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Procalcitonin as a diagnostic biomarker of sepsis: A tertiary care centre experience

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ABSTRACT

Introduction: Despite the advancement in diagnostic modalities of sepsis, it is still a leading cause of morbidity and mortality. Differentiation between sepsis and non-infectious disease states remains a diagnostic challenge. Procalcitonin (PCT) is useful for the diagnosis of sepsis but it varies in cut-off ranges at different clinical settings. The aim of this study was to correlate serum PCT levels with cultures and to evaluate the best cut-off values with high sensitivity and specificity for PCT.
Methodology: This prospective study included 305 patients from different medical wards; the patients were classified into group I: controls (n = 46), group II: culture-negative sepsis (n = 76) and group III: culture-positive sepsis (n = 196). Mean p value <0.05 was considered significant.
Results: PCT levels were significantly higher in group II and group III as compared with group I. In group II, the best cut-off point for PCT was 1.3 ng/ml with 87.30% sensitivity and 78.26% specificity (area under curve 0.86). In group III, the best cut-off value of 2.20 ng/ml with 98.47% sensitivity and 89.13% specificity was found (AUC 0.96).
Conclusion: Procalcitonin can accurately differentiate culture-negative and culture-positive sepsis from non-infectious diseases, thus making it a promising biomarker in diagnosis of bacterial sepsis.

Introduction

Sepsis is a heterogeneous infectious disease associated with high rates of morbidity and mortality. A global incidence of 31.5 million cases per year has been reported in a recent meta-analysis [1]. Sepsis carries one of the highest infectious burdens in Asian countries, especially in India, where mortality attributable to sepsis can be as high as 56.2% [2]. Despite of its association with high morbidity and mortality, sepsis remains an elusive condition to diagnose timely and accurately. This complex entity is clinically characterized by alterations in physiologic parameters such as temperature, pulse rate, respiratory rate and white blood cell counts [3,4]. However, these signs of infection are non-specific, non-sensitive and can pose immense diagnostic challenges to clinicians.

By far, bacteria are the commonest etiological agents of sepsis and cultures turn out to be positive in only 50% of the cases. Recent studies on early diagnosis of sepsis have focused on microorganisms from blood cultures but bacterial cultures require at least 24–48 h to make early therapeutic decisions. In addition, cultures are unrevealing in many cases [5–7]. Molecular techniques can expedite pathogen detection but are unsuccessful in differentiating colonization from true infection [8,9]. Clinically suspected patients of sepsis, who remain culture-negative, pose additional challenges in the decision making for administration of antibiotics.

In light of these reasons, a dire need has been felt to search for reliable biomarkers of sepsis. A biomarker with high sensitivity and negative predictive value (NPV), which can exclude suspected sepsis early could be a very useful addition to the diagnostic armamentarium for management of sepsis. Procalcitonin (PCT), a polypeptide is one such biomarker that has demonstrated highest reliability in the early diagnosis of sepsis, especially of bacterial etiology [10–12]. In bacterial sepsis, serum PCT increases by 100–1000 fold within 4 h after the onset of systemic infection and peaks at between 8 and 24 h [13]. Serum PCT levels increase proportion-

