Early Biomarker-Guided Prediction of Bloodstream Infection in Critically Ill Patients: C-Reactive Protein, Procalcitonin, and Leukocytes

Frederik Boetius Hertz,12,6 Magnus G. Ahlström,3 Morten H. Bestle,4,5 Lars Hein,4 Thomas Mohr,7 Jens D. Lundgren,7 Tina Galle,6 Mads Holmen Andersen,3 Daniel Murray,7 Anne Lindhardt,10 Theis Skovsgaard Itonov,9,14 and Jens Ulrik Staehr Jensen7,11,5

1Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark, 2Department of Clinical Microbiology, Slagelse Hospital, Slagelse, Denmark, 3Department of Clinical Microbiology, Herlev & Gentofte Hospital, Herlev, Denmark, 4Department of Anaesthesia and Intensive Care, Copenhagen University Hospital—North Zealand, Copenhagen, Denmark, 5Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, 6Department of Anaesthesia and Intensive Care, Gentofte University Hospital, Copenhagen, Denmark, 7CHIP & PERSIMUNE, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark, 8Department of Anaesthesia and Intensive Care, Glostrup University Hospital, Copenhagen, Denmark, 9Department of Anaesthesiology, Aarhus University Hospital, Aarhus, Denmark, 10Department of Anaesthesiology, Sjællands Universitets Hospital Køge, Køge, Denmark, and 11Department of Internal Medicine, Respiratory Medicine Section, Herlev & Gentofte Hospital, Herlev, Denmark

Background. Bloodstream infections (BSIs) often lead to critical illness and death. The primary aim of this study was to determine the diagnostic accuracy of the biomarkers C-reactive protein (CRP), procalcitonin (PCT), and leukocyte count for the diagnosis of BSI in critically ill patients.

Methods. This was a nested case–control study based on the Procalcitonin And Survival Study (PASS) trial (n = 1200). Patients who were admitted to the intensive care unit (ICU) within 24 hours, and not expected to die within 24 hours, were recruited. For the current study, we included patients with a BSI within ±3 days of ICU admission and matched controls without a BSI in a 1:2 ratio. Diagnostic accuracy for BSI for the biomarkers on days 1, 2, and 3 of ICU admission was assessed. Sensitivity, specificity, and negative and positive predictive values were calculated for prespecified thresholds and for a data-driven cutoff.

Results. In total, there were 525 patients (n = 175 cases, 350 controls). The fixed low threshold for all 3 biomarkers (CRP = 20 mg/L; leucocytes = 10 × 10⁹/L; PCT = 0.4 ng/mL) resulted in negative predictive values on day 1: CRP = 0.91; 95% CI, 0.91–0.94; CRP = 0.91; 95% CI, 0.91–0.94; CRP = 0.91; 95% CI, 0.91–0.94; CRP = 0.91; 95% CI, 0.91–0.94; CRP = 0.91; 95% CI, 0.91–0.94. Combining the 3 biomarkers yielded similar results as PCT alone (P = .5).

Conclusions. CRP and PCT could in most cases rule out BSI in critically ill patients. As almost no patients had low CRP and ~20% had low PCT, a low PCT could be used, along with other information, to guide clinical decisions.

Keywords. bloodstream infection; BSI; CRP; leukocyte; PCT.

Bloodstream infections (BSIs) are a major cause of critical illness and carry a high risk of death [1]. Timely antimicrobial administration remains the cornerstone of the multifaceted management of bacterial infections [2, 3]. Conventional blood cultures and isolation of microorganisms in blood culture are still considered the “gold standard” for diagnosis of BSI [4, 5]. This is, however, a time-consuming process with a culture-positive response time of 24–48 hours [4]. For a definitive negative blood culture, at least 5–7 days are needed [4]. Delayed or inappropriate antibiotic treatment is therefore a potentially modifiable factor [1–3]. Furthermore, there is a substantial risk of unnecessary use of antibiotics for both over- and underdiagnosis of BSI, as the latter can be the cause of misapplication of antibiotics [6]. Tools to timely and accurately differentiate between patients with and without BSI are therefore needed.

