Presepsin for the Detection of Late-Onset Sepsis in Preterm Newborns

Chiara Poggi, MD[a], Tommaso Bianconi, MD[a], Elena Gozzini, MD[a], Marta Generoso, MD[a], Carlo Dani, MD[b]

abstract

BACKGROUND: Late-onset sepsis (LOS) is among the leading causes of morbidity and mortality in preterm newborns, and currently available diagnostic tools are inadequate. The objective of this study was to evaluate the accuracy of presepsin (P-SEP) as novel biomarker of bacterial infection for the diagnosis of LOS in preterm newborns.

METHODS: We prospectively studied newborns ≤32 weeks' gestational age with LOS (n = 19) and noninfected controls (n = 21) at 4 to 60 days' postnatal age. At enrollment, and 1, 3, and 5 days later, we ascertained the C-reactive protein, procalcitonin, and P-SEP in the LOS group, whereas P-SEP alone was ascertained in the control group.

RESULTS: P-SEP at enrollment was higher in the LOS than the control group (median 1295 vs 562 ng/L, P = .00001) and remained higher throughout the study period. In the LOS group, P-SEP had a borderline reduction at day 1 versus values at enrollment (median 1011 vs 1295 ng/L, P = .05), whereas C-reactive protein and procalcitonin at day 1 did not differ from baseline values. The receiver operating characteristic curve of P-SEP at enrollment shows an area under the curve of 0.972. The best calculated cutoff value was 885 ng/L, with 94% sensitivity and 100% specificity. Negative likelihood ratio was 0.05, and positive likelihood ratio was infinity.

CONCLUSIONS: We demonstrated for the first time in a cohort of preterm newborns that P-SEP is an accurate biomarker for the diagnosis of possible LOS and may also provide useful information for monitoring the response to therapeutic interventions.

WHAT'S KNOWN ON THIS SUBJECT: Early diagnosis of LOS in preterm infants may be challenging because of the questionable accuracy of blood culture and the common markers of infections, such as C-reactive protein and procalcitonin.

WHAT THIS STUDY ADDS: Our study demonstrated for the first time that P-SEP is an accurate biomarker for the diagnosis of LOS in preterm infants and might contribute to the monitoring of infant response to therapeutic interventions.

Late-onset sepsis (LOS) is a major cause of morbidity and mortality in preterm newborns, occurring approximately in 8% to 30% of very low birth weight (LBW) infants[1] and in 40% of extremely LBW infants.[2] LOS-related mortality in very LBW newborns ranges from 2% in cases of infection due to coagulase-negative Staphylococci to 30% to 50% in cases of infection caused by aggressive pathogens, such as the *Klebsiella-Enterobacter-Serratia* group, *Pseudomonas*, and *Candida* species.[1,3,4] The occurrence of LOS in extremely LBW newborns significantly impairs their neurodevelopmental outcome at 22 months of life in survivors.[5]

Early diagnosis of LOS in preterm infants may be challenging because of the questionable accuracy and latency of blood culture, and the best single biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-6, interleukin-8, or their combination has not been identified.[6–10] Therefore, it was recently suggested that additional studies are necessary to identify more accurate biomarkers of neonatal sepsis.[8]

Presepsin (P-SEP), or soluble CD14 subtype, is a trunked portion of soluble CD14, which is released by shedding from the surface of various immune cell lines, such as macrophages, monocytes, and neutrophils, after its stimulation by pathogens.[11,12] Soluble CD14 is a glycoprotein receptor that can induce immune pathways after interaction with the complex of lipopolysaccharide and lipopolysaccharide binding protein. After its release from the cell surface, soluble CD14 is cleaved by bacterial lysosomal enzymes to the N-terminal peptide of 64 amino acids, termed P-SEP.[11,12] Although its function is still unclear, P-SEP is believed to interact with B and T cells to modulate the specific immune response.[12] P-SEP has recently been demonstrated to be a reliable

diagnostic and prognostic marker of sepsis in adults,[13–15] and preliminary reference values of P-SEP have been evaluated in a small cohort of preterm and term infants.[16–18] However, the possible role of P-SEP as a sepsis biomarker has not been tested in this population.

