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Discriminative Value of Inflammatory Biomarkers for Suspected Sepsis

Ephraim L. Tsalik, MD, PhD, **L. Brett Jaggers, MD**, **Seth W. Glickman, MD**, **Raymond J. Langley, PhD**, **Jennifer C. van Velkinburgh, PhD**, **Lawrence P. Park, PhD**, **Vance G. Fowler, MD**, **Charles B. Cairns, MD**, **Stephen F. Kingsmore, MB, ChB, BAO, DSc**, and **Christopher W. Woods, MD, MPH***
Department of Medicine, Duke University School of Medicine, Durham, North Carolina (ELT, LBJ, LPP, VGF, CWW); Department of Medicine, Durham VA Medical Center, Durham, North Carolina (ELT, LBJ, CWW); Department of Emergency Medicine, University of North Carolina School of Medicine, Chapel Hill, NC (SWG, CBC); The National Center for Genome Resources, Santa Fe, NM (RJL, JCV, SFK)

Abstract

Background—Circulating biomarkers can facilitate sepsis diagnosis enabling early management and improved outcomes. Procalcitonin (PCT) has been suggested to have superior diagnostic utility compared to other biomarkers.

Methods—Adults with suspected sepsis in the Emergency Department were enrolled. PCT, CRP, and IL-6 were correlated with infection likelihood, sepsis severity, and septicemia. Multivariable models were constructed for length-of-stay and discharge to a higher level of care.

Results—Of 336 enrolled subjects, 60% had definite infection, 13% possible infection and 27% no infection. Of those with infection, 202 presented with sepsis, 28 with severe sepsis, and 17 with septic shock. Overall, 21% of subjects were septicemic. PCT, IL6, and CRP levels were significantly higher in septicemia (median PCT 2.3 vs. 0.2ng/mL; IL-6 178 vs. 72pg/mL; CRP 106 vs. 62mg/dL, $p<0.001$). Biomarker concentrations increased with greater likelihood of infection and sepsis severity. Using ROC analysis, PCT best predicted septicemia (0.78 vs. IL-6 0.70 and CRP 0.67) but CRP better identified clinical infection (0.75 vs. PCT 0.71 and IL-6 0.69). A PCT cut-off of 0.5ng/mL had 72.6% sensitivity and 69.5% specificity for bacteremia as well as 40.7% sensitivity and 87.2% specificity for diagnosing infection. A combined clinical-biomarker model revealed that CRP was marginally associated with length-of-stay ($p=0.015$), but no biomarker independently predicted discharge to a higher level of care.

Conclusions—In adult Emergency Department patients with suspected sepsis, PCT, IL-6, and CRP highly correlate with several infection parameters, but do not meaningfully predict length-of-stay or need for discharge to a higher level of care.

Keywords

Sepsis; Procalcitonin; Interleukin-6; C-Reactive Protein; Sensitivity and Specificity

Corresponding Author: Christopher W. Woods, Durham VA Medical Center, 508 Fulton Street, Service 113, Durham, NC 27705, 919-286-0411 ext. 6681, 919-286-6895, fax Woods004@mc.duke.edu.

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Introduction

Sepsis is not a single disease, but rather a highly heterogeneous syndrome that is the net result of host and pathogen interactions triggering networks of biochemical mediators and inflammatory cascades. Clinical expression is variable and severity is influenced by several factors: infectious etiology; site of infection; genetic background of the patient; co-morbid conditions; immune status; age; time to clinical intervention; and care provided to the patient. Patients frequently present to the Emergency Department (ED), where distinguishing sepsis from non-infectious systemic inflammatory response syndrome (SIRS) is paramount for provision of timely, effective therapy. The frequency with which sepsis is incorrectly diagnosed as a non- infectious process is difficult to ascertain but has significant treatment and outcome implications. The converse, mislabeling non-infectious processes as sepsis, can also have substantial clinical implications whereby necessary treatments are withheld in lieu of inappropriate antimicrobial therapy[1]. The rates of non-infectious etiologies misdiagnosed as sepsis ranges from 14–18% in the ED population[2–4].

Much effort has been directed toward the identification of biomarkers to aid in the clinical diagnosis and management of sepsis. Ideally, a sepsis biomarker should accomplish the following: decrease the time to diagnosis; differentiate between infectious and non-infectious SIRS; and reflect the effectiveness of antimicrobial treatment and other measures of source control. Multiple sepsis biomarkers have been investigated that meet one or more of these criteria, yet the ability to distinguish infectious from non-infectious processes remains elusive[5]. Recently, there has been growing interest in procalcitonin (PCT) as a biomarker that can meet the above criteria.