Common markers to qualify a diagnosis of BSI include C-reactive protein (CRP), procalcitonin (PCT), and leukocyte counts [7–9]. These markers are useful in the diagnosis of BSI; however, noninfectious causes may also lead to increases in blood levels, which is why the gold standard biomarker has yet to be found [5]. In critically ill patients, these challenges are more pronounced as these patients often suffer from noninfectious conditions associated with increased levels of inflammatory biomarkers, for example, trauma, surgery, burns, and cancer [10]. There is limited knowledge on how these biomarkers perform with regard to detecting BSIs in such a population. The aim of this study was to determine the diagnostic accuracy of
commonly used biomarkers (CRP, PCT, and leukocyte count, as well as their combination) for BSI in critically ill patients.

METHODS

Study Design and Participants

This was a nested case–control study based on a cohort of patients included in the randomized controlled trial Procalcitonin And Survival Study (PASS), described in detail elsewhere [11, 12]. Patients had to be ≥18 years of age and enrolled within 24 hours of admission to the intensive care unit (ICU). For all patients included in PASS, microbiological samples from blood, urine, airways, and other suspected sites were performed according to the standard of care.

Case Definition

Cases were defined as patients with BSI within the time frame of 72 hours before and 72 hours after ICU admission; the majority of patients (114 [65%]) with bacteremia had BSI in the 24 hours before ICU admission. We defined BSI as detection of a clinically significant bacterium or fungus in blood culture. Clinically significant bacteria were defined as all bacteria except the following, often considered contaminants: coagulase-negative staphylococci (CoNS), Micrococcus species, Corynebacterium species, and Catibacterium acnes.

Control Definition

Control patients were defined as patients who did not have a clinically significant BSI within 72 hours before and 72 hours after ICU admission. Patients were matched in a nested case–control analysis. We used a greedy matching algorithm based on the nearest-neighbor matching method [13]. We matched patients with BSI in the cohort with patients from the cohort without BSI. Patients were matched on propensity scores modeled with the variables age, gender, Charlson comorbidity index, and APACHE-II score. We matched cases and controls in the ratio 1:2.

Data Collection

Data were collected during the randomized controlled trial, and collection was performed according to Good Clinical Practice (GCP) as stated by the European Medicines Agency (EMA). For the current analyses, we included demographic data (age, gender, hospital, and ICU admission dates), comorbidities, microbiological test results, measured inflammatory markers (including CRP, PCT, and leukocyte counts), and antimicrobials. We included the 10 most frequently used antimicrobials in this study and categorized these into primary (cefuroxime, piperacillin/tazobactam, and meropenem) and supporting (ciprofloxacin, clarithromycin, metronidazole, and vancomycin) as these are most commonly used in conjunction with either of the primary antibiotics and antifungals (fluconazole, caspofungin, and ambisome). All biomarkers were evaluated to determine the diagnostic accuracy on day 1, day 2, and day 3 after ICU admission, and within the same time frame for detecting BSI ±72 hours of ICU admission. For each day, only individuals with nonmissing values for the different biomarkers were included in the analyses.

Laboratory Methods

In brief, blood cultures in Denmark are cultured at the Departments of Clinical Microbiology and processed according to current guidelines for routine clinical bacteriology, using the BACTEC Tm (Becton Dickinson, Franklin Lakes, NJ, USA) detection system. Blood culture flasks are incubated for 5–7 days. Blood samples were drawn in the early morning at all sites and stored at 2°C–4°C, after which they (same morning) were transferred for analysis at a central laboratory before 9 AM. Results were available before 11 AM the same morning. Blood analysis was made using the Kryptor-PCT (Brahms Diagnostica, Hennigsdorf, Germany), which is a sandwich immune assay.

Statistical Analyses

We constructed receiver operating characteristics (ROC) curves using untransformed CRP, PCT, and leukocyte count on day 1, day 2, and day 3 of admission to the ICU to calculate sensitivity and specificity for BSI for all values and computed ROC curves based on these sensitivity and specificity values. We used area under the ROC curves as the effect size for comparison. For the multivariable model, we used CRP (continuous variable), leucocytes (factor variable; 0–4 vs 4–9 vs >9 [cells pr. μL]), PCT (modeled with a restricted cubic spline with 3 knots), age (continuous variable), sex (male vs female), and APACHE-II score (continuous variable). The multivariable models were repeated for day 1, day 2, and day 3. Ninety-five percent CIs were calculated with the bootstrap method. For sensitivity reasons, all the above was done for both the matched data and the unmatched (full cohort). Extra sensitivity analyses were performed where fungemia were considered negative blood culturing. Further, we did a sensitivity analysis with only patients whose primary admission cause was septic shock and a sensitivity analysis where the primary admission cause was infection. This was done for the day 1 biomarkers only. We used the DeLong’s test for correlated ROC curves to test all ROC curves pairwise for differences between the AUCs [14].