On this basis, we hypothesized that P-SEP would be an accurate biomarker of possible LOS in preterm infants. To test this hypothesis, we planned this prospective study to evaluate the changes in P-SEP serum concentration in preterm newborns with and without possible LOS and to assess the changes in P-SEP serum concentration following the beginning of antibiotic treatment.

METHODS

Patient Population

This prospective single-center study was carried out in the NICU of Careggi University Hospital of Florence, Italy. The study ran from May 2013 to April 2014 and was approved by the local ethics committee. Infants were enrolled in the study if they were born ≤32 weeks' gestational age and were 4 to 60 days' postnatal age. Exclusion criteria were the presence of major congenital malformations, fetal hydrops, or lack of parental consent.

Study Design

Infants who developed possible LOS (LOS group) were consecutively enrolled during the study period. Blood was sampled at enrollment (T_0) for culture and count and for measuring P-SEP, PCT, and CRP. These biomarkers were measured 1 (T_1), 3 (T_3), and 5 (T_5) days after the first sample.

For each patient enrolled in the LOS group, the next infant born who did not develop signs and symptoms of infection and fulfilled the inclusion criteria was enrolled in the control group, and his or her P-SEP was

measured at T_0, T_1, T_3, and T_5 from waste blood samples.

Infection Definitions

For the purpose of this study, the following definitions were used: LOS was defined as sepsis occurring after 72 hours of life.[19] "Possible sepsis" was diagnosed when patients developed clinical signs and symptoms of infection and abnormal CRP (>5 mg/L).[19,20] "Probable sepsis" was diagnosed when patients developed clinical signs and symptoms of infection, abnormal CRP, and white cell blood count $>30\,000$ or $<5000/mm^3$, with negative blood culture.[19,20] "Proven sepsis" was diagnosed when patients developed clinical signs and symptoms of infection, abnormal CRP and white cell blood count, and positive blood culture. "Severe sepsis" was diagnosed when patients developed acute respiratory distress syndrome or cardiovascular dysfunction or ≥2 other organ dysfunctions, and "septic shock" was defined as sepsis with cardiovascular dysfunction.[20] "Hematologic failure" was defined as the presence of thrombocytopenia $<80\,000/mm^3$ or platelet count decline $>50\%$ from the baseline, or international normalize ratio >2.[20] "Pneumonia" was diagnosed when patients developed clinical signs of respiratory distress (tachypnea, intercostal retractions and grunting, need for oxygen supplementation, and/or respiratory supports) and typical chest x-ray findings in the presence of probable sepsis and positive tracheal aspirate culture.

Clinical signs and symptoms of infections that were considered included temperature instability (rectal, $<36°C$ or $>38°C$), pulmonary dysfunction, new-onset crisis of apnea, feeding intolerance, lethargy, bradycardia or tachycardia (heart rate <100 or >180 beats per minute), hypotension, mottled or ashen appearance, and coagulopathy. Laboratory markers of infection also included the evaluation of metabolic

acidosis (serum pH <7.20 with normal $PaCO_2$), and hyperglycemia or hypoglycemia (>180 or <45 mg/dL), respectively.

Classification of infants according to infection definitions was made by a clinician unaware of P-SEP measurement.

Infection Biomarkers and Blood Culture

P-SEP was determined in whole blood samples collected in a 150-μL EDTA-containing tube from heel puncture or in an EDTA-containing syringe from vein puncture. P-SEP was measured at the bedside point of care by chemoluminescent enzyme immunoassay with the automated analyzer PATHFAST (Gepa Diagnostics, Milan, Italy).[21] Each determination required 50 μL of whole blood and was completed in 15 minutes.[16,21] PCT (reference range: <0.5 ng/mL) was measured on serum samples in our central laboratory (BRHAMS PCT, Roche Diagnostic, Milan, Italy), and CRP (reference range: <5 mg/L) was measured at the bedside point of care on whole blood samples (i-CHROMACRP, SYCOmed, Lemgo, Germany).

Blood samples for cultures were obtained from peripheral vein (≥1 mL) using the common sterile procedure. Standard laboratory methods were used to identify the microorganisms that grew on blood sample cultures.

