

Microbiological diagnosis was confirmed in 287 patients (42%), 81 (28%) of them with positive blood cultures. The CRP and PCT median differences between survivors and nonsurvivors were not statistically significant. In contrast, the median DD in survivors was 1475 ng/mL (IQR, 955-2627 ng/mL) vs 2489 ng/mL (IQR, 1698-4573 ng/mL) in nonsurvivors (P=.0001).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and laboratory characteristics according to final diagnosis defined by the expert committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical characteristics</td>
<td>No infection, n=124</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52±21</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>64 (52%)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>2 (1-4, 124)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>8.5 (5-13.5, 124)</td>
</tr>
<tr>
<td>Comorbidities, b n (%)</td>
<td>68 (55%)</td>
</tr>
<tr>
<td>Bacteremia, c n (%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>MAP</td>
<td>90 (83-106, 123)</td>
</tr>
<tr>
<td>PF ratio</td>
<td>322 (237-393, 119)</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>95 (80-110, 123)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37 (36.5-37.0, 115)</td>
</tr>
<tr>
<td>WBC (cells/mL)</td>
<td>10700 (8200-13 100, 123)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 (0.8-1.4, 122)</td>
</tr>
<tr>
<td>CRP (mg/mL)</td>
<td>4.8 (1-10.4, 121)</td>
</tr>
<tr>
<td>PCT (ng/mL)</td>
<td>0.21 (0.05-0.61, 119)</td>
</tr>
<tr>
<td>DD (ng/mL)</td>
<td>1706 (950-2497, 122)</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR, observations available) for continuous variables, except for age, which is presented as mean±SD, and n (percentage) for categorical variables. MAP indicates mean arterial pressure; PF ratio, partial pressure of oxygen in the alveoli/fraction of inspired oxygen; WBC, white blood cell.

a Comparison between groups using parametric or nonparametric tests according to data distribution.

b Comorbidities: at least one of the conditions described in the “Confounding and sensitivity analysis” section.

c Bacteremia: percentage of positive blood cultures among total requested.
3.3. Prognostic value of biomarkers and severity scores

The discriminatory ability for mortality, as determined by the AUC-ROC for each biomarker and for severity scores, is presented in Table 3. For overall mortality, the AUC-ROC values were DD, 0.68; CRP, 0.55; and PCT, 0.59, and the SOFA and APACHE II scores were 0.76 and 0.72, respectively. The differences between the AUC of DD vs SOFA and APACHE II scores were not statistically significant (Table 3). The linear relation between each biomarker and the log odds (the link function for logistic regression) of 28-day mortality was explored by graphic representations of locally weighted regressions. According to this smoothed scatterplot, the only biomarker that exhibited a strong linear relationship with 28-day mortality was DD (Fig. 2).

In univariate logistic regression, using biomarkers as continuous independent variables, again, DD was the only marker with a statistically significant association with mortality (OR, 1.000226; 95% CI, 1.000133–1.000319; \(P = .0001\)). The factors associated with overall 28-day mortality according to the logistic regression analysis are presented in Table 4. We identified in the multivariable analysis a statistically significant interaction only between SOFA score and PCT values, which rendered to be not interpretable to their corresponding OR (Table 4). When assessing multicollinearity, the variable with the largest variance inflation factor was APACHE II, with 2.29. Thus, the only biomarker with a dose-response relation with respect to overall mortality was DD.

These findings remained without relevant changes when we fitted different multivariate models for sensitivity analysis (data not shown): (1) comorbidities recoded with an independent category for cancer and/or trauma, (2) patients with infection or sepsis (\(n = 560\)) and patients with sepsis (\(n = 454\)) according to the clinical consensus, and (3) DD as a continuous independent variable.