We used the ROC curves and 3 different relevant thresholds to calculate sensitivity, specificity, negative predictive value, and positive predictive value for all 3 biomarkers. The first threshold was the maximum Youden’s index (day 1: CRP < 156; leukocyte count < 10.5 × 10⁹/L; and PCT < 2.9 ng/mL), the second threshold included high sensitivity and high negative predictive value (CRP < 20 mg/L; leukocyte count < 10 × 10⁹/L; and PCT < 0.4 ng/mL), and the third threshold included high
specificity and high positive predictive value (CRP < 200 mg/L; leukocyte count < 25 × 10^9/L; and PCT < 15 ng/mL).

Statistical analyses were performed using R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

We included 1176/1200 (98%) patients from the PASS study cohort who had blood samples available; 24 patients were
excluded (2%) due to missing biomarkers. Among these, 175 (15%) had BSI, and these were matched with 350 controls, yielding a total of 525 patients (Supplementary Figure 1). The clinical characteristics of the matched groups are presented in Table 1, and the unmatched groups are presented in Supplementary Table 1. In a sensitivity analysis, we tested the performance of the markers in the complete PASS study cohort (n = 1176).

Characteristics of the Diagnostic Markers

For the predefined thresholds and for the data-driven (Youden index) threshold, we calculated how many patients ± BSI were below the used cutoff. For Youden’s index (day 1: CRP < 156 mg/L; leukocyte count < 10.5 × 10⁹/L; and PCT < 2.9 ng/mL), we found that for CRP, 160 patients without BSI and 39 with BSI were below the cutoff, respectively. For leucocyte counts, 118 patients without BSI and 41 with BSI were below the cutoff, respectively. For the second threshold that included high sensitivity and high negative predictive value (CRP < 20 mg/L; leukocyte count < 10 × 10⁹/L; and PCT < 0.4 ng/mL), we found that for CRP, 20 patients without BSI and 2 with BSI were below the cutoff, respectively. For leucocyte counts, 118 patients without BSI and 41 with BSI were below the cutoff, respectively, while for PCT 72 patients without BSI and 7 with BSI were below the cutoff, respectively. Of the 79 patients with PCT < 0.4 ng/mL, 51 had no verified infectious focus before admission to the ICU, and among these individuals, 38 received at least 1 antibiotic.

Diagnostic Accuracy

In Tables 2, 3, and 4, we present the sensitivity, specificity, positive predictive value, and negative predictive value of the 3 different biomarkers for the risk of BSI in patients admitted to the ICU, including days 2–3. These analyses were performed on the matched population. Supplementary Table 2 shows the analyses with optimal cutoffs for the unmatched population.

Overall, using the optimal cutoff for day 1, CRP had a negative predictive value (NPV) of 0.80 (95% CI, 0.76–0.85; cutoff = 155.62 mg/L), while the use of a fixed low threshold (CRP = 20 mg/L) improved NPV on day 1 to 0.91 (95% CI, 0.75–1.00). Looking at leucocyte counts, using the optimal cutoff for day 1 gave an NPV of 0.74 (95% CI, 0.68–0.80; cutoff = 10.5 × 10⁹/L), with the fixed low threshold (leucocytes = 10 × 10⁹/L)