Clinical Data

For each enrolled infant, gestational age, birth weight, postnatal age at enrollment, antenatal steroids, mode of delivery, Apgar score at 5 minutes, respiratory distress syndrome, surfactant treatment, mechanical ventilation (high-frequency oscillatory ventilation and patient triggered-ventilation), noninvasive ventilation (nasal intermittent mandatory ventilation, continuous positive airways pressure, bilevel positive airways pressure, and heated humidified high flow nasal cannula), patent ductus arteriosus, mortality, and hospital admission duration were

recorded. The main complications of prematurity, such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), and retinopathy of prematurity were also recorded. For newborns of the LOS group isolated pathogens, severe sepsis, septic shock, and death due to sepsis were also collected.

Intraventricular hemorrhage was diagnosed and staged according to the classification of Papile et al,[22] bronchopulmonary dysplasia was defined as oxygen requirements at 36 weeks' postconceptional age,[23] NEC was diagnosed and staged according to Bell's criteria,[24] and retinopathy of

prematurity was diagnosed and staged according to the current International Classification.[25]

Treatment of LOS and Septic Shock

In our NICU, prophylactic antibiotics (piperacillin plus netilmicin) were administered on admission to the NICU and stopped after 3 to 4 days of treatment if bacterial cultures (blood, tracheal aspirate, urine) remained negative in infants without clinical signs and symptoms of infections. Patients who developed possible LOS were treated with intravenous vancomycin (10 mg/kg every 18 hours for postnatal age <14 days or every 12 hours for postnatal age

TABLE 1 Demographic and Clinical Characteristics of LOS and Control Groups

	LOS Group (n = 19)	Control Group (n = 21)	P
Gestational age, wk	25.6 ± 2.0	28.8 ± 2.0	.00001
Birth wt, g	684 ± 215	1021 ± 233	.00003
Apgar score at 5 min	8 (7–8)	8 (8–8)	.45
Male gender	6 (31)	10 (48)	.35
Cesarean delivery	9 (47)	16 (76)	.10
Antenatal steroids	16 (84)	16 (76)	.69
Respiratory distress syndrome	19 (100)	20 (95)	1.00
Surfactant	17 (89)	12 (57)	.03
Mechanical ventilation	15 (79)	7 (33)	.005
HFOV	15 (70)	5 (24)	.001
Patient-triggered ventilation	14 (74)	6 (29)	.01
Noninvasive ventilation	18 (95)	20 (95)	1.00
NIMV	14 (74)	14 (67)	.73
CPAP/BiPAP	18 (95)	14 (67)	.05
HHHF	14 (74)	8 (38)	.03
Patent ductus arteriosus	17 (89)	12 (57)	.03
Intraventricular hemorrhage	3 (16)	3 (14)	1.00
Grade ≥3	2 (10)	1 (5)	.59
Periventricular leukomalacia	0 (0)	0 (0)	NA
Bronchopulmonary dysplasia	5 (26)	2 (9)	.22
NEC	1 (5)	1 (5)	1.00
Retinopathy of prematurity	4 (21)	1 (5)	.17
Stage ≥3	1 (5)	0 (0)	.47
Mortality	4 (21)	0 (0)	.17
NICU stay, d	54 ± 28	35 ± 18	.02
Total stay, d	82 ± 48	66 ± 31	.10
Age at enrollment, d	25 ± 19	28 ± 19	.32
Severe sepsis	14 (74)	—	—
Respiratory failure	14 (74)	—	—
Renal failure	2 (10)	—	—
Hematologic failure	2 (10)	—	—
Liver failure	1 (21)	—	—
Septic shock	5 (26)	—	—
Volume load	5 (26)	—	—
Dopamine	4 (21)	—	—
Dobutamine	5 (26)	—	—
Death from sepsis	2 (10)	—	—

Mean ± SD, n (%), or median and (interquartile range). BiPAP, bilevel positive airways pressure; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; HHHF, heated humidified high-flow nasal cannula; NA, not applicable; NIMV, nasal intermittent mandatory ventilation; PTV,; PVL, periventricular leukomalacia.