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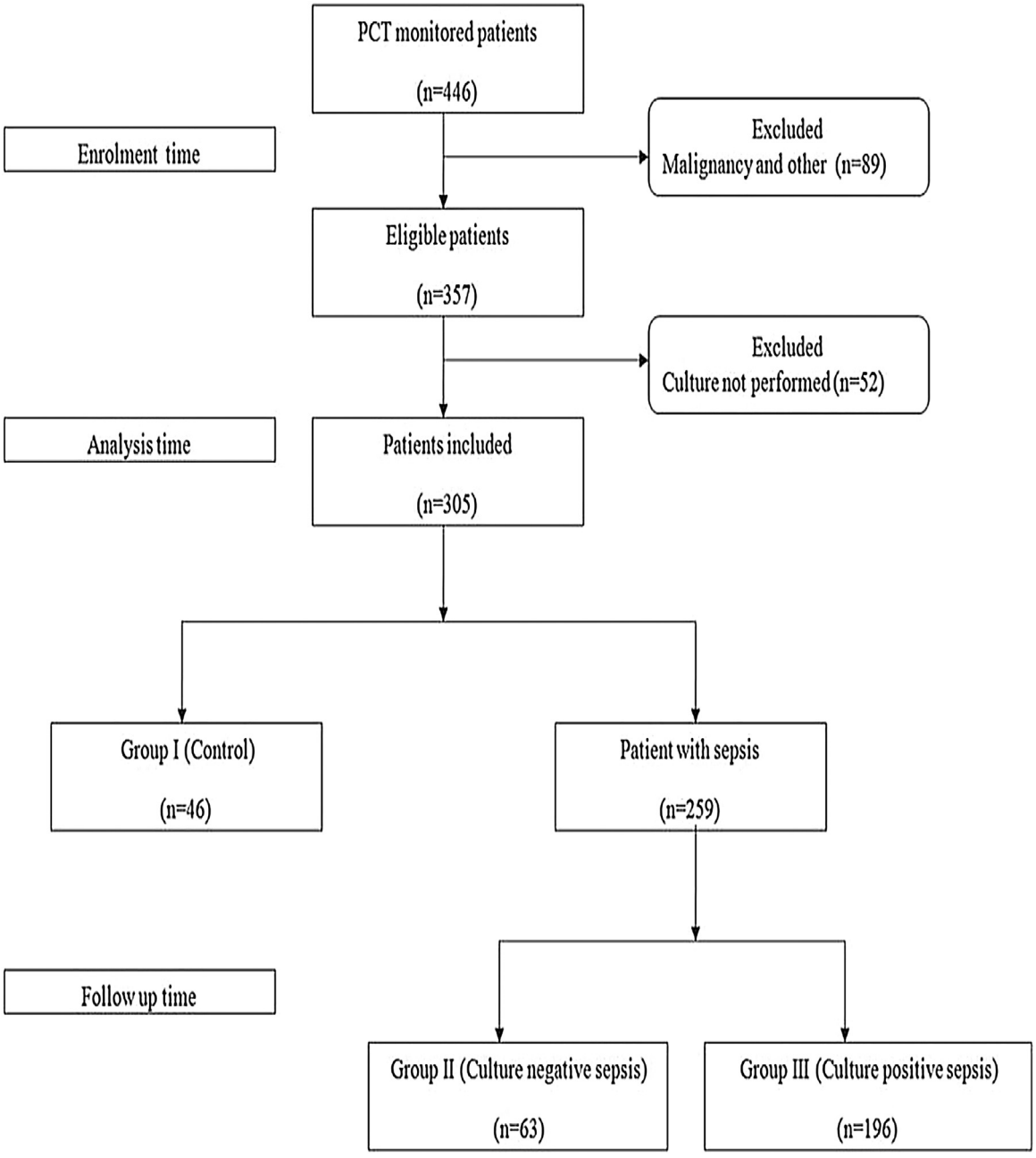

Fig. 1. Flow diagram representing selection criteria and grouping of patient population.

ately to the increasing severity of sepsis and hence may contribute to early identification and better risk stratification of these patients [14–16]. There are only few published studies that have evaluated PCT as a biomarker of bacterial sepsis with concurrent correlation with culture results [5,16,17]. Accordingly, we performed this study to investigate the utility of PCT as a diagnostic marker in sepsis at a tertiary care hospital in North India. We aimed to determine serum PCT levels and correlate with culture results and further evaluate sensitivity, specificity, positive predictive value (PPV), and NPV for PCT to predict its diagnostic performance.

Materials and methods

Patient selection and study design

We performed a prospective observational study on 259 consecutive adult patients who were hospitalized and treated in our institute with sepsis of bacterial etiology from September 2016 to October 2017.