Table 3. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for a Fixed Low Threshold of 3 Different Biomarkers on the Risk of Positive Blood Culture in Patients With Septic Shock Admitted to the ICU

| Biomarker   | Day | Cutoff | Sensitivity (95% CI) | Specificity (95% CI) | Positive Predictive Value (95% CI) | Negative Predictive Value (95% CI) |
|-------------|-----|--------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| CRP, mg/L   | 1   | 20     | 0.99 (0.97–1.00)     | 0.06 (0.03–0.08)     | 0.34 (0.33–0.35)                  | 0.91 (0.75–1.00)                  |
| CRP, mg/L   | 2   | 20     | 0.99 (0.97–1.00)     | 0.05 (0.03–0.08)     | 0.35 (0.34–0.36)                  | 0.88 (0.69–1.00)                  |
| CRP, mg/L   | 3   | 20     | 0.98 (0.94–1.00)     | 0.07 (0.04–0.10)     | 0.36 (0.35–0.37)                  | 0.85 (0.67–1.00)                  |
| Leucocytes, x10⁹/L | 1   | 10    | 0.80 (0.75–0.86)     | 0.29 (0.24–0.34)     | 0.36 (0.34–0.38)                  | 0.75 (0.68–0.81)                  |
| Leucocytes, x10⁹/L | 2   | 10    | 0.89 (0.84–0.94)     | 0.24 (0.19–0.29)     | 0.38 (0.36–0.40)                  | 0.81 (0.73–0.89)                  |
| Leucocytes, x10⁹/L | 3   | 10    | 0.92 (0.87–0.97)     | 0.23 (0.18–0.28)     | 0.39 (0.37–0.41)                  | 0.84 (0.75–0.93)                  |
| PCT, ng/mL  | 1   | 0.4   | 0.96 (0.93–0.98)     | 0.21 (0.16–0.25)     | 0.38 (0.36–0.39)                  | 0.91 (0.84–0.96)                  |
| PCT, ng/mL  | 2   | 0.4   | 0.98 (0.95–0.99)     | 0.17 (0.13–0.21)     | 0.38 (0.36–0.39)                  | 0.94 (0.87–0.98)                  |
| PCT, ng/mL  | 3   | 0.4   | 0.96 (0.93–0.99)     | 0.20 (0.15–0.24)     | 0.38 (0.37–0.40)                  | 0.90 (0.83–0.97)                  |

Matched population.

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin.

Table 2. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Optimal Cutoff (Calculated as the Maximum of Youden’s Index) of 3 Different Biomarkers on the Risk of Positive Blood Culture in Patients With Septic Shock Admitted to the ICU

| Biomarker   | Day | Cutoff | Sensitivity (95% CI) | Specificity (95% CI) | Positive Predictive Value (95% CI) | Negative Predictive Value (95% CI) |
|-------------|-----|--------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| CRP, mg/mL  | 1   | 156    | 0.77 (0.70–0.83)     | 0.47 (0.42–0.52)     | 0.42 (0.39–0.45)                  | 0.80 (0.76–0.85)                  |
| CRP, mg/mL  | 2   | 86     | 0.70 (0.76–0.88)     | 0.35 (0.30–0.40)     | 0.39 (0.36–0.41)                  | 0.78 (0.71–0.84)                  |
| CRP, mg/mL  | 3   | 66     | 0.77 (0.70–0.84)     | 0.31 (0.25–0.37)     | 0.38 (0.35–0.40)                  | 0.72 (0.64–0.79)                  |
| Leucocytes, x10⁹/L | 1   | 11    | 0.76 (0.69–0.82)     | 0.35 (0.30–0.40)     | 0.36 (0.34–0.39)                  | 0.74 (0.68–0.80)                  |
| Leucocytes, x10⁹/L | 2   | 13    | 0.73 (0.65–0.79)     | 0.45 (0.40–0.51)     | 0.41 (0.37–0.44)                  | 0.76 (0.71–0.82)                  |
| Leucocytes, x10⁹/L | 3   | 13    | 0.73 (0.65–0.81)     | 0.45 (0.38–0.51)     | 0.42 (0.38–0.46)                  | 0.75 (0.69–0.82)                  |
| PCT, ng/mL  | 1   | 3     | 0.86 (0.81–0.91)     | 0.55 (0.49–0.60)     | 0.49 (0.45–0.52)                  | 0.88 (0.85–0.92)                  |
| PCT, ng/mL  | 2   | 14    | 0.59 (0.52–0.66)     | 0.78 (0.74–0.82)     | 0.58 (0.53–0.64)                  | 0.79 (0.76–0.82)                  |
| PCT, ng/mL  | 3   | 10    | 0.61 (0.54–0.69)     | 0.77 (0.72–0.82)     | 0.58 (0.53–0.65)                  | 0.79 (0.76–0.83)                  |

Matched population.