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TABLE 2 Diagnosis and Culture Results in Infants in the LOS Group

Diagnosis	n	Cultures	Chest X-Ray	Abnormal Clinical and Laboratory Data	Pathogens
Proven sepsis	10	Positive BC	Normal	Yes	7 CONS
					1 *Klebsiella pneumoniae*
					1 *Enterococcus faecalis*
					1 *Streptococcus agalactiae*
Pneumonia	4	Positive TA, negative BC	Abnormal	Yes	3 *Stenotrophomonas maltophilia*
					1 *Sphingomonas* spp
Proven sepsis and pneumonia	1	Positive BC, positive TA	Abnormal	Yes	1 CONS
Probable sepsis	4	Negative BC	Normal	Yes	—

BC, blood culture; CONS, coagulase-negative *Staphylococcus*; TA: tracheal aspirate.

≥14 days), plus intravenous amikacin (15 mg/kg every 48 or 36 or 24 hours for postnatal age ≤7 days, for 8–28 days or ≥29 days, respectively) after blood culture for infection determination. All patients were treated for 10 consecutive days. This empirical antibiotic combination (vancomycin plus amikacin) was chosen according to the most frequent pathogens isolated in our NICU and eventually adjusted according to the results of blood culture and antibiogram.

Statistical Analysis

To calculate sample size, we assumed that the difference in P-SEP serum concentration between the LOS and control group would be at least 300 ng/L, considering that the reported difference between septic and nonseptic adult patients is ~500 ng/L.[14,15] We also considered that the SD for P-SEP in nonseptic preterm newborns is ~300 ng/L (normal values 643.1 ± 303.8 ng/L).[16] Thus, we estimated that a sample size of 14 patients in each group would allow us to as arrive at a statistically significant difference of 300 ± 300 ng/L of P-SEP between infants in the LOS and control groups with 80% power at the $P = .05$ level.

The clinical characteristics of the 2 groups were described as mean and SD, rate and percentage, or median and interquartile range. Infection markers are given as median and interquartile range. Statistical analysis was performed by using 2-sided Student t test for parametric continuous variables, Fisher exact test for categorical variables, and Mann-Whitney U test for continuous nonparametric variables. The Wilcoxon signed rank test was used to analyze nonindependent data of continuous nonparametric variables as intragroup changes of infection biomarkers. The receiver operating characteristic curve (ROC) for P-SEP values at T_0 was analyzed to calculate the area under the curve and the most accurate cutoff value for P-SEP. Moreover, we calculated the positive and negative predictive values, and the positive and negative likelihood ratios of P-SEP at its best cutoff value.

RESULTS

Our study included 40 patients, 19 in the LOS group and 21 in the control group, who were enrolled between 6 and 59 days of life. During the study period, the incidence of LOS was 19 of 167 (11.4%). Infants in the LOS group had lower gestational age and birth weight, a higher rate of noninvasive respiratory support and mechanical ventilation, a higher rate of patent ductus arteriosus, and longer NICU stay than infants in the control group (Table 1).

Among patients in the LOS Group, 4 infants were diagnosed with probable sepsis, 10 with proven sepsis, 1 with proven sepsis and pneumonia, and 4 with pneumonia (Table 2). Moreover, 74% (14 of 19) had severe sepsis, 26% (5 of 19) septic shock, and 10% (2 of 19) died (Table 1).

Table 3 shows infection marker values: P-SEP values were higher in the LOS group than in the control group at T_0 (1295 [977–1500] vs 562 [337–726] ng/L; $P = .00001$), T_1(1011 [861–1309] vs 481 [310–704 ng/L; $P < .00001$), T_3(968 [538–1344] vs 459 [302–622] ng/L; $P = .004$), and T_5(889 [388–1031] vs 422 [291–509] ng/L; $P = .01$) (Fig 1).

In the LOS group, the P-SEP level slightly decreased at T_1 compared with T_0, whereas T_3 and T_5 P-SEP levels were significantly lower (Fig 2). Conversely, P-SEP levels did not vary in the control group. With regard to