The study population comprised of patients from different medical wards; various parameters were recorded to facilitate the calculation of Sequential Organ Failure Assessment Score (SOFA) score. Demographic variables, clinical details and other baseline characteristics of eligible patients were also documented. Initially enrolled patients were classified into non-infectious controls (group I) and suspected sepsis depending on clinical assessment (Fig. 1); further followed up and on the availability of microbiological culture results, patients were grouped into following:

Group I (control group): patients with non-infectious internal medicine morbidity. The admission diagnoses in these patients were: acute heart failure, hypertensive cardiomyopathy, acute renal failure, acute cerebrovascular disease, epilepsy, Crohn's disease and neoplastic disease.

Group II (culture-negative sepsis group): clinical suspicion of infection with negative culture results.

Group III (culture-positive sepsis group): patients with sepsis along with microbiologically documented source of infection. At the time of analysis, group III was further subdivided into group III (a) Gram positive sepsis and group III (b) Gram negative sepsis.

Sepsis has been redefined as infection associated with an increase in the SOFA score by 2 or more points in the recently released new consensus definitions (Sepsis-3) by the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine (SCCM) in 2016 [18–21]. Two independent clinicians (also co-authors) blinded to the diagnosis were involved to confirm patient inclusion/exclusion into sepsis group. No discrepancy was found between the two operators. Patients with history of recent surgery or transplant, malignancy, suspected or documented non-bacterial infections and those managed on immunosuppressant agents were excluded (Fig. 1). Additionally, patients were followed up till discharge or any adverse outcomes, and patients who were lost to follow-up were not included.

Infection identification and diagnostic criteria

According to the International Sepsis Forum Consensus Conference, infections were clinically diagnosed on the basis of clinical presentation, laboratory findings, microbiologic evidence and imaging studies [22]. The managing physicians on the basis of clinical impression and bacterial culture results documented site of infection. Briefly, abdominal infections included abdominal abscesses, peritonitis, enteritis, pancreatic and biliary tract infections. A case of urinary tract infection was diagnosed through suggestive signs and symptoms including fever, dysuria, pyuria, frequency, positive Gram stain and suggestive imaging. Isolation of $>10^5$ colony forming units (cfu)/ml of microorganisms (or 10^3 cfu/ml in catheterized patients) on urine cultures were deemed positive. Respiratory tract infection including pneumonia required a high clinical suspicion plus lobar infiltrates on chest X-ray. On recovery of etiologic agents from blood or pleural fluid, patients were deemed as culture positive. Alternatively, semi-quantitative cultures of respiratory secretions were considered positive if they yielded moderate to heavy growths of bacterial agents with Gram stain examination revealing few epithelial cells ($\leq$10 per high power field). Primary bloodstream infection was diagnosed when the bacterial agent recovered on blood culture was unrelated to an infection at another site [23]. All sepsis patients were managed by the treating clinicians according to the standard institutional protocol based on recommendations from the Surviving Sepsis campaign [24].

Specimen collection, laboratory processing and PCT measurement

Blood samples for culture and measurement of PCT were drawn simultaneously from each patient before commencement of antibiotic therapy and sent to microbiology laboratory for further processing. Meanwhile from the control group, blood was collected only at the time of admission. Each blood culture comprised two sets of one aerobic and one anaerobic broth bottles (BACTEC plus) per patient. Blood culture vials were incubated in the BACTEC automated blood culture system (BD Biosciences, Maryland, USA) for 5 days. Subcultures were prepared from positive broths. Also, microbiological investigations were carried out depending on anatomic site of infection. These included culture of sputum/endotracheal aspirates, pleural or ascitic fluids, urine, pus and other biological materials or fluids (for example, abdominal abscesses, peritonitis and biliary infections) as per treating clinician's requisition. Standard laboratory methods were employed for the identification of organisms from the positive cultures.

