The diagnostic role of soluble triggering receptor expressed on myeloid cells-1 and procalcitonin for early detection of neonatal sepsis

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Background/aim
Sepsis is a substantial cause of death in neonates less than or equal to 28 days of life. As the bacteriologic method needs much time and it may give false-negative results in septic neonates' diagnosis, the present study aims to appraise the diagnostic role of both soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and procalcitonin (PCT) for early detection of neonatal sepsis.
Patients and methods
This case–control study included 40 septic neonates and other 40 nonseptic neonates as control. They were subjected to history taking, full clinical examination, and assessment of sTREM-1, PCT by ELISA, C-reactive protein in serum, in addition to CBC and blood culture test.
Results
sTREM-1 and PCT showed significant increase in septic group when compared with controls. Moreover, their levels were significantly higher in positive blood culture septic neonates than negative blood culture septic neonates. C-reactive protein level was significantly higher in late-onset sepsis group than early-onset sepsis group.
Conclusion
Serum sTREM-1 and PCT could be used as new biomarkers for rapid and early detection of neonatal septicemia, leading to prompt initiation of antibiotic therapy for achieving better outcomes in those cases.

Keywords:
blood culture, diagnosis, neonatal sepsis, procalcitonin, soluble triggering receptor expressed on myeloid cells-1

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Introduction

Sepsis is a substantial cause of death in neonates less than or equal to 28 days of life despite the major development in antibiotics and the other supportive therapies [1]. The WHO estimated that 45% of under 5-year mortalities occur during the first month of infant life [2]. Incidence of neonatal sepsis differs from 1 to 4/1000 live births in developed countries to 10–50/1000 live births in developing countries [3]. Many research studies have been done for blood culture as well as clinically and laboratory helpful methods for sepsis diagnosis in neonates. The gold diagnostic standard for sepsis is the detection of pathogenic organism in blood culture. However, the isolation of organisms may not be possible for many reasons [4].

Inflammation and endothelial cell injury are major determinants of the host response that leads to the complex pathophysiology of sepsis, so markers related to inflammation and tissue damage could be used in both sepsis diagnosis and follow-up. These biomarkers have shown a great advance in early recognition of sepsis for prompt antibiotic therapy intervention and they are also helpful in outcome prediction. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), procalcitonin (PCT), C-reactive protein (CRP), and interleukin-10 are biomarkers used in clinical practice [5]. Biological markers of sepsis like PCT and CRP have been already used for detection of bacterial infection, but they are indirect indicators, so their sensitivity and specificity are not 100% [6].

sTREM-1 is a newly detected member of immunoglobulin (Ig) superfamily of receptors expressed on monocytes and neutrophils, in addition to alveolar and hepatic macrophages' surfaces [7]. This 30-DKa glycoprotein is regulated by neutrophils after contact of monocytes and macrophages with lipopolysaccharides, gram-positive and gram-negative

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bacteria, as well as fungi [8]. sTREM-1 activation induces an increase in the pathogenic activity of neutrophils, overproduction of proinflammatory cytokines, and reduction of interleukin-10 levels [9].

PCT is a calcitonin precursor and a polypeptide that consists of 116 amino acids. It has an essential role in identifying nonsystemic inflammatory response syndrome as well as neonatal sepsis [1]. PCT rises earlier than CRP and peaks for shorter duration and returns to its normal value faster in response to therapy [10]. CRP is an acute-phase reactant, and it is a widely used inflammatory marker in detecting the inflammatory response to sepsis. It is a sensitive marker of inflammation and tissue damage [11].

The main purpose of this study was to appraise the diagnostic role of both sTREM-1 and PCT for early detection of neonatal sepsis because bacteriologic method needs much time and it may give false-negative results in neonates. Besides, the frequent sampling for serial blood cultures is really difficult.

Patients and methods

Patients and study design

A case–control study included 80 neonates who were divided into two equal groups as following: (a) 40 full-term and near-term neonates were recruited from the neonatal ICU of El Demerdash Hospital to participate in this study. They were diagnosed to have sepsis (case group) depending on clinical assessment, hematological scoring system, and Tollner score. Scoring more than or equal to 3 and more than or equal to 10 for both hematological scoring system and Tollner scores, respectively, was considered as sepsis. (b) A group of other 40 postnatal age-matched and sex-matched neonates without clinical finding of sepsis was included as controls (control group). They were chosen from neonatology outpatient coming for follow-up.