The analyses with secondary outcomes did not show significant differences in median DD values between patients admitted (\(n = 85\)) and not admitted (\(n = 599\)) to the ICU (1821 ng/mL [IQR, 953–3513 ng/mL] vs 1596 ng/mL [IQR, 987–2704 ng/mL], respectively, \(P = .092\)) neither in median length of stay among survivors according to tertiles of DD (9 days [IQR, 5–16 days] vs 9 days [IQR, 5–17 days] vs 11 days [IQR, 6.5–18.5 days], \(P = .233\)).

4. Discussion

Our findings reveal that high DD levels in this study population are associated with overall mortality, and DD levels above 2409 ng/mL (third tertile in our series) serve as a strong independent indicator of 28-day mortality in these patients. This association remains after adjusting for clinical conditions that may present high DD as cancer and trauma as well as not only in patients with suspected infection but also in those subgroups with confirmed infection and/or sepsis.
Activation of the coagulation cascade is a common and early event in patients with infection and sepsis, and many of the molecules involved in this process are also important amplifiers of the inflammatory response. D-dimer is an activation marker of fibrinolysis and, therefore, of coagulation. The amount of circulating DD in our study population had a linear association with overall 28-day mortality, and the log odds of 28-day mortality and DD values.

Despite the previously described association between high levels of DD and mortality [40,41], until today, to our knowledge, DD measurements alone have not been considered in any predictive models of mortality or quantification of organ dysfunction except for DIC. Notably, before our research, we were lacking studies designed specifically at seeking an association between DD levels by itself and mortality from sepsis. However, it has been confirmed that the presence of overt DIC diagnosed using the International Society for Thrombosis and Haemostasis DIC scoring system (prothrombin time, platelet count, fibrinogen, and a fibrin-related marker including DD or soluble fibrin monomer) is independently predictive of mortality [42]. In addition, Gando et al [43], Sivula et al [44], and Cauchie et al [45] showed that patients with sepsis and DIC, according to the International Society for Thrombosis and Haemostasis scoring system, had a significantly higher mortality compared with patients without DIC [42]. Actually, scoring for DIC has added prognostic value in better predicting mortality than the use of APACHE II score alone [46]. Angstwurm et al [46] found that, for each “DIC point” in the scoring system, the OR for mortality was 1.29, whereas in comparison, for each APACHE II point, the OR for mortality was 1.07.

On the other hand, the prognostic value of PCT plasma levels in predicting survival in adults with suspected sepsis is still controversial. Our results reveal that PCT was not associated 28-day mortality. Claeyys et al [13] suggested that PCT and CRP basal levels do not predict the outcome in patients with septic shock because of a substantial overlap of the ranges between survivors and nonsurvivors. However, Jensen et al [47], in 3642 measurements in 472 ICU patients, showed that serial monitoring of PCT levels predicted better the outcome than a single measurement as well as the higher levels

Table 4  Logistic regression analysis for overall 28-day mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis OR (95% CI)</th>
<th>Multivariate analysis OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.01-1.03)</td>
<td>1.02 (1.00-1.03)</td>
</tr>
<tr>
<td>Male</td>
<td>0.87 (0.54-1.40)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1.72 (1.03-2.85)</td>
<td>1.35 (0.74-2.49)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1.27 (0.64-2.50)</td>
<td></td>
</tr>
<tr>
<td>APACHE II (each point)</td>
<td>1.11 (1.07-1.15)</td>
<td>0.98 (0.92-1.04)</td>
</tr>
<tr>
<td>SOFA (each point)</td>
<td>1.45 (1.31-1.61)</td>
<td>2.51 (1.62-3.89)</td>
</tr>
<tr>
<td>PCT (ng/mL) T1 (&lt;0.20)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>T2 (&gt;0.20 y&lt;2.64)</td>
<td>2.12 (0.84-5.36)</td>
<td>3.43 (0.59-19.84)</td>
</tr>
<tr>
<td>T3 (&gt;2.64)</td>
<td>2.15 (0.81-5.66)</td>
<td>5.35 (0.95-30.1)</td>
</tr>
<tr>
<td>Effect modification (interaction) between SOFA and PCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL) T1 (&lt;6.9)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>T2 (&gt;6.9 y&lt;18.5)</td>
<td>2.10 (0.92-4.79)</td>
<td>2.89 (1.24-6.74)</td>
</tr>
<tr>
<td>T3 (&gt;18.5)</td>
<td>1.49 (0.61-3.67)</td>
<td>2.08 (0.78-5.52)</td>
</tr>
<tr>
<td>DD (ng/mL) T1 (&lt;1180)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>T2 (&gt;1180 y&lt;2409)</td>
<td>2.21 (1.05-4.65)</td>
<td>2.07 (0.93-4.62)</td>
</tr>
<tr>
<td>T3 (&gt;2409)</td>
<td>4.27 (2.11-8.64)</td>
<td>3.03 (1.38-6.62)</td>
</tr>
</tbody>
</table>

