

Diagnostic Utility of Cerebrospinal Fluid Procalcitonin in Neonatal Meningitis

Meghana N

Mysore medical college and research centre

Prathik Bandiya (✉ prathikbh@gmail.com)

Indira Gandhi Institute of Child Health <https://orcid.org/0000-0002-8212-2655>

Niranjan H S

Indira Gandhi Institute of Child Health

Naveen Benakappa

Indira Gandhi Institute of Child Health

Bhavana J

Indira Gandhi Institute of Child Health

Tapas Bandyopadhyay

Atal Bihari Vajpayee Institute of Medical Sciences & Dr Ram Manohar Lohia Hospital

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Abstract

We aimed to study the diagnostic utility of cerebrospinal fluid (CSF) procalcitonin in neonates with meningitis. All the neonates with sepsis who qualified for lumbar puncture were prospectively evaluated. The neonates were classified as Meningitis and No meningitis group based on predefined criteria. CSF procalcitonin was estimated in these neonates along with cytological and biochemical parameters. A total of 113 neonates were included in the study with 29 in meningitis group and 84 in no meningitis group. The median procalcitonin levels was higher in babies with meningitis as compared to those without meningitis [0.194 (0.034 - 0.534) in meningitis group vs 0.012 (0.012-0.012) ng/ml in no meningitis group, $p < 0.001$]. The area under curve (AUC) for CSF procalcitonin was 0.867 (0.77 -0.95) and at a cut off level of 0.120 ng/ml CSF procalcitonin had a sensitivity of 83%, specificity of 84% and positive and negative predictive likelihood ratios of 5.35 and 0.20 respectively for the diagnosis of meningitis.

Conclusion: CSF procalcitonin has a good diagnostic accuracy similar to other parameters in the diagnosis of neonatal meningitis and can be considered as an additional diagnostic marker particularly, when CSF culture is negative and cytochemical analysis is inconclusive.

Trial registration number and date: CTRI/2018/09/015720 ; 14/09/2018

Introduction

Neonatal meningitis is a potentially life threatening serious infection in neonates. The reported incidence of this condition is much higher at 0.8–6.1 per 1000 live births, with a mortality of 40–58% in developing countries.¹ The survivors of the disease are at risk of numerous adverse short-and long-term outcome.² Hence, early detection and appropriate antimicrobial treatment are cornerstone of management so as to reduce the complications associated with this condition.²

Although, culture of cerebrospinal fluid (CSF) is the gold standard for diagnosis but the yield is often low (15-30%) and in majority of the time the decision to treat meningitis is solely based upon the assessment of cellularity and biochemical parameters.³ Further, studies have shown significant overlap between normal and abnormal CSF values in neonates both in terms of cellularity as well as biochemical parameters with preterm neonates having higher cell, sugar and protein values in CSF as compared to older children and adults.² Moreover since the incidence of traumatic taps are higher, it may further affect the interpretation of CSF parameters as well in neonatal age group.⁴ Hence, neonatal meningitis is often over diagnosed in clinical setting which usually leads to unnecessary exposure of neonates to prolonged duration of antibiotics which in turn increases the risk of adverse effects due to exposure to drugs as well as it also increases the risk of antimicrobial resistance.^{5,6} Hence, there is an urgent need for a new inflammatory marker which can accurately diagnose neonatal meningitis in babies with neonatal sepsis and hence, in turn will reduce the rates of above said complications associated with the disease as well as its treatment. One of such marker is procalcitonin which is a precursor of calcitonin and is a reliable

marker of infection and the associated inflammation.² Several studies in neonatal sepsis on serum procalcitonin levels have found it be useful both for the diagnosis as well as prognosis.⁷ Although, studies in adult population have shown that CSF procalcitonin to be a reliable marker for diagnosis of meningitis.⁸ However, there is a dearth of literature regarding its role in the diagnosis of neonatal meningitis. Hence this study was planned to evaluate the role of CSF procalcitonin in diagnosis of neonatal meningitis.