PCT estimation in the serum was done using the commercially available electro chemiluminescense immunoassay (Elecsys® BRAHMS PCT from Roche Diagnostics, Berlin, Germany) using a Cobase 411 analyzer. PCT levels >0.5 ng/ml were taken as clinically significant as per manufacturer's instruction. Values above 100 ng/ml were not delineated further by the equipment; hence reported as $\geq$100 ng/ml and all such values were taken as 100 ng/ml for the purpose of calculations.

Statistical analysis

Demographic and clinical data that were continuous and equally distributed variables were reported as mean values with standard deviation between all three groups and subgroups. Categorical variables were summarized as frequencies with percentages and analyzed using the $\chi 2$ statistic. Observations with missing values were excluded. Quantitative variables were analyzed using One-way ANOVA and qualitative variables by Fisher exact test.

Receiver operating characteristic (ROC) curves were constructed and area under the curve (AUC) was computed to assess the diagnostic performance of PCT followed by calculation of the Youden index, PPV, NPV, positive likelihood ratio, and negative likelihood ratios. For all statistical tests, statistical significance was assumed if a null hypothesis could be rejected at a P value of <0.05. Based on the day of death or discharge, Kaplan–Meier survival analysis was performed for all three groups. Statistical analyses were performed in SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA).

Ethical clearance

The ethics committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, Uttar Pradesh (India) approved the study. All procedures involving human participants in this study were in accordance with the ethical standards.

Results

Characteristics of the enrolled subjects

The study patients were classified into three groups as defined in methodology. Group I, controls (n = 46); group II, culture negative sepsis (n = 63); and group III, culture-positive sepsis (n = 196). The mean age of the septic patients was significantly higher than that of the controls. Mean PCT value was significantly different in all 3 groups, being highest in-group III (17.49%). Overall mortality rate attributable to sepsis was 28% (n = 73) (Table 1).

Source of infection

The respiratory tract (40%) and abdomen (33%) were predominant foci of clinically suspected bacterial infections. In culture positive sepsis patients, bloodstream was the major site of infection (46%) followed by urinary tract (26%) and respiratory tract (19%).

PCT differentiation in culture positive sepsis

Out of 196 patients, 59% (116) were infected by Gram-negative bacteria (GNB) and 41% (80) by Gram-positive bacteria (GPB). Thirty positive cultures were polymicrobial and remaining 166 mono-microbial. In Gram-negative cultures, *Klebsiella pneumoniae* was the most common pathogen (n = 41, 35.34%) with mean PCT value 25.05 ± 37.48 ng/ml followed by *Escherichia coli* (n = 25, 21.55%) mean 17.49 ± 26.22 ng/ml and *Acinetobacter baumanni* (n = 21,18.10%) mean PCT value 14.71 ± 28.99 ng/ml.

Interestingly, *Citrobacter freundii* was isolated in only 5 cultures, but mean PCT value 23.38 ± 30.04 ng/ml was higher than

Table 1
Group wise demographics and laboratory data distribution, ANNOVA[a], Fisher extact test [b].

Characters	Group I (controls)			Group II (culture negative sepsis)			Group III (culture positive sepsis)		
No. of patients	46			63			196		
	Mean ± SD			Mean ± SD		P value	Mean ± SD		P value
Age	42.47 ± 17.06			38.65 ± 18.42		0.007	38.74 ± 19.10		0.0003
Sex M/F	30/16			41/22		0.51[b]	123/73		0.467[b]
PCT(ng/ml)	0.81 ± 0.91			12.71 ± 15.61		0.0036[a]	17.49 ± 25.92		<0.0001[a]
Mortality	3 (6.52%)			15 (23.80%)			58 (29.59%)		0.0006[b]
	Survivors (n = 43)	Non-survivors (n = 3)		Survivors (n = 48)	Non-survivors (n = 15)		Survivors (n = 138)	Non-survivors (n = 58)	
PCT (ng/ml)	0.78 ± 0.84	1.70 ± 1.91	–	8.48 ± 10.22	19.58 ± 18.96	>0.10[a]	12.79 ± 21.93	20.21 ± 28.91	0.0002[a]

Table 2
Mean PCT values corresponding to isolated bacterial pathogens with mortality.