Literature on the use of PCT as a sepsis diagnostic first appeared in 1993[6]. Since then, it has been tested in various infectious and non-infectious syndromes. The clinical need to differentiate infectious from non-infectious SIRS is particularly great in the ED: Diagnosing or excluding infection among patients with suspected sepsis can alter the trajectory of care in fundamental ways (*e.g.* starting antibiotics; admit vs. discharge). Studies to address the utility of PCT for sepsis diagnosis have had limitations: many are small (<100 subjects); focus on selected sub-populations such as critically ill/ICU, trauma, burn, pediatric, or geriatric populations; or were performed in non-U.S. EDs[2, 7–15]. This latter point is particularly relevant since most patients with suspected sepsis in the U.S. utilize the ED as the first point of healthcare contact. In contrast, outside the U.S. such assessments are typically performed by primary care physicians in the outpatient setting.

In the present study, we assess the utility of PCT measurement to differentiate infectious and non-infectious SIRS. The work we present is distinguished by its larger study population, ED presentation (*i.e.* earlier in the disease course), adult population, and breadth of outcome measures evaluated. The goal of this study is to characterize the relationships between PCT, IL-6, CRP and several clinically relevant outcomes including the following: infection likelihood; sepsis severity; septicemia (bacteremia or fungemia); and clinical outcomes including length of stay and discharge to a higher level of care.

Methods

Study site and patients

Subjects included in this analysis are derived from two previously described patient cohorts: The Community Acquired Pneumonia & Sepsis Outcome Diagnostics (*CAPSOD*) study is a prospective, multi-center NIH sponsored study developing novel diagnostic and prognostic tests for severe sepsis in the ED (ClinicalTrials.gov NCT00258869). The second is the Duke Febrile Illness Cohort (DFIC), which focuses on the underlying etiologies of fever in ED

patients (Grant/Cooperative Agreement Number U38/CCU423095)[4, 16]. Eligible subjects were identified during day- and night-time hours in the Duke University Medical Center ED (annual census 70,000) and the Durham Veterans Affairs Medical Center (annual census 40,000). Screening occurred between July 2003 and February 2009. Inclusion and exclusion criteria are the same for both studies. Inclusion criteria consisted of known or suspected infection on the basis of clinical data at the time of screening and the presence of two or more SIRS criteria within a 24-hour period[17]. SIRS criteria include temperature ≤ 36° C or ≥ 38° C, heart rate ≥ 90 bpm, respiratory rate ≥ 20 breaths/min or $PaCO_2$ < 32 mmHg, and white blood cell count ≥ 12,000 or ≤ 4,000 cells/mm^3 or > 10% bands. Patients were excluded if <18 years old, if they had an imminently terminal co-morbid condition, HIV/AIDS with CD4 count < 50 cells/mL, receiving antibiotics for a condition unrelated to the presenting illness, or if they were participating in an ongoing clinical trial.

Data collection

Following informed consent, patients or their representatives completed a questionnaire about demographic factors and medical history. Biological specimens were collected including blood cultures and cultures of other sites as ordered by treating providers. Other baseline measurements included complete blood count, blood chemistries, urinalysis, and radiography. Trained study coordinators reviewed and abstracted vital signs, microbiology, laboratory, and imaging results obtained during the ED encounter. Additional outcomes assessed at thirty days included mortality, length of hospital stay, admission to an intensive care unit (ICU), length of ICU stay, in-hospital mortality, and discharge disposition (home, skilled nursing facility, hospice, inpatient, or death). Data was collected in electronic case report forms with decision support logic and stored in a HIPAA-compliant database on site (DFIC cohort) or with a third party (Prosanos Inc., Harrisburg PA for the CAPSOD cohort).

Adjudication of infections and patient status

One of two study physicians with board certification in emergency medicine or internal medicine reviewed all study data and the complete patient medical record including hospital admission and discharge summaries, progress notes, consultant notes, laboratory results (excluding biomarker data), microbiology results, and radiography reports. The following adjudications were made blind to outcome data: likelihood of infection; site of infection if present; and causative organisms. We used a previously published 5-point scale to define the likelihood of infection[4, 5]. Category 1 infection was defined as having an identified etiologic agent with clinical evidence of infection and no evidence of a non-infectious process. Category 2 was the same as Category 1 but in the absence of an identified etiologic agent. Category 3 was reserved for indeterminate cases in which infection could neither be confirmed nor excluded. Category 4 was defined as no evidence of infection but without evidence of a non-infectious process. Finally, Category 5 was without evidence of infection but also required the identification of a non-infectious etiology. We modified this scale by grouping categories 4 and 5 into a recoded Category 4 defined as “no evidence of infection”. Inter-rater reliability for infection classification was determined based on an independent adjudication of a 10% sample of patient records. Agreement was high (Kappa = 0.82). Blood culture contamination was based on previously published criteria and included the likelihood the organism represents a skin contaminant, the number of independent positive and negative cultures, other concurrent microbiology results, and clinical compatibility[18, 19].