Exclusion criteria

Neonates with major congenital malformations, chromosomal abnormalities, fetal hydrops, metabolic errors, perinatal asphyxia, neurological problems at admission, symptoms of ductus arteriosus, and prior use of intravenous Igs were excluded from the study.

Ethical approval

This study was approved by Medical Research Ethical Committee of the National Research Center, Egypt, with registration no. 20/121. A written informed consent for all participants was collected from their parents after explaining the aim and the methodology of the study.

Methods

All cases and controls were subjected to full history taking, as well as general and local examinations. The septic group was evaluated using clinical sepsis scores, including Griffin score [12] and Tollner score [13]. Overall, 4 ml of blood was withdrawn from all participants, and the following laboratory investigations were carried out:

(1) Complete blood count was done using KX-21 (Sysmex, Kobe, Japan).
(2) Semiquantitative CRP was measured by latex agglutination, using kits of Omega Diagnostic Ltd (Alva, UK).
(3) Blood culture: 2 ml of blood was injected into the Bact/Alert culture bottle under complete aseptic conditions. The inoculated culture bottles were placed in the Bact/Alert instrument (bio-Mérieux, Marcy l'Etoile, France) as soon as possible, for incubation and monitoring. Positive samples were gram stained and subcultured on blood agar, MacConkey agar, and Sabouraud dextrose agar supplemented with chloramphenicol (Oxoid, Basingstoke, England) and incubated in appropriate temperature (37°C). Full identification of organisms was done with Vitek 2 compact (bio-Mérieux). Coagulase-negative Staphylococcus was identified as a causative pathogen for sepsis by its isolation from two positive blood cultures, according to the method of El-Madbouly *et al.* [14].
(4) Measurement of serum levels of sTREM-1 and PCT: serum sTREM-1and PCT were measured by ELISA using kits of Biotech Co. Ltd (Shanghai, China) and Glory Science Co. Ltd (Hong Kong, China), respectively, with a detection range of 3–900 ng/l for sTREM-1 and 0.5–10 ng/ml for PCT.

Statistical analysis

All statistical calculations were done using computer program Statistical Package for Social Science statistical program, version 18 (IBM Corporation, K28 Cairo-Alexandria Desert Road, Smart Village Business Park, Building B144 Giza, Egypt). Mean and SD were used as descriptive statistics for quantitative variables (ratio and ordinal), whereas frequency was used for nominal variables. The nonparametric Mann–Whitney test was used to test group difference for quantitative variables, whereas χ^2

test was used for nominal variables. Spearman correlation was used to study correlation between variables. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic value for sTREM-1 and PCT for prediction of sepsis.

Results

Our study enrolled 80 neonates who were divided into two equal groups. The characteristics of the all studied neonates and their mothers are illustrated in Table 1. The case (septic) group composed of 40 neonates, with a mean gestational age of 37.5±0.16 weeks and mean birth weight 3.01±0.16 kg. The control (nonseptic) group composed of 40 healthy neonates with mean gestational age of 38.37±0.82 weeks and mean birth weight of 3.27±0.21 kg. Neonates with sepsis have lower birth weight and gestational age in comparison with healthy controls ($P<0.05$). The case group consisted of 17 (32.5%) females and 23 (67.5%) males, whereas the control group consisted of 13 (32.5%) males and 27 (67.5%) females ($P<0.05$). Maternal history of diabetes mellitus was statistically significant higher in cases than controls ($P<0.05$). Approximately 67.5% of our septic neonates were born by cesarean section (CS). Apgar score at 1 and 5 min was significantly higher in septic than nonseptic control neonates ($P<0.05$).

Levels of sTREM-1, PCT, CRP, and total leukocyte count (TLC) were significantly higher in septic neonates than healthy controls ($P<0.05$). On the contrary, platelets count had a statistically significant higher level in healthy controls than septic cases ($P<0.05$), as shown in Table 2.