Bacterial culture	No. of patients	No. of isolates	Mean ± SD	Survivors	Non-survivors
Gram Negative Bacillus					
Acinetobacter baumanni	32	41	14.71 ± 28.99	13	19
Acinetobacter lwoffii	2	2	–	2	0
Citrobacter freundii	5	5	23.38 ± 30.04	5	0
Escherichia coli	22	38	17.49 ± 26.22	13	9
Klebsiella pneumoniae	35	55	25.05 ± 37.48	19	16
Morganella morganii	1	1	–	0	1
Proteus mirabilis	1	1	–	0	1
Pseudomonas aeruginosa	11	22	16.56 ± 32.05	8	3
Pseudomonas species	7	9	15.2 ± 26.59	7	0
Gram Positive cocci					
Methicillin Sensitive Staphylococcus aureus	6	6	11.08 ± 12.90	6	0
Methicillin Resistant Staphylococcus aureus	37	47	12.42 ± 20.10	34	3
Enterococcus faecalis	20	24	3 ± 0.56	17	3
Enterococcus faecium	16	28	9.21 ± 11.28	14	2
Streptococcus species	1	1		0	1
Total	196	280	–	153	58

that of *E. coli* and *A. baumanni* (Table 2). On comparing mean PCT values between Gram-negative, Gram-positive, and polymicrobial isolates, we found that Gram-negative bacterial pathogens had highest mean PCT values.

Discriminative performance of PCT

To estimate the diagnostic performance of PCT, cut-off value of 1.03 ng/ml and AUC = 0.920 (95% CI = 0.869–0.972) was found significant (P = <0.001) to differentiate culture negative sepsis from controls with sensitivity 87.30% and specificity 78.26% [Fig. 2(A)], while PCT cut-off value 2.20 ng/ml and AUC = 0.985, (95% CI = 0.965–1) differentiated culture positive sepsis from controls with 98.5% sensitivity and 89.13% specificity [(P = <0.001) [Fig. 2(B)]. We also analyzed PCT to differentiate culture positive sepsis in comparison with culture negative sepsis and found significant cut-off 2.58 ng/ml [(AUC = 0.608, 95% CI = 0.512–0.703)] with sensitivity91.33%, but the specificity of this test was quite low 41.27% only [Fig. 2(C)].We classified group III into culture positive gram negative and culture positive gram positive subgroups and analyzed ROC for same and found AUC = 0.612 at 3.01 ng/ml cut-off value of PCT with 75% sensitivity, and 46.34% specificity [Fig. 2(D)] (Table 3).

PCT can predict mortality

Kaplan Meyer survival analysis was used to predict PCT as predictor of mortality. Significant differences were observed between PCT values in all 3 groups with decrease in the survivors and an increase in the non-survivors.In group I, mean PCT value for survivors was 0.78 ± 0.84 ng/ml while it increased in non-survivors to 1.70 ± 1.91 ng/ml; group II survivors had mean PCT value 8.48 ± 10.22 ng/ml which increased in non-survivors to 19.58 ± 18.96 ng/ml and group III had highest mortality at mean PCT 20.21 ± 28.91 ng/ml; which reflects extremely significant association of hike in PCT with mortality (Table 1). Maximum survival was 80 days in group I, while it reduced to 77 days in group II and further reduced to 20 days in group III (Fig. 3).

Discussion

Using this prospective study, we describe key findings related to utility of PCT as a biomarker of sepsis. To the best of our knowledge, this is the first study to evaluate the diagnostic performance of PCT at several risk thresholds on the patient population from different medical wards; a model including culture negative sepsis, culture positive sepsis, culture positive Gram-negative and Gram-positive sepsis. Earlier studies were mostly performed in specialized units and in highly selected patient population (e.g. medical and surgical intensive care units).

Principal findings of this study include threshold for differentiating culture negative and culture positive sepsis. Additionally, we showed that PCT levels correlate with mortality in all the three groups. As far as we are aware, there are only two prior studies that had correlated PCT levels with culture results [5,16].