Study definitions

Likelihood of infection was recoded into a dichotomous outcome (Infection Present vs. Infection Absent). “Infection Present” is comprised of infection categories 1 (definite infection, identified etiologic agent), 2 (definite infection, no identified etiologic agent), and

3 (infection possible). Infection category 4 (no infection) defines the "Infection Absent" group.

Sepsis severity during the ED stay was defined using previously published criteria[20, 21]. Category 4 patients (no infection) were labeled as non-infected SIRS-positive. Sepsis was defined as SIRS with evidence of infection but no end-organ damage. The presence of end-organ damage defined Severe Sepsis and included metabolic (lactate > 1.5 × upper limit of normal or arterial pH < 7.30), hematologic (platelet count < 80,000/hpf), pulmonary (intubation or PaO_2/FiO_2 < 250), or renal (urine output < 0.5 ml/kg/hr despite adequate fluid resuscitation) derangements. Sepsis with hypotension despite fluid challenge (systolic blood pressure < 90 mmHg or mean arterial pressure < 65) or a blood lactate concentration ≥ 4 mmol/L defined Septic Shock. Severe Sepsis and Septic Shock were collectively termed "Complicated Sepsis" for the purposes of specified statistical analyses. Blood stream infections include either bacterial or fungal etiologies. The term "septicemia" is used to denote bacteremia or fungemia.

Discharge to a higher level of care is a composite outcome consisting of discharge to a skilled nursing facility if previously living at home, hospice enrollment, mortality within 28 days, or still hospitalized at 28 days. This previously published composite outcome was chosen because it represents clinically meaningful events in infectious and non-infectious diseases[22, 23].

Sample processing

Blood was collected for culture using sterile technique. The volume inoculated was not monitored and is subject to user variability. At the Durham Veterans Affairs Medical Center, the BacT/Alert® system (bioMérieux, Marcy l'Etiole, France) was used. At Duke University Medical Center, the BacT/Alert® system was used along with the BD BACTEC™ system (Becton, Dickinson and Company, Franklin Lakes, NJ). Upon their collection, samples for biomarker level determination were frozen. They were later thawed at room temperature, gently mixed, and analyzed within eight hours. Measurement of PCT, IL-6, and CRP are unaffected by a single freeze-thaw cycle[24–26]. PCT and IL-6 were measured on a Roche Elecsys 2010 analyzer (Roche Diagnostics, Laval, Canada) by electrochemiluminescent immunoassay (ECLIA). CRP was quantified using a chemiluminescent (CLIA) immunoassay on the Siemens Immulite® 2000 system (Siemens Healthcare Diagnostics Inc., Deerfield, IL). Samples in which the biomarker concentration exceeded the upper-limit of detection (PCT 100ng/mL, CRP 100mg/dL, IL-6 5000pg/mL) were diluted to obtain an accurate measurement. If after dilution, the concentration still exceeded the limit of detection, values were defined as the upper limit of detection. There were ten such cases for CRP, nine for IL-6, and five for PCT.

Statistical analysis

Unless otherwise specified, frequency (percentage) was reported for categorical variables and median (IQR) was presented for continuous variables. Differences in biomarker levels across each clinical category (infection likelihood, sepsis severity, and septicemia) were determined using Kruskall-Wallis followed by pairwise comparisons with Wilcoxon rank sum tests when appropriate. The performance of each biomarker as a sepsis diagnostic was demonstrated with ROC analysis. Sensitivities and specificities associated with specific biomarker cut-points were determined using JROCFIT 1.0.2 and JLABROC 1.0.1[27]. Negative binomial regression models were used to investigate associations between length of stay and pre-specified clinical predictors including biomarker levels[28]. Associations between discharge disposition and these same clinical predictors were tested using full-fitted

logistic regression models. All analyses were performed using SAS, Version 9.2 (Cary, North Carolina) except where noted.

Results

Subject characteristics

A total of 336 patients with suspected sepsis in the ED were enrolled (Table 1). The majority of subjects were admitted to the hospital (n=306; 91.1%) with a small number requiring ICU care (n=21, 6.3%). Mortality was low with only three in-hospital deaths (0.9%). Although enrollment criteria specified the presence of SIRS with a suspected infectious etiology, a review of all available clinical information through 28 days revealed that 89 subjects (26.5%) had non-infectious etiologies at the time of initial presentation (Category 4). Of the remaining 247 subjects, 202 (81.8%) had uncomplicated sepsis, 28 (11.3%) had severe sepsis, and 17 (6.9%) had septic shock. There were 203 Category 1 and 2 subjects (those with definite infection). We identified the etiologic agent in the majority (n=113, 55.7%). Thirty-two different organisms contributed to this group, although *Staphylococcus aureus* (n=36) and *Escherichia coli* (n=24) together accounted for 53.1% of identified etiologies. For subjects with definite or possible infection, we were able to define the anatomic site of infection in 83.4% (206/247). Lung, urinary tract, and skin together accounted for the most common sites of infection (60.6% of identified sites). Blood cultures were true positive in 55 of 259 (21.2%) subjects from whom cultures were collected.