TABLE 3 Markers of Infection in Infants in the LOS and Control Groups

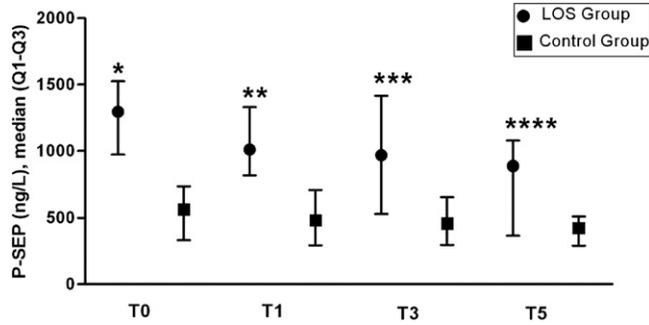|	Time 0	Time 1	Time 3	Time 5
LOS group ($n = 19$)				
P-SEP, (ng/L), n	1295 (977–1500), 19	1011 (861–1309), 19	968 (538–1344), 15	889 (388–1031), 15
PCT, (ng/mL), n	4.8 (2.5–33.7), 19	1.6 (0.8–3.0), 19	0.9 (0.5–1.4), 14	0.3 (0.2–0.4), 13
CRP, (mg/L), n	16.2 (10.6–26.6), 19	19.9 (13.8–43.4), 19	13.0 (6.7–17.3), 15	5.4 (2.5–9.5), 15
Control group ($n = 21$)				
P-SEP, (ng/L), n	562 (337–726), 21	481 (310–704), 21	459 (302–622), 21	422 (291–509), 21

Median (interquartile range), n.

FIGURE 1
Changes and comparison of P-SEP values in infants in the LOS and Control groups. *P = .00001; **P = .00006; ***P = .004; and ****P = .01 LOS vs control group.

PCT and CRP, their values did not change at T_1 compared with T_0 but significantly decreased at T_3 and T_5 (Fig 2). Figure 3 shows the longitudinal P-SEP behavior for each patient in the LOS group.

The area under the ROC curve for P-SEP was 0.972 (95% confidence interval [CI] 0.92–1.00) (Fig 4). In our population P-SEP achieved the best accuracy for prediction of probable sepsis at the cutoff of 885 ng/L with 94% sensitivity (95% CI 74–100) and 100% specificity (95% CI 84–100). The positive and negative predictive values were 100% (95% CI, 83–100) and 95% (95% CI, 80–100). The negative likelihood ratio was 0.05 (95% CI, 0.02–0.36), and the positive likelihood ratio was infinity.

DISCUSSION

Early diagnosis of LOS in preterm infants is challenging because of aspecific clinical pattern and the presence of confounding comorbidities.[6,7] Although positive blood culture is considered the gold standard for the diagnosis of sepsis in newborns,[19,20] its suboptimal sensitivity, varying from 11% to 78%, is well known.[6,7] This may be due to the low blood volume available for cultures and intermittent or low bacteremia.[6,7] Consequently, antibiotic treatment discontinuation is not recommended in infants with probable sepsis, even if the blood culture is negative.[6] Thus, the role of biochemical markers, such as CRP and PCT, in supporting the diagnosis of probable sepsis is important.

Although CRP is widely used to diagnose sepsis and monitor the response to antibiotic treatment in newborns, its utility is questionable because its peak values are reached only after a 2- to 3-day delay after the infective stimulus, and its value can increase after noninfective inflammatory events.[8,11] Conversely, PCT shows earlier peak values than CRP, occurring 10 to 12 hours after infection, and has recently been demonstrated to be accurate for the diagnosis of nosocomial sepsis in very LBW infants, but it has not been extensively investigated for this purpose.[6,26] This situation calls for the study of the accuracy of other tools for the early diagnosis and monitoring of sepsis in preterm infants.

Our study is the first that investigates the possible role of P-SEP in the diagnosis of LOS in preterm infants. In agreement with previous studies in adult septic patients,[13,14] we found that P-SEP levels are significantly higher in infants with LOS compared with controls, suggesting its potential utility in the early diagnosis of sepsis. These findings confirm previous observations that sCD14 blood levels, the precursor of P-SEP, increase in septic term and preterm newborns, paralleling the increase in pro-inflammatory cytokines.[27,28]