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin.
improving the NPV to 0.75 (95% CI, 0.69–0.81). Finally, using the optimal cutoff for day 1 for PCT gave an NPV of 0.88 (95% CI, 0.85–0.92; cutoff $= 2.92$ ng/mL). Use of the fixed low threshold (PCT $= 0.4$ ng/mL) improved the NPV on day 1 to 0.91 (95% CI, 0.84–0.96).

The best displayed predictive abilities were seen for PTC on day 2, with an NPV of 0.94 (95% CI, 0.87–0.98) compared with 0.88 (95% CI, 0.69–1.00) for CRP when using fixed low thresholds (cutoff $= CRP < 20$ and PCT $< 0.4$ ng/mL).

**Individual Biomarkers as Predictor of Positive Blood Culture**

The ROC curves for the individual biomarkers (CRP, PCT, and leukocyte) as predictors for positive blood cultures on days 1–3 are shown in Figure 1A–C. PCT had a higher predictive value on all days, compared with CRP and leukocyte. On day 1, the AUC was 0.76 (95% CI, 0.72–0.80), with similar predictive values of PCT on days 1–3. For CRP, all curves indicated limited predictive performance for BSI. The best predictive performance for CRP was seen on day 1, with an AUC of 0.62 (95% CI, 0.57–0.67). Predictive performance for leukocyte counts was very similar between days and was found to be 0.57 (95% CI, 0.516–0.623) on day 1. When we only included individuals with a primary admission cause of septic shock or infection, we found slightly lower AUCs for PCT of 0.71 (95% CI, 0.64–0.78) and 0.70 (95% CI, 0.62–0.78), respectively (Supplementary Figures 2 and 3).

**Combined Biomarkers as a Predictor of Positive Blood Culture**

Finally, we combined the 3 inflammatory markers PCT, CRP, and leukocyte counts on days 1–3. The results are shown in Figure 2A–C. The combination of the 3 markers improved the predictive performance on all days, especially when compared with CRP and leukocyte alone. The combination did not improve the predictive performance compared with PCT alone. The ROC curves produced an area under the ROC curve (AUROC) of 0.765 (95% CI, 0.722–0.808) on day 1.

**Table 4. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for a Fixed High Threshold of 3 Different Biomarkers on the Risk of Positive Blood Culture in Patients With Septic Shock Admitted to the ICU**

| Biomarker | Day | Cutoff | Sensitivity (95% CI) | Specificity (95% CI) | Positive Predictive Value (95% CI) | Negative Predictive Value (95% CI) |
|-----------|-----|--------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| CRP, mg/L | 1   | 200    | 0.61 (0.53–0.68)     | 0.57 (0.52–0.63)     | 0.42 (0.37–0.46)                  | 0.75 (0.71–0.79)                  |
| CRP, mg/L | 2   | 200    | 0.48 (0.39–0.56)     | 0.64 (0.59–0.70)     | 0.41 (0.35–0.46)                  | 0.70 (0.67–0.74)                  |
| CRP, mg/L | 3   | 200    | 0.23 (0.16–0.30)     | 0.73 (0.67–0.78)     | 0.31 (0.23–0.39)                  | 0.64 (0.61–0.67)                  |
| Leucocytes, $\times 10^9$/L | 1   | 25     | 0.20 (0.14–0.25)     | 0.87 (0.83–0.90)     | 0.42 (0.33–0.52)                  | 0.68 (0.67–0.70)                  |
| Leucocytes, $\times 10^9$/L | 2   | 25     | 0.19 (0.13–0.25)     | 0.90 (0.87–0.93)     | 0.50 (0.38–0.62)                  | 0.68 (0.67–0.70)                  |
| Leucocytes, $\times 10^9$/L | 3   | 25     | 0.18 (0.11–0.26)     | 0.88 (0.84–0.92)     | 0.45 (0.33–0.59)                  | 0.67 (0.64–0.69)                  |
| PCT, ng/mL | 1   | 15     | 0.58 (0.51–0.66)     | 0.80 (0.76–0.84)     | 0.60 (0.54–0.65)                  | 0.79 (0.76–0.82)                  |
| PCT, ng/mL | 2   | 15     | 0.58 (0.50–0.65)     | 0.80 (0.76–0.84)     | 0.59 (0.54–0.65)                  | 0.79 (0.76–0.82)                  |
| PCT, ng/mL | 3   | 15     | 0.51 (0.43–0.59)     | 0.84 (0.80–0.88)     | 0.63 (0.56–0.70)                  | 0.77 (0.74–0.80)                  |

Matched population.