Association with infection and sepsis

Infection likelihood was categorized as Definite Infection, Possible Infection, and No Infection (see Methods and Table 2). Figure 1 presents median biomarker levels as a function of these categories. All three biomarkers distinguished Definite Infection from both No Infection and from Possible Infection. Although the Possible Infection group revealed higher biomarker concentrations relative to the No Infection group, the differences were not as significant in comparison to the Definite Infection group using Wilcoxon rank-sum testing (PCT p=0.055; IL-6 p=0.17; CRP p=0.052). To define the operating characteristics of the three biomarkers, we dichotomized infection likelihood for ROC analysis (Definite and Possible Infection grouped into “Infection Present”; Table 3 and Figure 2). CRP had the greatest AUC for identifying infection (0.75 vs. 0.72 for PCT and 0.69 for IL-6). Ninety percent sensitivity was observed with a CRP cut-off of 7mg/dL (specificity 33%) whereas 90% specificity was observed with a cut-off of 107mg/dL (sensitivity 39%). A CRP cut-off of 40mg/dL demonstrated a sensitivity and specificity of 68%. Models using biomarker combinations revealed a marginal improvement in diagnostic accuracy when PCT was added to CRP: The AUC was 0.75 with CRP alone and increased to 0.78 with CRP and PCT. We also hypothesized that because viral and fungal pathogens are not strong triggers of PCT, this biomarker may perform better when such cases are excluded. After excluding ten subjects with either viral or fungal etiologies, the ROC analysis for PCT did not change (AUC 0.71).

Thus far we have shown that PCT, IL-6, and CRP are each significantly different in patients with and without infection, but are of intermediate clinical utility. We next considered whether any biomarker could distinguish the sepsis severities (Figure 1). PCT, IL-6, and CRP were significantly lower in SIRS patients compared to every level of sepsis severity (uncomplicated sepsis, severe sepsis, and septic shock; $p<0.0001$ for each comparison). PCT and IL-6 were each significantly higher in patients with severe sepsis (median 1.3ng/mL and 211pg/mL, respectively) or septic shock (median 1.3ng/mL and 261pg/mL, respectively) compared to those with sepsis (median 0.19ng/mL and 66pg/mL, respectively; $p\leq0.008$ for each comparison). Levels of CRP were also higher in patients with severe sepsis (median

100mg/dL) or septic shock (median 94mg/dL) compared to those with sepsis (82mg/dL; p=0.14 and 0.12, respectively). However, statistical significance was only observed when sepsis was compared to complicated sepsis (composite of severe sepsis and septic shock; p=0.043).

In contrast to earlier results showing that CRP best discriminated those with and without infection, PCT was the biomarker that best discriminated the presence of septicemia (AUC for PCT 0.79, IL-6 0.70, CRP 0.67). Restricting the outcome to bacteremia only (by removing two cases of fungemia) did not change to the AUC materially for any of the biomarkers (PCT 0.80, IL-6 0.71, CRP 0.69). Notably, CRP was independently associated with septicemia even after accounting for PCT concentration but did not appreciably improve the AUC in ROC analysis. IL-6 was not independently associated with either infection likelihood or septicemia after adjusting for PCT and CRP. A PCT cutoff of 0.5ng/mL is frequently cited for diagnosing bacterial sepsis and bacteremia[7, 11, 14]. This cutoff resulted in 72.6% sensitivity and 69.5% specificity for septicemia; and 40.7% sensitivity and 87.2% specificity for the diagnosis of infection. Removing cases of fungal or viral infection resulted in little change (<1% absolute increase in sensitivity and specificity).

Clinical outcomes

Mortality was low (0.9%) in this cohort of undifferentiated ED patients with suspected sepsis. Therefore, we investigated whether pre-specified clinical variables and biomarkers were associated with length of hospital stay and the likelihood of discharge to a higher level of care. We hypothesized that the following variables would be associated with length of stay: age; pre-enrollment nursing home care; immunosuppression; comorbid lung disease; blood culture positivity; ICU care; and each of the three biomarkers. Multivariable modeling revealed older age, ICU care, positive blood cultures, and CRP were independently associated with longer hospitalization (Table 4). Since blood culture results are not available at the time of ED evaluation, we removed this variable from the model. However, PCT still was not associated with length of stay (p-value 0.94) even though it is the biomarker most predictive of blood culture positivity.