The results presented in Table 3 exhibited that levels of sTREM-1 and PCT were significantly higher in positive blood culture septic neonates than negative blood culture septic neonates ($P<0.05$), whereas insignificant change was obtained in CRP. However, our results reported that level of CRP showed statistically significant higher level in late-onset sepsis (LOS) than early-onset sepsis (EOS) ($P<0.05$), as shown in Table 4.

Table 1 Characteristics of the studied population of neonates and their mothers

Variables	Control group (*N*=40)	Septic group (*N*=40)	*P* value
Body weight (kg)	3.27±0.21	3.01±0.16	0.001*
Gestational age (weeks)	38.37±0.82	37.5±0.16	0.001*
Length (cm)	48.9±1.42	48.6±1.12	0.570
Apgar at 1 min	5.00±0.00	4.8±0.40	0.003*
Apgar at 5 min	9.85±0.36	8.8±0.40	0.001*
Sex			
Male	13 (32.5)	27 (67.5)	0.04*
Female	27 (67.5)	13 (32.5)	
Delivery mode			
Vaginal	8 (20)	13(32.5)	0.200
CS	32 (80)	27(67.5)	
Rupture of membranes			
Yes	4 (10)	8 (20)	0.348
No	36 (90)	32 (80)	
Maternal DM			
Yes	3 (7.5)	13 (32.5)	0.01*
No	37 (92.5)	27 (67.5)	

Data are expressed as mean±SD and *n* (%). CS, cesarean section; DM, diabetes mellitus. *Significant difference at *P* value less than 0.05.

Table 2 Comparison between case (septic) group and control (nonseptic) group as regarding laboratory data

Variables	Control group (*N*=40)	Septic group (*N*=40)
sTREM-1	66.38±16.62	225.65±32.69*
CRP	2.3±10.46	10.72±11.97*
Procalcitonin	0.859±0.19	5.41±2.1*
Total leukocytic count	8.97±0.83	12.23±3.23*
Platelets	320.9±37.64	207.33±82.4*

All data are expressed as mean±SD. CRP, C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1. *Significant difference at *P* value less than 0.05.

Table 3 Comparison between septic neonates with positive blood culture and negative blood culture as regarding C-reactive protein, procalcitonin, and sTRM-1

Variables	Septic neonates with positive blood culture group (*N*=28)	Septic neonates with negative blood culture group (*N*=12)
sTREM-1	192.57±44.68	136.85±22.40*
CRP	4.04±4.57	19.76±13.03
Procalcitonin	6.08±1.83	3.85±2.03*

All data are expressed as mean±SD. CRP, C-reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1. *Significant difference at *P* value less than 0.05.

Table 4 Comparison between septic neonates with early-onset sepsis and late-onset sepsis as regarding C-reactive protein, procalcitonin, and soluble triggering receptor expressed on myeloid cells-1

Variables	Septic neonates with EOS (*N*=23)	Septic neonates with LOS (*N*=17)
sTREM-1	185.21±48.80	163.19±42.1
CRP	4.04±4.57	19.76±13.03*
Procalcitonin	5.14±2.15	5.78±2.11