Methods

This was a prospective observational study conducted between Jan 2018 to May 2019 in a level 3 tertiary care neonatal unit in South India. The study was approved by the institutional ethics committee, and informed consents were obtained from the parents before inclusion in the study. The study was registered in Clinical Trial registry of India (CTRI), with trial reg no of CTRI/2018/09/015720

Study population

Inclusion criteria

All neonates (\leq 28 days of age) with signs and symptoms suggestive of sepsis and who qualified for lumbar puncture as per the unit protocol were included in the study.⁹

Exclusion criteria

Neonates who received antibiotics for more than 3 days before obtaining lumbar puncture, sick neonates who are expected to survive for less than 24 hours, major congenital malformations, presence of deep-seated focus of infection other than meningitis e.g. abscess, septic arthritis etc and coagulopathy.

Clinical data

Detailed base line information were recorded including gestation age (i.e. preterm or term), age at presentation, type of sepsis (early [$<$ 3 days of onset of symptoms] or late [\geq 3 days of onset of symptoms]), clinical symptoms and signs.

Laboratory analysis

All the neonates included in the study underwent lumbar puncture under strict aseptic precautions. CSF was analysed immediately for cell count (total, polymorph and neutrophil count) along with sugar, protein, gram stain, culture and procalcitonin levels. Procalcitonin level estimation was done by ELISA method (Cloud clone corp, USA).

In the present study meningitis was defined as either positive CSF culture, or abnormal CSF analysis with or without clinical manifestation of central nervous system infection). Abnormal CSF analysis in term neonates was defined as either CSF WBC count $>8 / \text{mm}^3$ or glucose $<20 \text{ mg/dl}$ or protein $>150 \text{ mg/dl}$

and in preterm neonates as CSF WBC count $\geq 10 \text{ mm}^3$ or glucose $< 24 \text{ mg/dl}$ or protein $> 170 \text{ mg/dl}$ and no meningitis as if CSF WBC count $< 25 / \text{mm}^3$ and glucose $\geq 25 \text{ mg/dl}$ and protein $< 170 \text{ mg/dl}$. The enrolled neonates were followed up till discharge or death.¹⁰

Statistical analysis

Patient information was collected in a predesigned proforma. Statistical analysis was done using the SPSS statistical package (version 18.0). Data were expressed as mean \pm standard

deviation (SD) or median (IQR) for continuous variables and as percentages for categorical variables. Student's t test (unpaired) was used for analysis of continuous variables. Categorical variables were compared by chi-square test or Fisher's exact test as applicable. The results were considered significant at 5% level of significance ($P < 0.05$).

The receiver operating characteristic (ROC) curves were drawn, and the sensitivity, specificity, and areas under ROC curves (AUCs) were compared to evaluate the diagnostic performance of each indicator of neonatal meningitis,

Sample size estimation

Based on the previous study by Reshi et al¹¹ the sensitivity of procalcitonin to diagnose neonatal meningitis is 92%. Assuming 5% level of significance and 90% power and 10% absolute precision, the required sample size was 113 patients to estimate the diagnostic accuracy in meningitis.

Results

The flow of participants into the study is presented in Fig. 1. A total of 221 neonates were assessed for eligibility out of which 108 neonates were excluded for various reasons and 113 neonates were finally included in the study. On the basis of CSF analysis and culture results the neonates were classified into 2 groups: Meningitis group consisting of 29 neonates and No meningitis group consisting of 84 neonates (Fig 1). Table 1 shows the baseline characteristics of meningitis and no meningitis group. The baseline characteristics were comparable across both the groups. However, majority of the enrolled neonates had late onset sepsis [LOS n=105 (93%), EOS n= 8 (7%)]. Blood and CSF culture positivity rates among enrolled neonates were 19.4% and 5% respectively. Microbiological distribution shows infection with gram negative and gram positive pathogens to be 9.7% and 5.3 % of the enrolled cases respectively. Table 2 shows the CSF analysis as well as the concentration of CSF procalcitonin and CRP levels in neonates with or without meningitis. CSF analysis revealed significant elevation in the total cells count, neutrophil count and protein values in babies with meningitis. Further, there was also significant elevation in the levels of CSF CRP [3.4 (2.1-8.3) mg/l in meningitis group vs 3.1 (1.3-6.8)] mg/l in no meningitis group, $p=0.003$] and procalcitonin levels [0.194 (0.034 - 0.534) in meningitis group vs 0.012 (0.012-0.012) ng/ml in no meningitis group, $p < 0.001$] in babies with meningitis as compared to those without meningitis.

