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MAJOR ARTICLE

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

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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) <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 = 10×10^9/L; PCT = 0.4 ng/mL) resulted in negative predictive values on day 1: CRP = 0.91; 95% CI, 0.75–1.00; leukocyte = 0.75; 95% CI, 0.68–0.81; PCT = 0.91; 95% CI, 0.84–0.96). 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 differentiation 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

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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 *Cutibacterium 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 leucocyte 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 $< 10.5 \times 10^9$/L; and PCT < 2.9 ng/mL), the second threshold included high sensitivity and high negative predictive value (CRP < 20 mg/L; leukocyte count $< 10 \times 10^9$/L; and PCT < 0.4 ng/mL), and the third threshold included high

Table 1. Characteristics of Study Population

	No Bloodstream Infections (n = 350), No. (%) or Median (IQR)	Bloodstream Infections (n = 175), No. (%) or Median (IQR)
30-d mortality	70 (20)	31 (18)
Charlson comorbidity index score		
1	155 (44)	71 (41)
2	42 (12)	12 (6.9)
≥3	4 (1.1)	2 (1.1)
Specific comorbidities		
Myocardial infarction	3 (0.86)	0 (0)
Congestive heart failure	18 (5.1)	6 (3.4)
Peripheral vascular disease	10 (2.9)	7 (4)
Cerebrovascular disease	11 (3.1)	5 (2.9)
Dementia	1 (0.29)	1 (0.57)
Chronic pulmonary disease	84 (24)	26 (15)
Rheumatoid disease	9 (2.6)	3 (1.7)
Peptic ulcer disease	0 (0)	0 (0)
Mild liver disease	11 (3.1)	8 (4.6)
Diabetes without complications	61 (17)	18 (10)
Diabetes with complications	2 (0.57)	0 (0)
Hemiplegia or paraplegia	2 (0.57)	0 (0)
Renal disease	7 (2)	8 (4.6)
Cancer	21 (6)	13 (7.4)
Moderate or severe liver disease	0 (0)	2 (1.1)
Metastatic solid tumor	10 (2.9)	4 (2.3)
AIDS	1 (0.29)	0 (0)
Female gender	192 (55)	91 (52)
BMI	25 (22–29)	25 (23–28)
Apache II score	18 (13–26)	20 (14–26)
Dialysis therapy	44 (13)	43 (25)
Drug at admission[a]		
Primary		
Cefuroxime	160 (46)	57 (33)
Piperacillin/tazobactam	138 (39)	83 (47)
Meropenem	33 (9.4)	27 (15)
Supporting antibacterial therapy		
Ciprofloxacin	208 (59)	119 (68)
Clarithromycin	48 (14)	18 (10)
Metronidazol	214 (61)	110 (63)
Vancomycin	12 (3.4)	8 (4.6)
Antifungal therapy		
Ambisome	1 (0.29)	2 (1.1)
Caspofungin	5 (1.4)	3 (1.7)
Fluconazol	72 (21)	43 (25)
Primary causes of admission[b]		
Cerebral	56 (16)	39 (22)
Respiratory	243 (69)	106 (61)
Circulatory	132 (38)	102 (58)
Gastrointestinal	65 (19)	33 (19)
Renal	46 (13)	34 (19)
Postoperative	72 (21)	23 (13)
Bleeding	16 (4.6)	4 (2.3)
Hepatological	13 (3.7)	10 (5.7)
Hematological	6 (1.7)	4 (2.3)
Infection (present before ICU admission)	96 (27)	53 (30)
Poison	8 (2.3)	3 (1.7)
Trauma	7 (2)	4 (2.3)
Septic shock	125 (36)	107 (61)
Mechanical ventilation	242 (69)	114 (65)
Surgery	100 (29)	46 (26)
Other	39 (11)	10 (5.7)
Focus of infections		
Abdominal	13 (3.7)	9 (5.1)
Abscess (nonabdominal[a])	1 (0.29)	1 (0.57)
Bone, joint, and prosthesis	1 (0.29)	0 (0)
Catheter-related	0 (0)	0 (0)
Endocarditis	1 (0.29)	1 (0.57)
Gastroenteritis	1 (0.29)	0 (0)
Meningitis	1 (0.29)	5 (2.9)
Pneumonia	51 (15)	14 (8)
Skin and soft tissue	2 (0.57)	2 (1.1)
Urinary tract	12 (3.4)	4 (2.3)
Other/unspecified	13 (3.7)	17 (9.7)
CRP, mg/mL		
Day 1	165 (79–271)	225 (161–271)
Day 2	158 (66–247)	178 (102–263)
Day 3	119 (58–210)	121 (70–193)
Leucocytes, $\times 10^9$/L		
Day 1	13 (9–19)	15 (11–23)
Day 2	13 (10–20)	16 (12–22)
Day 3	14 (10–20)	17 (12–21)
Procalcitonin, ng/mL		
Day 1	2.4 (0.54–12)	24 (5.4–70)
Day 2	3.2 (0.7–11)	23 (4.4–61)
Day 3	2.4 (0.56–9.2)	16 (3.6–43)

Abbreviation: BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range.

[a]Abdominal abscess included under abdominal focus.