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin.

**Figure 1.** A–C, The figures show ROC curves for the predictive value of three biomarkers on the risk of blood stream infection on day 1–3. Abbreviations: CRP, C-reactive protein; ROC, receiver operating characteristics.
We observed that low blood levels of CRP and PCT on the first ICU day could in most cases rule out BSI. However, the combination of all biomarkers did not improve the predictive performance of either PCT or CRP alone for the prediction of BSI in this cohort of critically ill patients. More patients had “low” PCT than “low” CRP; thus PCT could rule out BSI in more patients, despite having the same NPV.

The findings of the current study are in agreement with a previous investigation [15] that assessed the performance of PCT levels to rule out BSI in patients suspected of having community-acquired infection [15]. They evaluated 9 cutoff values for PCT and excluded patients with fever of unknown origin. They found 0.4 ng/mL to be the PCT diagnostic threshold value because this particular value was associated with a negative predictive value as high as 98.8% [15]. We chose the same threshold for our analyses. They only included patients hospitalized for community-acquired infections, and <20% of patients received antibiotics before admission. Another retrospective study compared the accuracy of PCT, serum lactate concentration, total white blood cell count, and the neutrophil-lymphocyte count ratio to diagnose BSI in adult patients presenting to a hospital with suspected sepsis. They found the lowest PCT among patients with negative blood cultures and suggested that a PCT of <0.5 ng/mL may be a suitable cutoff [16]. Here the AUROC was 0.83 for PCT [16]. They presented a rigorous distribution of pathogens, potential pathogens, and likely contaminants, but did not record any clinical data.

In a study investigating markers to predict BSI in critically ill patients at an ICU [5], the authors found that the diagnostic accuracy of PCT and CRP for the diagnosis of BSI was insignificant [5]. Yet, they excluded patients with fungemia and included only 64 patients with confirmed BSI [5]. Nonetheless, here APACHE II, SOFA, and Charlson comorbidity index scores were similar between patients with BSI and patients without BSI [5]. Additionally, CRP and PCT levels increased significantly with infectious disease, although they remained insignificant in predicting BSI; neutrophil-to-lymphocyte count ratio was not a useful marker in that study [5].

Hospital-acquired infections frequently occur in patients with other noninfectious conditions, and at least half of patients admitted to an ICU are infected [7, 8]. It can be challenging to obtain microbiological samples verifying an infection, which is particularly true for the critically ill patients often receiving broad-spectrum antibiotics [5, 7]. Noninfectious conditions are often associated with increased biomarker levels, creating an additional challenge in diagnosing infection [7]. PCT may be a valuable tool to evaluate the risk of BSI in critically ill patients admitted to the ICU, but PCT-guided antimicrobial escalation in the ICU did not improve survival and led to organ-related harm as well as prolonged admission to the ICU in a study by Jensen et al. [12]. These results illustrate that the critically ill patient may present with concurrent infections that necessitate antibiotics, even if BSI is not present and PCT is low. Therefore, the use of such markers, in an antibiotic stewardship algorithm, will require attention to other indications for antibiotic treatment. The current study does, however, provide data to help inform the use of the specific markers in an ICU population. CRP is a more nonspecific marker; it is not diagnostic for any specific inflammatory condition, while PCT release is most often induced by bacterial infection and not colonization [15]. In critically ill patients and those in the ICU, PCT may have greater accuracy and therefore be preferable to CRP. However, in our current study, the NPVs for CPR and PCT were similar on day 1 when used at a fixed low threshold. Possibly the NPV of PCT and CRP can prevent

Figure 2. A–C, The figures show ROC curves for the predictive value of combined inflammatory markers PCT, CRP, and leukocyte counts for the risk of bloodstream infection on days 1–3. Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operating characteristics.
unnecessary antibiotic escalation, yet the strategy must be evaluated further.

Of note, we performed hypothesis testing (data not shown) comparing ROC curves for each individual inflammatory marker for day 1 to day 3. It was clear that the predictive performance for BSI of each marker decreased over time, with the best predictive performance found on day 1 (Tables 2, 3, and 4; Figure 1A–C). PCT did, however, show the best predictive performance over time.