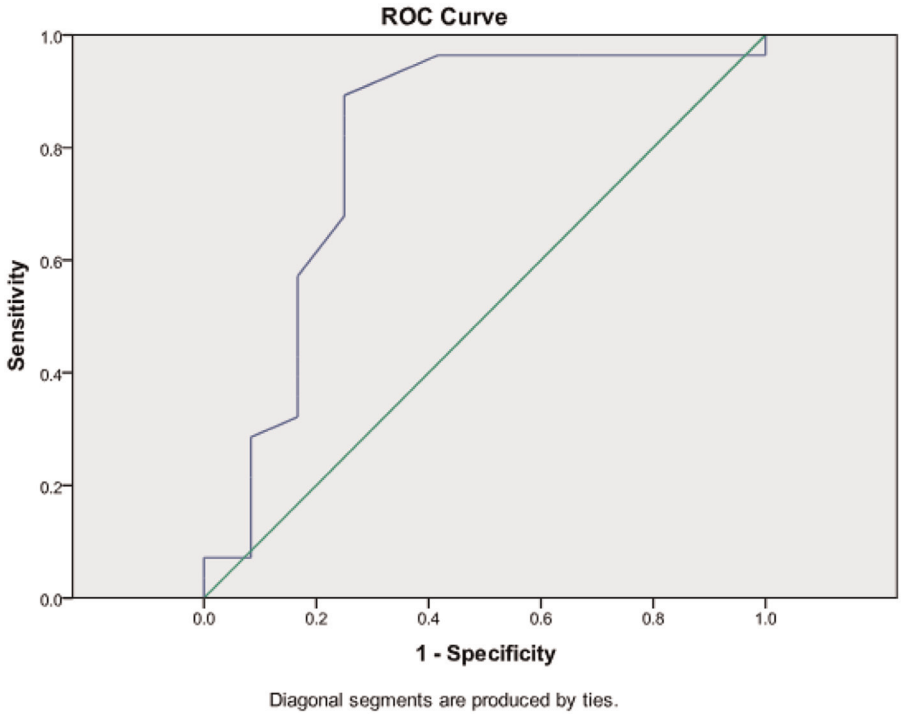
All data are expressed as mean±SD. CRP, C-reactive protein; EOS, early-onset sepsis; LOS, late-onset sepsis; sTREM-1, soluble triggering receptor expressed on myeloid cells-1. *Significant difference at *P* value less than 0.05.

Table 5 Spearman correlations of procalcitonin and soluble triggering receptor expressed on myeloid cells-1 with other parameters

Variables	Parameters	Pearson correlation	Significant (2 tailed)
Procalcitonin	sTREM-1	0.810*	0.001
	Platelets	–0.574*	0.000
	Total leukocytic count	0.644*	0.000
	CRP	0.547*	0.000
	HCT	–0.685*	0.000
	Hb	–0.654*	0.000
	Apgar at 1 min	–0.409*	0.000
	Apgar at 5 min	–0.757*	0.000
	Weight	–0.439*	0.000
Variable			
	Platelets	–0.611*	0.000
	Total leukocytic count	0.654*	0.000
	CRP	0.458*	0.000
sTREM-1	HCT	–0.715*	0.000
	Hb	0.663*	0.000
	Apgar at 1 min	–0.379*	0.001
	Apgar at 5 min	–0.773*	0.000
	Weight	–0.574*	0.000

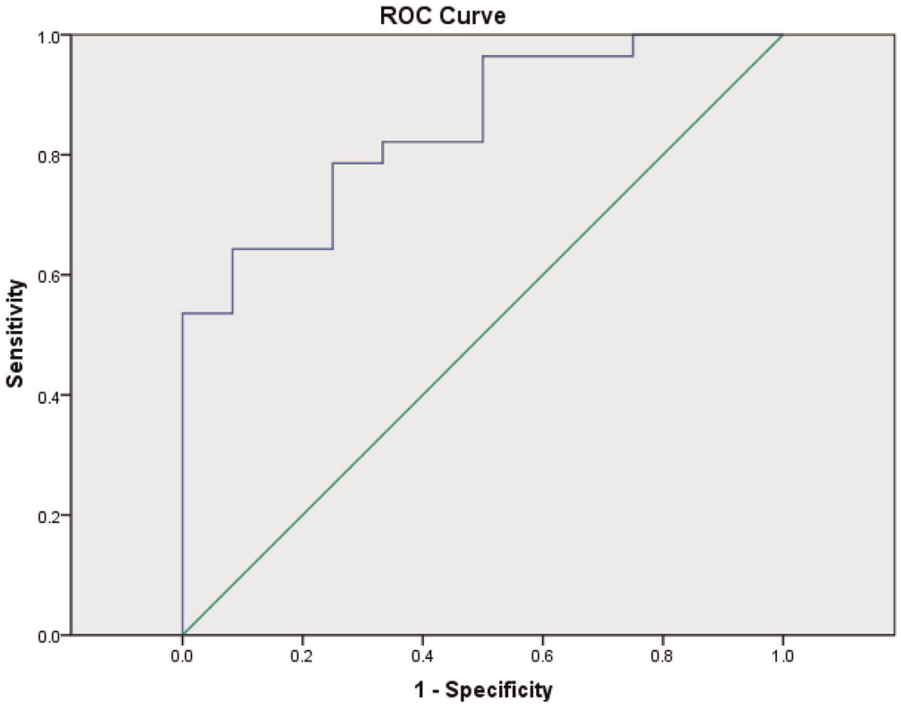
CRP, C-reactive protein; Hb, hemoglobin; HCT, hematocrit; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.
*Significant correlation at *P* value less than 0.01.