Table 3, fig. 2 and 3 shows the diagnostic accuracy of various CSF parameters in the diagnosis of neonatal meningitis. The area under curve (AUC) for different CSF parameters were 0.867 (0.77 -0.95) for procalcitonin, 0.55 (0.41 -0.68) for CSF CRP, 0.969 (0.939 - 0.999) for CSF protein, 0.756 (0.647 -0.865) for CSF sugar, 0.90 (0.82-0.98) for neutrophil count and 0.910 for total leukocyte count (0.85-0.97).

At a cut off value of 0.120 ng/ml CSF procalcitonin had a sensitivity of 83%, specificity of 84% and positive and negative predictive likelihood ratios of 5.35 and 0.20 respectively

Discussion

The present study has shown that CSF procalcitonin is a reliable biomarker in the diagnosis of neonatal meningitis with AUC of 0.867 (0.77 -0.95). Further, at cut- off limit of 0.120 ng/mL, it has an acceptable diagnostic accuracy for the diagnosis of neonatal meningitis (sensitivity 83%, specificity 84%, LR+ 5.35).

Serum procalcitonin levels at the cut-off limit of 2.0-2.5 ng/ml serves as a reliable biomarker for diagnosis of bacterial sepsis [sensitivity of 0.85, confidence interval (CI) (0.76; 0.90) and specificity of 0.54, CI (0.38; 0.70)] as well as deciding on the duration of antibiotic use in neonates.⁷ However, the role of CSF procalcitonin in the diagnosis of neonatal meningitis has not been evaluated rigorously in neonatal population. Studies in adult and pediatric age group population have shown it to be a reliable marker for the diagnosis of meningitis as well as its ability to differentiate between viral and bacterial etiologies of meningitis.^{12,13}

In the study by Reshi et al it was observed that median CSF PCT levels were significantly higher in neonates with meningitis in comparison to those without meningitis.¹¹ They hypothesized that PCT in CSF is likely derived from the plasma itself as blood–brain barrier gets disrupted due to infectious process. The median PCT values observed in their study were much higher than our study [median PCT in meningitis and non- meningitis group were 0.47 (0.38–0.88) and 0.26 (0.21–0.28) respectively] this could be explained by a higher blood and/or CSF culture positivity rate (56% vs 24%) as well as more robust definition of bacterial meningitis used in their study as compared to our study (either positive CSF and/or blood culture or positive gram staining). However, the values are in concordance with the study done by Rajial et al with cytochemistry proven meningitis.¹⁴ Further, we found that at a level of 0.12 ng/ml, CSF procalcitonin had a sensitivity of 83% and specificity of 84% with area under curve of 0.86 indicating good diagnostic value of this marker for diagnosis of meningitis. These cut off values are much lower as compared to previous studies. This can be explained by lower CSF culture positivity rate in our study as compared to previous study. Other inflammatory markers have also been evaluated in neonatal meningitis and one of the important marker being CSF CRP. In our study CSF CRP had a lower diagnostic ability as compared to CSF procalcitonin. At a value of 7 mg/dl it had a sensitivity of 42% and specificity of 82% with AUC of 0.55 indicating lower diagnostic efficiency and similar results have been observed in other studies which have evaluated this marker.¹⁵ We also observed CSF procalcitonin had a similar diagnostic efficiency as compared with CSF protein and neutrophil count and was in conjunction to the findings observed in other studies. (11)

Our study is not without limitations. We measured only a single value of CSF procalcitonin and a repeat value after completion of antibiotic treatment would have improved its diagnostic ability. Additional measurement of serum levels of procalcitonin would have helped to identify the severity of sepsis and its relation with CSF values.