Most subjects (n=325, 96.7%) were living independently prior to enrollment. However, 33 subjects were discharged to a higher level of care than before hospitalization. We tested the same variables defined above in a model for risk of discharge to a higher level of care (Table 5). In multivariable logistic regression, age (OR 1.77 per decade; 95% CI 1.31–2.41), comorbid lung disease (OR 6.89; 95% CI 2.26–21.0), ICU care (OR 7.55; 95% CI 1.76–32.4), and immunosuppression (OR 0.09; 95% CI 0.01–0.59) were independently associated with this outcome.

Discussion

Sepsis is a complex, heterogeneous disorder that is frequently misdiagnosed with significant clinical consequences[2–4]. The ability to diagnosis or exclude suspected sepsis is vitally important to patient outcomes. To that end, biomarkers have been investigated as the means to do this, although most have fallen short due to poor specificity for infection.

PCT has been evaluated in multiple clinical settings as a tool to distinguish bacterial infection from other inflammatory states and infectious processes[29]. In addition, PCT has demonstrated diagnostic, prognostic, and management utility. Of particular relevance to this study, four meta-analyses have reported on PCT performance in the diagnosis of sepsis and/or bacteremia. Two suggested that PCT is superior to other markers such as CRP and should be used in sepsis diagnosis[7, 15] whereas the others found either a moderate or poor ability for PCT to identify sepsis in critically ill patients[11, 14]. As evidenced by these divergent results,

it remains unclear what role PCT can and should play in the management of septic patients. Our study expands this dialogue by focusing on a larger and more heterogeneous adult patient population, the ED patient with suspected sepsis. It is also strengthened by the extensive clinical phenotyping we performed. Infection status was determined by blinded study physicians based on results of systematic reviews of available clinical, microbiological, and radiographic data. As a result, 27% of SIRS patients initially suspected of having infection were later determined to have a noninfectious etiology.

Building on these clinical phenotypes, we show that PCT is highly associated with various sepsis-related outcomes including infection likelihood, severity of infection, and septicemia. PCT was not unique in this role, however; IL-6 and CRP were likewise associated with these sepsis-related outcomes. Specifically, all three biomarkers were significantly higher in patients with clinical and microbiological evidence of infection. We also observed a progressive increase in biomarker concentrations as sepsis severity increased from non-infected SIRS to uncomplicated sepsis to complicated sepsis (severe sepsis or septic shock). Although two small cohort studies of sepsis (one in the ICU[8], the other in the ED[30]) observed that PCT but not CRP could distinguish between severe sepsis and septic shock, we did not find that PCT, IL-6, or CRP could distinguish between these two clinical categories. Finally, we observed a high correlation between PCT and blood-stream infections with an AUC of 0.79. Whereas CRP and IL-6 were significantly higher in patients with blood-stream infections, they were not as discriminating as PCT, a finding consistent with published studies[31–34].

In contrast to most of the research on PCT in sepsis, we did not specifically target critically ill patients requiring ICU care. Findings from such populations are difficult to generalize to the undifferentiated and frequently less morbid ED patient with suspected sepsis, which represents the target population for this study. The difficulty in making an accurate diagnosis in this population is underscored by the large number of patients initially suspected of having sepsis but later determined to have non-infectious SIRS. Biomarkers play a pivotal role in making this distinction, and can also be used for prognostic purposes[35–39]. PCT is highly correlated with bacterial infection, both as a diagnostic and prognostic tool[5]. In contrast, IL-6 and CRP are frequently elevated in non-infectious illness and therefore, can serve as useful prognostic tools in this undifferentiated population consisting of both infected and non-infected critically ill patients[40–42]. We chose two outcomes as surrogates for morbidity -- length of stay and discharge to a higher level of care at 28 days. Whereas these outcomes may not be immediately relevant to ED-related care, they inform the need for hospitalization and prognosis. Interestingly, none of the three biomarkers were strongly associated with either outcome in multivariable analyses. Only CRP had a small but statistically significant contribution to a model predicting length of stay. Among the clinical variables, age and ICU care were both associated with longer lengths of stay and the need for a higher level of care at discharge. Furthermore, blood stream infections were associated with longer hospitalizations whereas comorbid lung disease had an odds ratio of 6.89 for discharge to a higher level of care. Interestingly, we found a strong negative association between immunosuppression and the need for a higher level of care. This finding was unexpected and should be verified in other contexts. It may have arisen due to the nature of this particular analysis, which has several limitations to it: There was a relatively small effective sample size with only 38 such events. However, we entered nine predictors into the model, which increases the risk for a type-I error and has potential for overfitting. Despite these limitations, we proceeded with our exploratory analysis in an effort to show that PCT, IL-6, and CRP are of limited utility in predicting length of stay or the need for discharge to a higher level of care once other clinical variables are accounted for.