Figure 1



ROC curve analysis for sTREM-1. ROC, receiver operating characteristics; TREM-1, soluble triggering receptor expressed on myeloid cells-1.

Figure 2



ROC curve analysis for procalcitonin. ROC, receiver operating characteristic.

The correlations between both PCT and sTREM-1 and other parameters are depicted in Table 5. PCT shows highly significant positive correlations with sTREM-1, TLC, and CRP ($P<0.01$). On the contrary, it shows highly significant negative correlations with platelets count, Apgar score at 1 and 5 min and birth weight ($P<0.01$). sTREM-1 shows a highly significant positive correlation with TLC and CRP ($P<0.01$). Meanwhile, it shows a highly significant negative correlation with platelets, Apgar score at 1 and 5 min, and birth weight ($P<0.01$). ROC curve analysis for using sTREM-1 in the diagnosis of sepsis shows that the area under the curve is 0.845, with cutoff level equal to 164.7 ($P=0.001$), with sensitivity of 64.3% and specificity of 91.7% (Fig. 1). However, ROC curve for using PCT in detection of sepsis shows that the area under the curve is 0.801 (more close to one better diagnostic value), with cutoff level equal 3.4 ($P=0.003$), with sensitivity of 89.3% and specificity of 75% (Fig. 2).

Discussion

In this study, birth weight and gestational age showed a significant reduction in septic group than controls. A study done by Afonso and Blots [15] concluded that LOS affects a significant percentage of neonates in neonatal ICU. LOS affects near-term and full-term infants. Infants having smaller birth weight have greater incidence of both early and late onset of sepsis [16]. This may be related to the less maturity of the neonatal immune system and low level of IgG in both neonates with lower birth weight and smaller gestational age [17].

In the present study, septic neonates born by CS were higher than those born by vaginal mode, but this was statistically insignificant. The study by Thapa *et al.* [18] revealed that deliveries by CS are a predictor for infections in neonatal period. Fetal lacerations occur in ~0.1–3.1% of CS deliveries sepsis, and vaginal deliveries have a protective effect against sepsis compared with elective CS in all gestational ages.

Neonates in the concurrent study having neonatal sepsis showed significantly lower Apgar score at 1 and 5 min than controls. Neonates with low Apgar scores tend to have poor adaptation for extrauterine factors owing to the stress that occurred during labor, so they are more susceptible to neonatal infections [19].

In our research, male neonates were more significantly affected by neonatal sepsis than females. Males are more sensitive to adverse perinatal and postnatal events. They are more liable to be born premature and with low birth weight, leading to increasing the sepsis risk [20]. The factors regulating the synthesis of globulin are situated on X chromosome, so males are more prone to sepsis than females [21]. Androgens have suppressive effect on cell-mediated

immunity, but female sex hormones have protective effects [22].

Most neonates with sepsis in our study had no history of maternal premature rupture of membranes (PROM), and this could be explained by the fact that ~67.5% of our affected neonates were born by CS. PROM is associated with increasing the risk of infection and inflammation. It may cause loss of barriers to ascending infections from maternal vagina. Prolonged PROM could be an independent risk factor for neonatal sepsis [23].

There is a significant increase in maternal diabetes mellitus in cases than controls. Hyperglycemia may promote lipid peroxidation leading to free radical generation. The colostrum of diabetic mothers have lower IgA and IgG than nondiabetic ones [24].

Within the sepsis group, EOS was higher at 57.5% than LOS at 42.5%. This observation was consistent with a previous study done by Paul *et al* [17] and Noor *et al*. [25].

TLC is of little clinical use for neonatal sepsis detection because of wide range of variation. In neonatal sepsis, both leukopenia and leukocytosis were observed. Neonates with sepsis develop thrombocytopenia owing to disseminated intravascular coagulopathy and destroying effect of bacterial endotoxins on platelets [17]. In our research, TLC was significantly higher in septic neonates, but platelet count was statistically higher in controls than cases.