We noted that PCT levels vary between the 3 groups, the levels being highest in culture positive sepsis and lowest in control group (culture sterile). Cut-off values for PCT provided by statistical analysis indicate its utility as a biomarker in diagnosis of sepsis. PCT threshold value of 1.03 ng/ml had 87% sensitivity, 78% specificity and 81.82% NPV to suspect bacterial sepsis, while cut-off value of 2.20 ng/ml had 98% sensitivity, 89% specificity and 93% NPV indicating culture positive sepsis. Statistical significance of these findings was found similar to previously referred studies [5,16]. The low

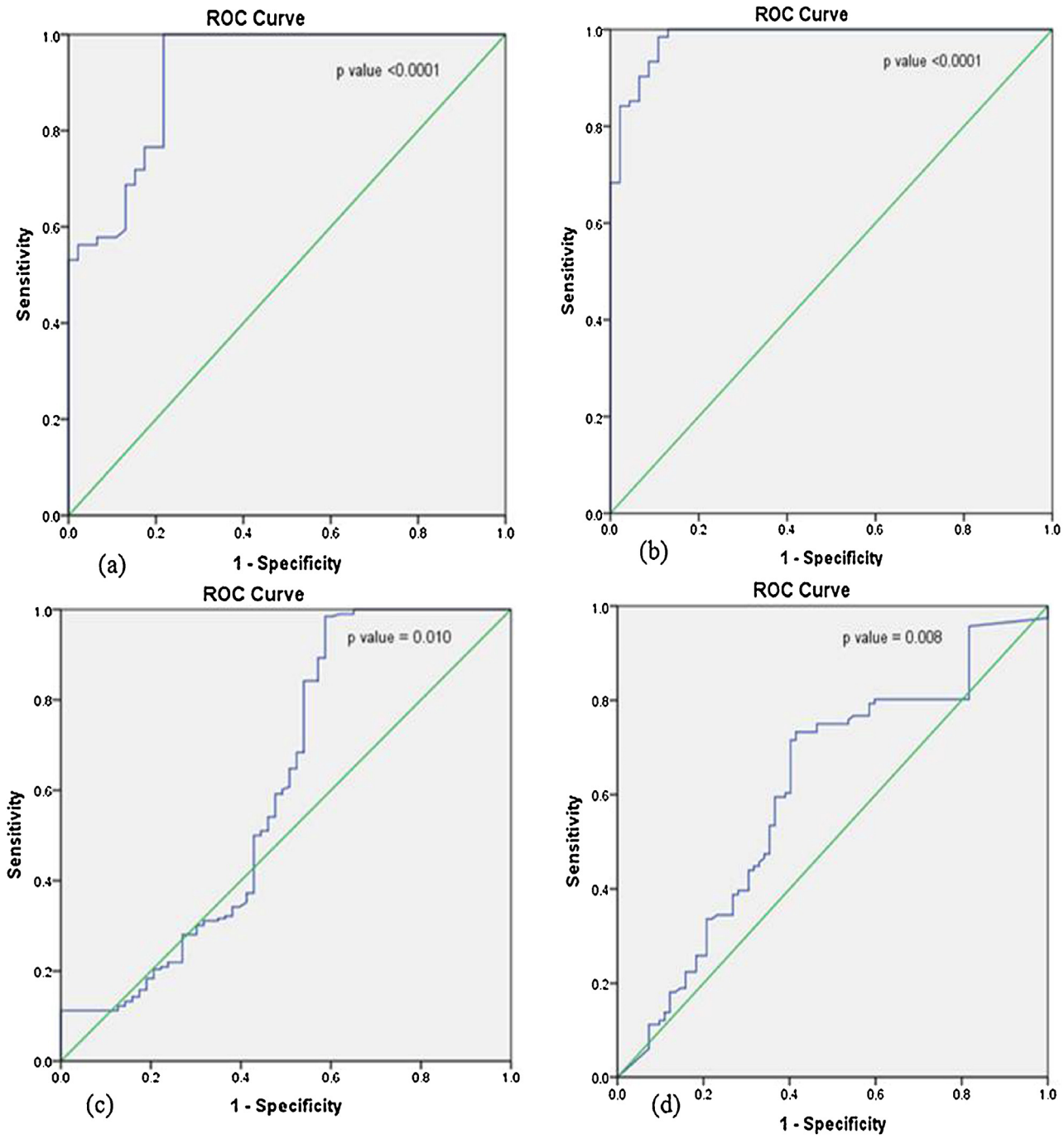

Fig. 2. (A) ROC and AUC curve for PCT value between Group I (control) and Group II (sepsis), (B) ROC and AUC curve for PCT value between Group I (control) and Group III (culture positive sepsis), (C) ROC – AUC between Gram-negative and Gram-positive culture positive isolates, (D) ROC – AUC between culture positive sepsis and culture negative sepsis.

Table 3
Diagnostic performance of PCT in various groups[a].

Variable	Cut off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