Comorbidities: at least one of the conditions described in the “Confounding and sensitivity analysis” section. Bacteremia: percentage of positive blood cultures among total requested. CRP, by tertiles; PCT, by tertiles; DD, by tertiles.

Fig. 2  Smoothed scatterplot exploring the lineal relation between the log odds of 28-day mortality and DD values.
predicted the nonsurvivors. Clec’h et al [48] and Meng et al [15] found that PCT was a reliable early prognostic marker in patients with septic shock and severe sepsis, respectively. In our study, the lack of association between PCT and mortality could be the result of having a single measurement early within the first 24 hours after admission to the emergency service and to the relatively young patient population (mean age, 51 years), health status (45% with no comorbidities), and with less serious medical conditions (median APACHE II, 10).

Some studies have shown a good correlation between CRP levels and the severity of sepsis and other inflammatory diseases [49]. Lobo et al [12] demonstrated in 313 patients that early CRP levels higher than 10 mg/dL upon admission to ICU were associated with increased mortality, incidence of respiratory and renal complications, and development of organ failure when compared with patients with levels under 1 mg/dL. Oberhoffer et al [50] evaluated in 175 patients with a diagnosis of sepsis and an ICU stay of more than 48 hours the correlation between CRP and PCT levels with those of tumor necrosis factor (TNF) α and IL-6. They found that both CRP and PCT were able to predict the cutoff points of increased values of TNF and IL-6, PCT being a better predictor than CRP with AUC of 0.814 for TNF-α more than 40 pg/mL and 0.794 for IL-6 more than 500 pg/mL vs 0.732 and 0.716, respectively, for CRP. However, Claeys et al [13] and Lee et al [51] found no association between CRP upon admission and mortality. Lee et al compared the predictive value of PCT and CRP with the validated score Mortality in Emergency Department Sepsis (MEDS) in 525 patients with sepsis admitted to the emergency service. They found an AUC of 0.76 for early mortality (<5 days) and of 0.70 for late mortality (6-30 days) for PCT, 0.68 and 0.63 for CRP, respectively, and 0.89 and 0.79 for MEDS, respectively, and concluded that PCT measurement was the most sensitive marker for mortality, whereas the MEDS score was the most specific. As previously described by these and other authors [13,51,52], we also failed to demonstrate an association between CRP levels upon admission and mortality.

The results of our study should be analyzed, taking into account some limitations inherent to the study design (observational study) and to the fact that patients admitted to the ED have less severe conditions than patients with sepsis who are admitted to ICUs. In addition, the DD cutoff values associated with mortality in the present study may be substantially different in other clinical settings and in patients with greater severity of sepsis. Furthermore, lack of association between CRP and PCT with mortality could be due to the lack of serial measurements over time to establish a more dynamic relationship between these biomarkers and short- and long-term mortalities.

In summary, our results suggest that high levels of DD are associated with 28-day mortality in patients with infection or sepsis identified in the ED. Furthermore, DD values could be extremely useful to identify patients who could be potential targets for therapeutic interventions aimed at resolving the coagulation disorder such as heparin [53] or recombinant activated protein C [54]. However, other studies should be conducted to validate DD as a prognostic marker in different populations and settings.

Acknowledgment

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