We found that P-SEP values at T_0 in patients with LOS were similar to those found in septic adults,[14,28] although the range was wider (300–2800 ng/L).[29,30] We found that P-SEP values at T_0 in our controls seem to be higher than those observed in nonseptic adults (<300 ng/L),[30] and are similar to the median value (578 ng/L) previously reported in healthy preterm infants.[16] Because we enrolled infants more immature than the previous study,[16] our results confirm that P-SEP levels are likely not influenced by gestational age.[16] Because newborns in our study were enrolled later than in the previous study, which assessed
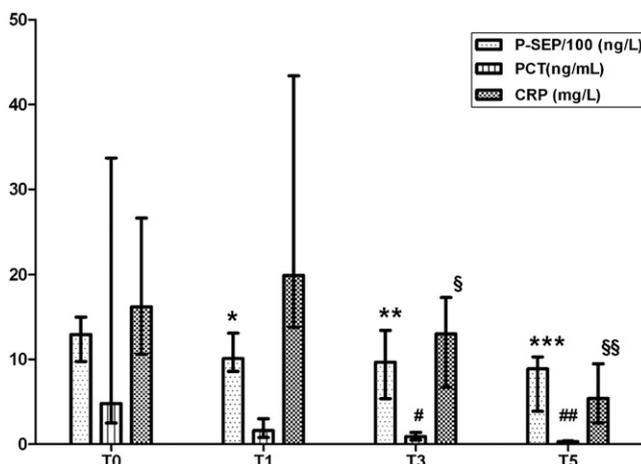

FIGURE 2
Changes in P-SEP, PCT, and CRP in the LOS group. Median and interquartile range. *P = .05 T1 vs T0 P-SEP; **P = .03 T3 vs T0 P-SEP; ***P = .02 T5 vs T0 P-SEP; #P = .001 T3 vs T0 PCT; ##P = .0001 T5 vs T0 PCT; §P = .04 T3 vs T0 CRP; §§P = .001 T3 vs T0 CRP.
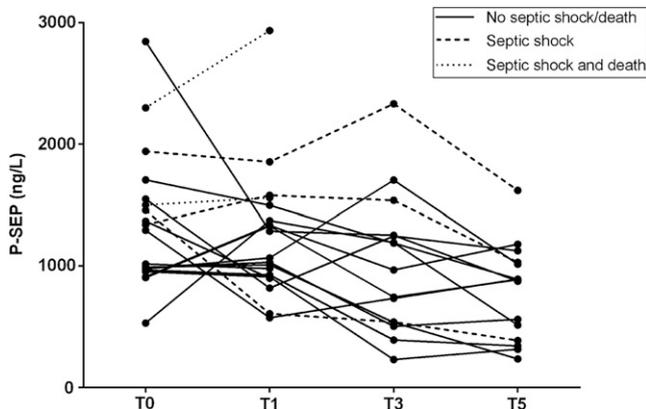
FIGURE 3
Changes of P-SEP over time in patients of the LOS group.

the normal values at 25 to 60 hours of life,[16] we also suggest that P-SEP levels are likely not influenced by postnatal age.

The ROC curve of P-SEP values at T_0 has a high area under the curve (0.972; 95% CI 0.92–1.00), indicating that P-SEP is an accurate test for the diagnosis of LOS in preterm infants when considering that the analog area under the ROC curve of PCT has been previously found to be 0.82 (95% CI 0.74–0.89).[26] The accuracy of P-SEP for the diagnosis of sepsis is higher than that of PCT in adult patients as well.[14,15,29,30] The cutoff value with the best accuracy in our study was 885 ng/L; at this value, the specificity was 100%, and sensitivity for diagnosis of probable LOS was 94%. Interestingly, this value is

higher than that reported in adults (317 ng/L),[30] but the reason why this occurs is unknown.