Group II Vs Group I PCT (ng/ml)	1.03	0.920 (0.869–0.972)	87.30	78.26	84.62	81.82	3.96	0.16
Group III Vs Group I PCT (ng/ml)	2.20	0.983 (0.965–1)	98.47	89.13	97.47	93.18	8.90	0.01
Group III Vs Group II PCT (ng/ml)	2.58	0.608 (0.512–0.703)	91.33	41.27	82.87	60.47	1.55	0.21
Group III (b) Vs Group III (a) PCT (ng/ml)	3.01	0.612 (0.530–0.693)	75.00	46.34	66.41	56.72	1.39	0.39

[a] Legend: Group I Control group, Group II-Culture negative, Group III Culture positive, Group III (a) Culture positive Gram-positive, Group III (b) culture positive Gram-negative, PPV: positive predictive value NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio.

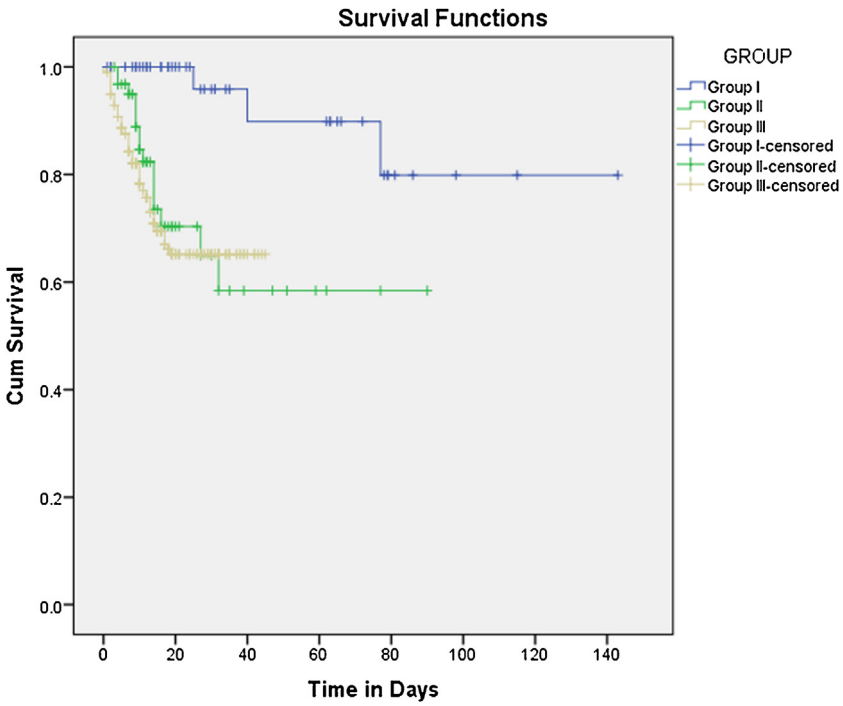

Fig. 3. Kaplan Meyer survival analysis of all three groups with censored cases.

specificity of culture negative sepsis compared to culture positive sepsis is due to little variance between PCT levels of group II and group III. Even at this close variance, cut-off 2.58 ng/ml may discriminate culture negative sepsis from culture positive sepsis with sensitivity of 91.33%; but it may predict false positivity too. Therefore specificity of this cut-off may or may not be helpful for differentiating between the two.