This limited role for PCT, IL-6, or CRP as prognostic tools is in contrast to several published reports as noted above. Possible reasons for this discrepancy include the targeted patient population (ICU vs. ED). It may also reflect the possibility that outcomes such as length of stay and need for a higher level of care at discharge may not be driven or reflected by inflammation. Other factors contributing to these clinical outcomes may include the following: the need for rehabilitation services; the degree of family support outside the home; patient financial resources; and/or morbidities not assessed in our analysis such as renal dysfunction or malignancy. Finally, we measured biomarker concentrations only at the time of ED evaluation. At this time point, biomarkers more accurately reflect pre-treatment morbidity and say little about a patient's response to treatment or disease progression in the hospital. Serial biomarker measurements could more accurately describe these parameters and may offer improved outcomes prognosis.

Biomarker panels represent another approach to improve sepsis diagnosis and outcome prediction. In this study, combinations of PCT, IL-6, and CRP did not meaningfully improve performance. However, other groups have shown that biomarker panels have diagnostic utility. Shapiro et al. investigated a 9-biomarker panel to investigate suspected sepsis in the ED (but did not include IL-6 or PCT)[39]. They showed that a combination of neutrophil gelatinase-associated lipocalin, protein C, and interleukin-1 receptor antagonist performed best with an AUC of 0.80 for severe sepsis, 0.77 for septic shock, and 0.79 for death. In the ICU setting, a composite 3-biomarker panel including neuropeptides arginine-vasopressin, apelin, and stromal-derived factor-1alpha had an AUC of 0.90 for sepsis[43]. Although such panels have yet to be validated, they represent a new direction for sepsis biomarker research. This approach will be further enhanced using 'omic technologies, which offer an unbiased strategy to identify the best performing biomarkers.

In conclusion, we demonstrate the clinical and etiological heterogeneity that poses diagnostic and treatment challenges for the ED provider. Biomarkers such as PCT, IL-6, and CRP are strongly associated with multiple sepsis-related categories such as infection likelihood, sepsis severity, and septicemia. However, we observed wide ranging biomarker concentrations within any given clinical category. Consequently, no cut-off point could be identified that yielded both high sensitivity and specificity in diagnosing infection or septicemia. PCT and CRP can still serve as useful adjuncts to standard clinical information when sepsis diagnosis remains but should not serve as the only criterion. In addition, all three biomarkers were significantly associated with morbidity (as measured by length of stay and discharge to a higher level of care), but this relationship was lost in multivariable analysis. Future efforts to discriminate sepsis from SIRS in the ED should focus on an expanded clinical-molecular diagnostic panel including PCT and CRP.

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Clinical Significance

Procalcitonin is an acute phase reactant that is preferentially elevated in bacterial infection.

Procalcitonin, CRP, and IL-6 strongly correlate with measures of infection. They serve as useful tools to improve diagnostic accuracy but are not adequately discriminating to stand alone as sepsis biomarkers.

Outcomes such as length-of-stay and discharge to a higher level of care are better predicted by clinical measures including age, ICU-care, bacteremia, and comorbid lung disease.

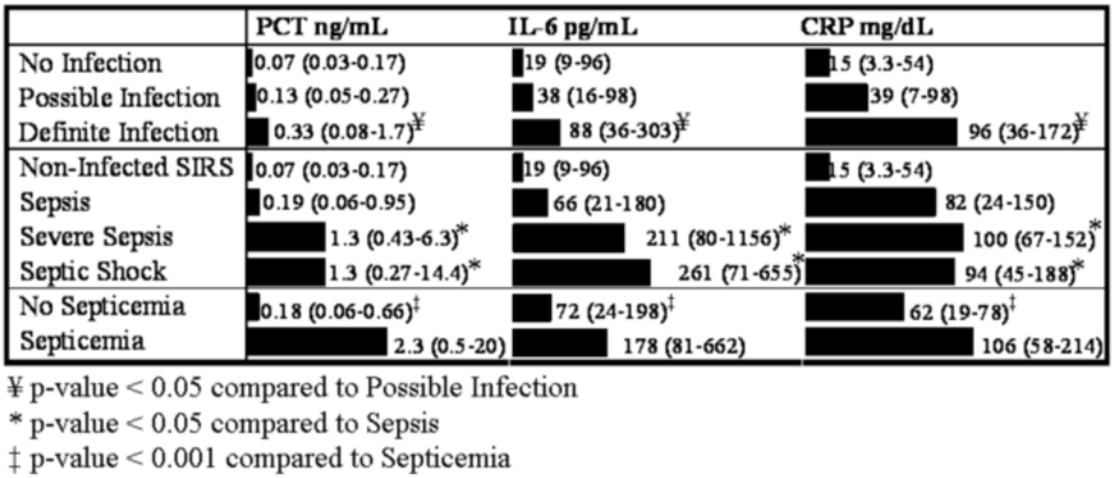

Figure 1.

Median (IQR) PCT, IL-6, and CRP concentrations stratified by likelihood of infection, sepsis severity, and blood culture results. The numerical scale is consistent within each column but differs for each biomarker. Significance testing was performed with Kruskall-Wallis followed by Wilcoxon rank sum tests.