In conclusion, CSF procalcitonin has a good diagnostic accuracy similar to other parameters in the diagnosis of neonatal meningitis and can be considered as an additional diagnostic marker particularly, when CSF culture is negative and cytochemical analysis is inconclusive.

Abbreviations

AF: Anterior fontanelle

AUC: Area under curve

CSF: Cerebrospinal fluid

EOS: Early onset sepsis

IQR: Interquartile range

LOS: Late onset sepsis

PCT: Procalcitonin

ROC: Receiver operating characteristic

SD: Standard deviation

TLC: total leukocyte count

CRP: C reactive Protein

Declarations

Authors' contributions

Prathik Bandiya: Concept and design; Drafting the manuscript

Meghana N: Data acquisition

Niranjan H S : Concept and design; Final approval of Manuscript

Naveen Benakappa: Final approval of the version

Bhavana J: Drafting the manuscript

This material is original research, has not been previously published and has not been submitted for publication elsewhere.

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Tables

Table 1: Comparison of baseline characteristics of meningitis and no meningitis group

Parameter	Meningitis group (n= 29)	No meningitis group (n= 84)	OR (95%CI)	P value
Male*	18 (66)	57 (68)	0.775 (0.322-1.867)	0.569
Mean age of presentation (in days)#	7 (2.5-17.5)	10 (3.2-22)	MD -2.33 (-0.651-1.845)	0.271
Preterm*	10 (34.5)	21 (25)	1.579 (0.635-3.927)	0.324
Blood culture positivity*	5 (19)	17 (20)	0.821 (0.273-2.469)	0.725
EONS*	3 (10)	5 (6)	1.823 (0.407-8.157)	0.427
Fever*	1 (3.5)	0 (0)		
Lethargy*	6(21)	33 (39)	0.403 (0.148-1.095)	0.069
Seizures*	11 (38)	2 (2)	0.492 (0.102-2.363)	0.367
Bulging AF*	2 (7)	1 (1)	6.148 (0.536-70.497)	0.099

* Data presented as n (%), #Data presented as median (IQR), EONS: early onset neonatal sepsis, AF: Anterior fontanelle

Table 2: CSF analysis and concentration of CSF procalcitonin and CRP levels in neonates with or without meningitis.

	Meningitis group	No meningitis group	P value
CSF Procalcitonin (ng/ml) [#]	0.194 (0.034 - 0.534)	0.012 (0.012-0.012)	< 0.001
Serum CRP (mg/l) [#]	7.5 (3-37.2)	6.8 (3-45.9)	0.637
CSF CRP (mg/l) [#]	3.4 (2.1-8.3)	3.1 (1.3-6.8)	0.003
Protein (mg/l) [#]	187.0 (152.2-236)	76.5 (53.7-99.7)	< 0.001
Sugar (mg/dl) [#]	33 (15.5-46.6)	47.9 (40.4-58.7)	0.505
Total Cells (per mm ³) [#]	21 (10-77)	2 (0-4.7)	<0.001
Neutrophils (per mm ³) [#]	11.0 (7-23)	0 (0)	<0.001

Data presented as median (IQR), CSF: cerebrospinal fluid, CRP: C reactive protein

Table 3: Diagnostic accuracy of various CSF parameters in the diagnosis of neonatal meningitis

	PCT (ng/ml)	Sugar (mg/dl)	Protein (mg/dl)	CSF CRP(mg/l)	TLC (per mm ³)	Neutrophil (per mm ³)
Accuracy	0.867 (0.777 -0.956)	0.756 (0.647 -0.865)	0.969 (0.939 - 0.999)	0.551 (0.416 -0.685)	0.913 (0.854- 0.972)	0.904 (0.822- 0.986)
Specificity	0.120	42.90	124.15	7.15	8	2
Sensitivity	83%	72%	93%	42%	86%	86%
Accuracy	84%	67%	92%	82%	87%	84%
ROC AUC	5.35	2.25	11.17	1.53	5.79	5.57
ROC AUC	0.20	0.41	0.08	0.86	0.12	0.16
Accuracy	84%	69%	92%	67%	86%	85%