In about 24.3% (n = 63) of our septic patients, the cultures were negative. This finding is concordant with various published studies that have reported 28–38% of patients accounting for culture negative sepsis [5,24]. We could have done Polymerase chain reaction (PCR) especially for the culture negative cases. However, whether this technique would have helped to identify and confirm a true bacterial pathogen is questionable. To understand this phenomenon in depth, more studies are required.

Mortality attributable to sepsis remains high despite of the advanced diagnostic algorithms utilized for its identification. A wide range of mortality ranging between 22% and 50% has been reported by several clinical trials [7,25]. Sepsis accounted for 28.2% (n = 73) of deaths in our study. We found hospital mortality rate for culture negative sepsis to be lower than that of culture positive sepsis (23.80% versus 29.59%). This observation is supported by previous studies [16,17,22]. However, a number of studies did not find a correlation between mortality and culture [24,26]. The reasons for these discrepant findings are not clear to us at the moment. Probably, these latter studies were not designed to attempt such comparisons.

In addition, we found significant PCT threshold ≥3.01 ng/ml had 75% sensitivity and 46% specificity in discriminating Gram-positive and Gram-negative bacterial infections. Concordant study by Leli et al. evaluated 1949 clinical specimens and found that PCT cut-off of 10.8 ng/ml could discriminate between sepsis caused by Gram-negative or by Gram-positive bacteria with a specificity of 82.5%. On comparison, huge difference in cut-off values and specificity may be attributed to variations in sample size, randomization, population and study design.

In this study, greater elevation in PCT levels was induced by GNB as compared to GPB. In about 32% of patients with Gram-negative sepsis, *K. pneumonia* and *E.coli* were the etiological agents whereas; 18% of the patients who developed Gram-positive sepsis were infected by MRSA, which is similar to a study by Van et al. [27]. Amongst the GNB, *K. pneumoniae* (25.05 ng/ml) had the highest mean PCT value while infections due to non-fermenters like *A. baumanni* exhibited a mean PCT value 14.71 ng/ml. This finding supports a previous study that had also reported greater elevations in PCT levels induced by Enterobacteriaceae as compared to non-fermentative GNB [17].

PCT also showed a good ability in predicting septic patient mortality as evidenced by its significantly higher concentrations in non-survivors than in the survivors. Similar observation from previous studies [5,16,17] enhances significance of this study. This finding is further supported by previous studies that have shown the usefulness of this biomarker in prognostic stratification of patients with sepsis in the critical care settings [28,29]. To the contrary, few studies did not find a correlation between culture positivity and mortality in specified subject groups [24,26]. Also, we would like to emphasize that clinicians may or may not be able to differentiate culture negative sepsis from culture positive sepsis with a PCT level alone. It can, however, may be helpful in guiding them in early clinical decision making, along with other relevant clinical information.

Conclusion

PCT can be considered as an effective and elegant addition to diagnostic algorithm for supporting clinical decision making, identification of sepsis and lessen dependence on cultures as well. Refined risk stratification and improved patient outcomes could result from the utilization of PCT based strategies. More multicentric randomized studies are needed to confirm the validity of our study findings.

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Competing interests

None declared.

Ethical approval

Not required.

Authors' contributions

Shefali Gupta: Study design, data collection and writing of the manuscript. Pradeep Jaswani: Data validation, data analysis, tabulation and review of the manuscript. R.K.Sharma, Amit Gupta, Narayan Prasad, Chinmoy Sahu and Suraksha Agrawal reviewed the manuscript. Kashi Nath Prasad planned and supervised the study, and critically reviewed as well revised the manuscript. All authors have read and approved the final manuscript.

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