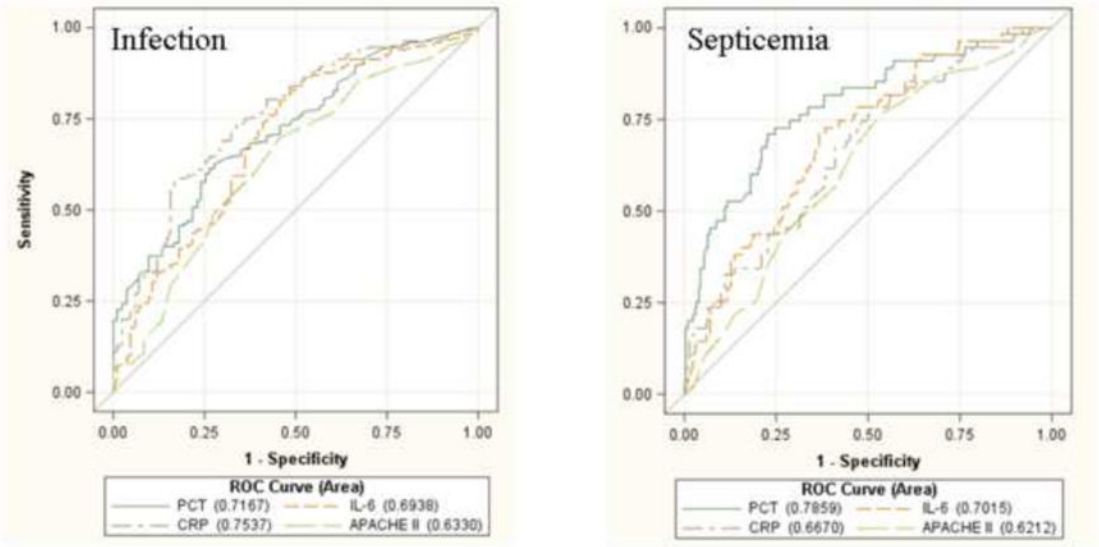

Figure 2.
ROC curves for the prediction of infection (left panel) and septicemia (right panel). Infection categories 1–3 define the presence of infection whereas infection category 4 defines the absence of infection.

Table 1

Characteristics of 336 patients with suspected sepsis at the time of ED presentation.

Variable	Frequency (%) or Median (IQR)
Age (yr), median (IQR)	52 (38–65)
Sex, *n* (%)	
Male	173 (51.5)
Female	163 (48.5)
Race, *n* (%)	
White	175 (52.1)
Black	141 (42.0)
Other	20 (6.0)
APACHE II score, median (IQR)	8 (5–13)
Comorbidities, *n* (%)	
Diabetes	75 (22.3)
Immunosuppression	51 (15.2)
Corticosteroids	36 (10.7)
Chemotherapy	13 (3.9)
Immunosuppression, other	15 (4.5)
Smoker	47 (14.0)
Chronic lung disease	46 (13.7)
Chronic renal failure	41 (12.2)
Neoplastic disease	30 (8.9)
Alcohol abuse	19 (5.7)
HIV	11 (3.3)
Drug abuse	15 (4.5)
Cirrhotic liver failure	7 (2.1)
Pre-hospitalization location, *n* (%)	
Home	325 (96.7)
Nursing home/Skilled nursing facility	11 (3.3)
Number hospitalized, *n* (%)	306 (91.1)
Length of stay in days, mean (median)	5.4 (4.0)
Number admitted to ICU, *n* (%)	21 (6.3)
Hospital mortality, *n* (%)	3 (0.9)
Discharge location, *n* (%)	
Home	293 (87.2)
Nursing home/Skilled nursing facility	24 (7.1)
Hospice	7 (2.1)
Still in hospital	7 (2.1)
Sepsis severity, *n* (%)	
Non-Infected SIRS	89 (26.5)
Sepsis	202 (60.1)
Severe Sepsis	28 (8.3)

Variable	Frequency (%) or Median (IQR)
Septic Shock	17 (5.1)

IQR = Interquartile range.

Table 2

Infection categorization, microbiological evaluation including sites of infection and etiologic agents.