Thus, P-SEP measurement seems to have better or similar accuracy than other biomarkers of neonatal sepsis given recent reports for CRP of a sensitivity of 68% and specificity of 92%; for IL-6, a sensitivity of 54% and specificity of 96%; for IL-8, a sensitivity of 78% and specificity of 70%[8]; and for PCT, a sensitivity of 97.5% and specificity of 88.9%.[9] Moreover, P-SEP alone showed higher sensitivity of the combination of PCT and IL-6 (91%), although slightly lower than the combination of PCT, IL-6 and CRP (98%).[10] Therefore, considering that use of IL-6 or IL-8 is not widespread, the addition of P-SEP to the other classic biomarkers, such
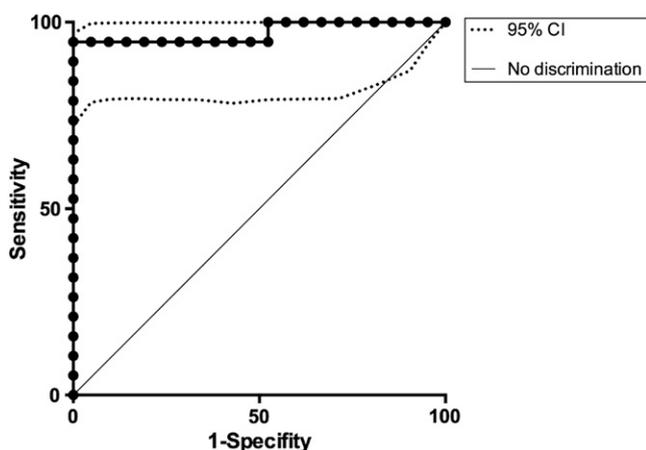
as CRP and PCT, would be potentially advantageous in clinical practice.

We observed that P-SEP progressively decreased in the LOS group, the difference being of borderline significance at T_1 and statistically significant at T_3 and T_5. These changes are similar to those that we observed for CRP and PCT, although these latter had a less marked decrease at T_1. However, these findings are in agreement with previous studies in adults[31] and support the potential role for P-SEP as a marker for monitoring the response to antibiotic treatment in preterm infants.

If our results are confirmed, we are confident that P-SEP can be included as a marker that increases the accuracy of sepsis screening for early diagnosis of suspected LOS in preterm infants. It might also help reduce false-positive diagnoses and thus antibiotic overtreatment that might increase these infants' risk of developing multidrug-resistant bacterial infection and, due to secondary dysmicrobism, NEC.[32] This role of P-SEP is also enhanced by the ease of bedside measurement, the need for small blood samples (50 μL), and its fast results (15 minutes).[21]

The limitations of our study are that the small size of our population did not permit us to stratify P-SEP values for gestational age and postnatal age, although in healthy preterm infants, P-SEP is not affected by gestational age.[16] Nor could we calculate ROC curves for CRP and PCT for comparison with the P-SEP ROC curve because CRP and PCT were not measured in control infants to limit blood sampling.

CONCLUSIONS

Our study demonstrates for the first time that P-SEP is significantly higher in preterm newborns with possible LOS compared with nonseptic control infants. Our results indicate that P-SEP is an accurate biomarker for the early diagnosis of LOS, because, at

FIGURE 4
ROC curve of P-SEP values at T_0 in the LOS group.

its best cutoff value of 855 ng/L, it has 100% specificity and 94% sensitivity. However, although these findings are promising, we believe that additional studies in larger populations are required to confirm and clarify the role of P-SEP in the screening of LOS in preterm infants.

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ANCIENT DOODLES: I attend many meetings and, while I have tried to move almost all of my correspondence and notes to digital format, I still never go anywhere without a pen in my pocket. I never know when I might need to write something. Moreover, having a pen allows me to doodle. While I would like to think that all meetings are riveting and I would remain fully engaged, sometimes my mind wanders and I start drawing on a handout or agenda. I am a terrible artist, so my doodles are angular, letter based, and simplistic.

As reported on CNN (World: November 3, 2014), individuals have been doodling for a long time. Scholars recently released pictures of doodles made by medieval scribes 700 years ago. These scribes could not reach into their pocket for a ballpoint pen, but had to create their own nibs by whittling the ends of feathers. Because this was a bit imprecise, the scribes often drew doodles to test the newly cut nib and make sure it was the correct width. However, as the doodles were not intended for public viewing, some were quite personal, vivid, and in a handwriting style not used in the formal texts they copied.

Some doodles were of animals, while others were caricatures of unpopular faculty (a type of doodle that evidently never went out of fashion). The doodles are often found in the bindings of the books as the scribes wrote on the outside of the first and last pages. Because these sides were glued to the covers, the doodles remained hidden from view for centuries. The doodles are more than curiosities, as scholars can now use the handwriting fragments to assign certain manuscripts to specific authors. As for me, I do not think that anyone will find my doodles particularly illuminating 700 years from now – but just in case, I am careful not to draw caricatures.

Noted by WVR, MD

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