[b]An individual can have >1 primary cause of admission.

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

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	0.82 (0.76–0.88)	0.33 (0.27–0.38)	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, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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.

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 < 10.5×10^9/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, while for PCT 191 patients without BSI and 25 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 < 10×10^9/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 leukocyte counts, using the optimal cutoff for day 1 gave an NPV of 0.74 (95% CI, 0.68–0.80; cutoff = 10.5×10^9/L), with the fixed low threshold (leucocytes = 10×10^9/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, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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 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.

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 1*A*–*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 2*A*–*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.

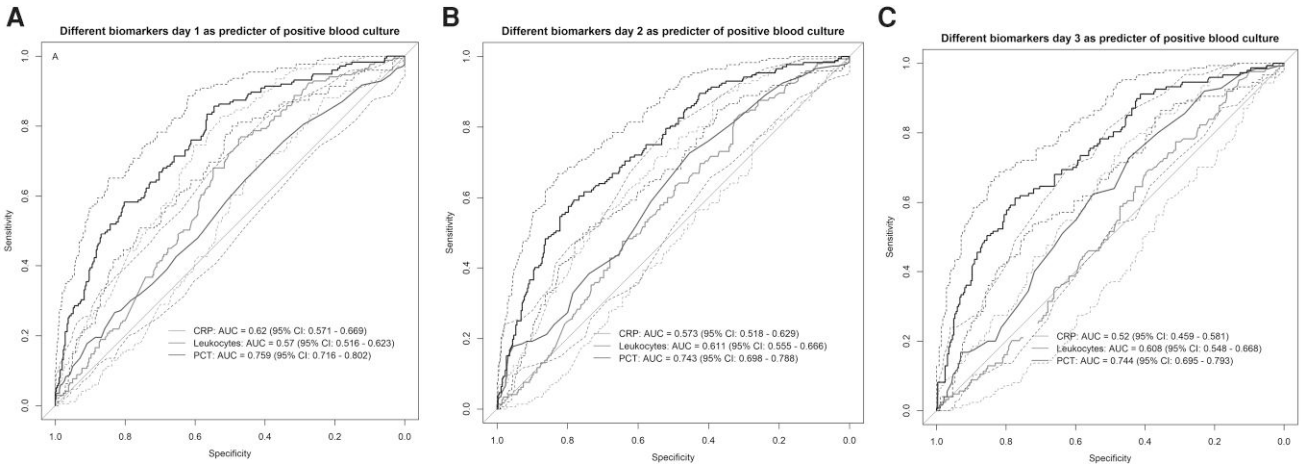

Figure 1. *A–C*, The figures show ROC curves for the predictive value of three biomarkers on the risk of blood stream infection on day 1–3. Abbreviations: CRP, C-reactive protein; ROC, receiver operating characteristics.

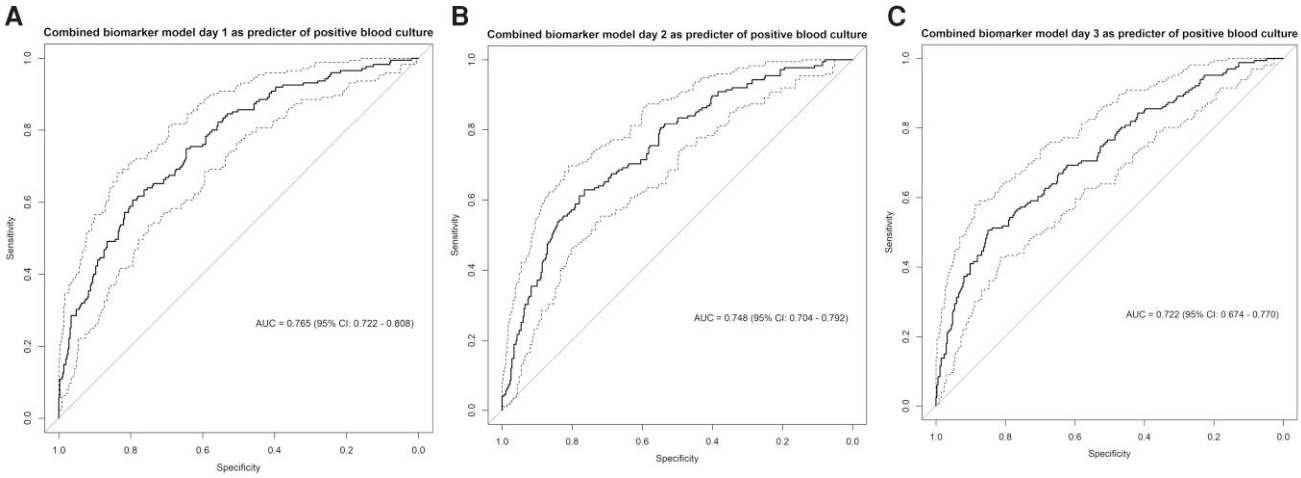

Figure 2. *A–C*, The figures show ROC curves for the predictive value of combined inflammatory markers PCT, CRP, and leukocyte counts for the risk of bloodstream infection on days 1–3. Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; ROC, receiver operating characteristics.

DISCUSSION

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

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 1*A*–*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.

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