In this study, of 40 clinically diagnosed neonatal sepsis, blood culture was positive in 28 (70%) cases. According to Noor *et al.* [25] and Shaha *et al.* [26], positive blood culture result ranged from 8 to 73%. Positive blood culture result confirms the diagnosis of sepsis, but neonatal sepsis cannot be excluded on the basis of negative culture results. These variations could be affected by different factors, including antibiotics use before blood culture withdrawal [27].

In the present study, we found statistically higher CRP levels in septic neonates than healthy controls and in LOS neonates than EOS ones, but there was no significant difference between positive blood culture cases and negative blood culture cases. Similar results were detected by El Menza *et al.* [11] and Oncel [28].

The mean value of PCT in neonates with sepsis was statistically higher than nonseptic control group. Similar findings were recorded by Adib *et al.* [29]. Blood culture-positive cases showed statistically significant higher levels than cases with negative culture results. The study of Zahedpasha *et al.* [30] showed that PCT levels are remarkably high in neonates with proven sepsis (clinical symptoms and signs of sepsis and positive blood culture) and reduced dramatically after antibiotic therapy.

The mean sTREM-1 level was significantly higher in septic group than controls. These results come in line with a previous study by Zidan *et al.* [31] and Adly *et al.* [32] Moreover, Gibot [33] proved that there is a significant increase in sTREM-1 level and its membrane bound form during neonatal infection.

In our study, sTREM-1 level was significantly higher in septic neonates with positive blood culture result than with negative culture result, but there was no significant difference in its level between septic neonates with EOS and LOS. Zidan *et al.* [31] observed that there is no statistically significant difference in the levels of sTREM-1 between positive and negative blood culture neonates. However, El-Madbouly *et al.* [14] proved higher levels of sTREM-1 in EOS than LOS septic newborns as well as positive blood culture cases compared with negative blood culture cases.

There was a negative correlation in our study between sTREM-1 level and birth weight. Adly *et al.* [32] found that sTREM-1 levels negatively correlated with birth weight and gestational age, and this may be attributed to quantitative and qualitative impairment of immune response in less mature babies with small weights. Likely, in another study, there was a negative correlation with birth weight, but there was no significant correlation with gestational age [33].In the present study, there was a positive correlation between sTREM-1 and CRP and TLC. These results are in harmony with those of Adly *et al.* [32]. Meanwhile, a study by Özdemir *et al.* [34] revealed no correlation between sTREM-1 and CRP. On the contrary, a study done by El-Madbouly *et al.* [14] showed that there is a positive correlation between CRP and sTREM-1 levels in septic neonates. A significant positive correlation with TLC denotes strong association with the degree of inflammatory response. Meanwhile, there was a negative correlation with platelets and birth weight [33].

In our work, PCT showed a significant positive correlation with sTREM-1, CRP, and TLC. In contrast, it showed significant a negative correlation with birth weight.

In this study, sTREM-1 sensitivity was 64.3% and specificity was 91.7% (better specificity); however, PCT sensitivity was 89.3% and specificity was 75% (better sensitivity) for detection of neonatal sepsis. A study done by Su *et al.* [35] showed that sTREM-1 is more sensitive than white blood count count, CRP, and PCT values for early detection of sepsis and grading of its severity. Adib *et al.* [29] found that PCT sensitivity in the early diagnosis of neonatal sepsis was 75%, whereas its specificity was 80%. The accuracy of sTREM-1 and PCT has been previously recorded in pneumonia and pancreatitis, so rapid assessment of their levels could be utilized as a fundamental tool for rapid diagnosis of neonatal infection [31]. The significance of assessment of sTREM-1 and PCT levels is the detection of neonatal sepsis earlier and more rapid, as bacteriological cultures need much time and may give false-negative results.

Conclusion

In conclusion, serum sTREM-1 and PCT could be used as new biomarkers for rapid and early detection of neonatal septicemia, leading to prompt initiation of antibiotic therapy for achieving better outcomes. However, further research studies having larger sample size with serial measuring sTREM-1 and PCT levels are needed to establish their reliability in early diagnosis of septicemia in neonates.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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