Our study has several limitations. First, not all blood cultures were acquired before administration of antibiotics. We speculate that this would skew the results toward no difference between groups. As such, the diagnostic accuracy of the biomarkers could be even greater if the blood culturing and biomarker measurements were timed better.

CONCLUSIONS

In this relatively large study evaluating CRP, PCT, and leukocyte count as predictors of BSI in critically ill patients, with no dropouts and Good Clinical Practice monitored data, we found an ability of PCT and CRP to rule out BSI in critically patients. PCT could rule out a larger number of patients from having this condition, which thus favors using this biomarker at a threshold of 0.4 ng/mL as we did, in an integrated manner together with other clinical and para-clinical data to rule out bloodstream infections and guide clinical decisions in this setting.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. The patients’ written consent was obtained during the randomized controlled trial “The Procalcitonin And Survival Study” (PASS), described in detail elsewhere [11, 12]. PASS was approved by the regional ethics committees in Denmark (H-KF272-753) and adheres to the Helsinki Declaration, revised in Seoul in 2008 [11, 12].

Transparency declaration. All authors affirm that this manuscript was conducted in an honest, accurate, and transparent way.

References

1. Kontula KSK, Skogberg K, Ollgren J, Jarvinen A, Lytytikainen O. Early deaths in bloodstream infections: a population-based case series. Infect Dis (Auck) 2016; 48:379–85.
2. Papadimitriou-Olvergis M, Perdikis K, Cois M, et al. Predictors for delayed antibiotic administration among bacteremia patients in the emergency department: differences between medical and surgical interns. Eur J Clin Invest 2020; 50: e13324.
3. Townsend SR. Antibiotic administration and timing: risks, delay, zombies. Crit Care Med 2021; 49:1818–21.
4. Arabestani MR, Rastiany S, Kazemi S, Mousavi SM. Conventional, molecular methods and biomarkers molecules in detection of sepsis. Adv Biomed Res 2015; 4:120.
5. Sen P, Demirdal T, Nemli SA, et al. Infection markers as predictors of bacteremia in an intensive care unit: a prospective study. Pak J Med Sci 2018; 34:1517–24.
6. Levy Hara G, Kanj SS, Pagani L, et al. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. Int J Antimicrob Agents 2016; 48:239–46.
7. Garvik OS, Pøvoa P, Magnusen B, et al. C-reactive protein and albumin kinetics before community-acquired bloodstream infections—a Danish population-based cohort study. Epidemiol Infect 2020; 148:E38.
8. Pereira MA, Rouxinol-Dias AL, Vieira T, Paiva JA, Pereira JM. Usefulness of early C-reactive protein kinetics in response and prognostic assessment in infected critically ill patients: an observational retrospective study. Acta Med Port 2019; 32: 737–45.
9. Duan S, Gu X, Fan G, Zhou F, Zhu G, Cao B. C-reactive protein or procalcitonin combined with rhinorrhea for discrimination of viral from bacterial infections in hospitalized adults in non-intensive care units with lower respiratory tract infections. BMC Pulm Med 2021; 21:308.
10. Niehues T, C-reactive protein and other biomarkers— the sense and non-sense of using inflammation biomarkers for the diagnosis of severe bacterial infection. LymphoSign J 2018; 5:35–47.
11. Jensen J-U, Lundgren B, Hein L, et al. The Procalcitonin And Survival Study (PASS)—a randomised multi-center investigator-initiated trial to investigate whether daily improve survival in intensive care unit patients. Calculated sample size (target population): 1000 patients. BMC Infect Dis 2008; 8:1–10.
12. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011; 39:2048–58.
13. Ho DE, Imai K, King G, Stuart EA. Matchit: nonparametric preprocessing for parametric causal inference. J Stat Softw 2011; 42:1–28.
14. Delong ER, Delong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44:837–45.
15. Chirouze C, Schuhmacher H, Rabaud C, et al. Low serum procalcitonin level associated with more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44:837–45.
16. Marik PE, Stephenson E. The ability of procalcitonin, lactate, white blood cell count and neutrophil-lymphotye count ratio to predict blood stream infection. Analysis of a large database. J Crit Care 2020; 60:135–9.

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