Variable	Frequency (%)
Infection Category	
Category 1 (Definite infection, Identified etiologic agent)	117 (34.8)
Category 2 (Definite infection, No identified etiologic agent)	86 (25.6)
Category 3 (Infection possible)	44 (13.1)
Category 4 (No infection)	89 (26.5)
Site of infection[1]	
Lung	46 (18.6)
Urinary Tract	41 (16.6)
Skin	38 (15.4)
Intra-abdominal	30 (12.1)
Vascular catheter-related	14 (5.7)
Ear-Nose-Throat	13 (5.3)
Central nervous system	9 (3.6)
Bone	7 (2.8)
Gynecologic	6 (2.4)
Cardiac	2 (0.8)
Unknown	41 (16.6)
Etiologic agent[2]	
Staphylococcus aureus	36 (31.9)
Escherichia coli	24 (21.2)
Klebsiella pneumoniae/oxytoca	11 (9.7)
Streptococcus pneumoniae	7 (6.2)
Streptococcus, other	5 (4.4)
Pseudomonas aeruginosa	4 (3.5)
Clostridium difficile	2 (1.8)
Cryptococcus neoformans	2 (1.8)
Influenza	2 (1.8)
Other bacterial	14 (12.4)
Other viral	3 (2.7)
Other fungal	3 (2.7)
Blood culture positive[3]	55 (21.2)

[1] Based on 247 Infection Categories 1–3 subjects.

[2] Percentages based on 113 subjects with an identified etiologic agent.

[3] Blood culture positive percentage based on 259 subjects who had blood cultures collected.

Table 3

ROC curve analysis data for PCT, IL-6, and CRP to differentiate infectious from non-infectious SIRS and septicemia.

	AUC	Cutoff	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV (%)
Infection						
PCT (ng/mL)	0.72	0.1	67.9	63.4	83.7	41.6
		0.5	40.7	87.2	89.8	34.6
		3.0	18.4	97.1	94.6	30.0
IL-6 (pg/mL)	0.69	40	58.4	67.4	83.2	36.9
		100	43.2	80.3	85.9	33.8
		500	14.1	96.2	91.1	28.8
CRP (mg/dL)	0.75	7	90.4	32.7	78.8	55.1
		40	67.6	68.4	85.6	43.2
		100	43.1	87.9	90.8	35.8
Septicemia						
PCT (ng/mL)	0.79	0.1	90.8	37.5	28.1	93.8
		0.5	72.6	69.5	39.0	90.4
		3.0	47.2	89.9	55.7	86.4
IL-6 (pg/mL)	0.70	40	90.2	33.9	26.9	92.8
		100	68.0	62.0	32.5	87.8
		500	27.0	89.4	40.7	82.0
CRP (mg/dL)	0.67	40	82.3	38.7	26.5	89.0
		100	60.1	65.6	32.0	85.9
		200	30.7	88.1	41.0	82.5

*Based on a prevalence of 73.5% for infection among patients with suspected sepsis and a prevalence of 21.2% for positive blood cultures among patients with suspected sepsis.

Table 4

Results of negative binomial generalized linear model identifying factors associated with length of hospital stay.

	Bivariable Model			Multivariable Model		
	Parameter Estimate	**95% CI**	**p-value**	**Parameter Estimate**	**95% CI**	**p-value**
Age (per decade)	0.064	0.010–0.18	**0.019**	0.070	0.015–0.124	**0.013**
Co-morbid lung disease	0.31	0.04–0.60	**0.028**	0.17	−0.11–0.45	0.24
ICU care	1.11	0.79–1.46	**<0.0001**	0.94	0.57–1.32	**<0.0001**
Immunosuppression	0.008	−0.26–0.28	0.95	−0.065	−0.33–0.20	0.64
Positive blood culture	0.55	0.29–0.78	**<0.0001**	0.42	0.17–0.66	**0.0008**
Pre-enrollment nursing home	0.57	0.09–1.11	**0.026**	0.32	−0.13–0.76	0.16
PCT ng/mL	0.089	0.003–0.015	**0.003**	−0.0025	−0.0082–0.0032	0.39
IL-6 pg/mL	0.0002	0.0001–0.0003	**<0.0001**	0.0000	−0.0001–0.0001	0.53
CRP mg/dL	0.0024	0.0016–0.0033	**<0.0001**	0.0012	0.0002–0.0021	**0.015**

Table 5

Results of logistic regression analysis identifying factors associated with discharge to a higher level of care.

	Bivariable Model			Multivariable Model		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (decade of life)	1.75	1.39–2.21	**<0.0001**	1.77	1.31–2.41	**0.0002**
Co-morbid lung disease	3.83	1.71–8.56	**0.001**	6.89	2.26–21.0	**0.0007**
ICU care	4.27	1.53–11.9	**0.006**	7.55	1.76–32.4	**0.007**
Immunosuppression	0.75	0.25–2.24	0.61	0.09	0.01–0.59	**0.012**
Positive blood culture	0.75	0.27–2.07	0.58	0.47	0.12–1.86	0.28
Pre-enrollment nursing home	3.69	0.93–14.6	**0.06**	1.40	0.27–7.23	0.69
PCT ng/mL	1.002	0.98–1.02	0.85	1.001	0.971–1.032	0.95
IL-6 pg/mL	1.002	0.999–1.01	0.26	1.000	0.999–1.000	0.53
CRP mg/dL	1.010	0.995–1.03	**0.18**	1.003	0.999–1.008	0.13