PCT: procalcitonin, CSF: cerebrospinal fluid, CRP: C reactive protein, TLC: total leukocyte count

Figures

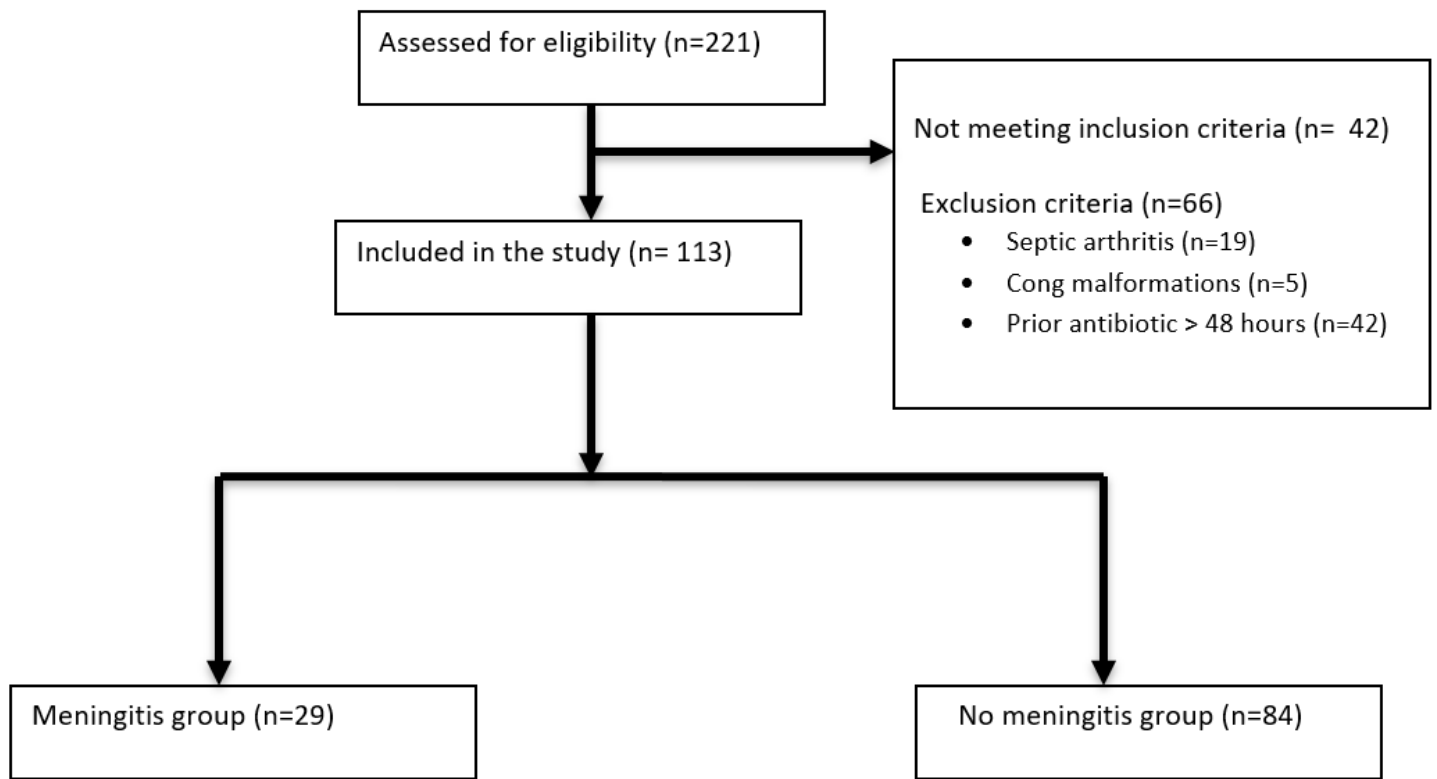


Figure 1

Flow diagram of study participants

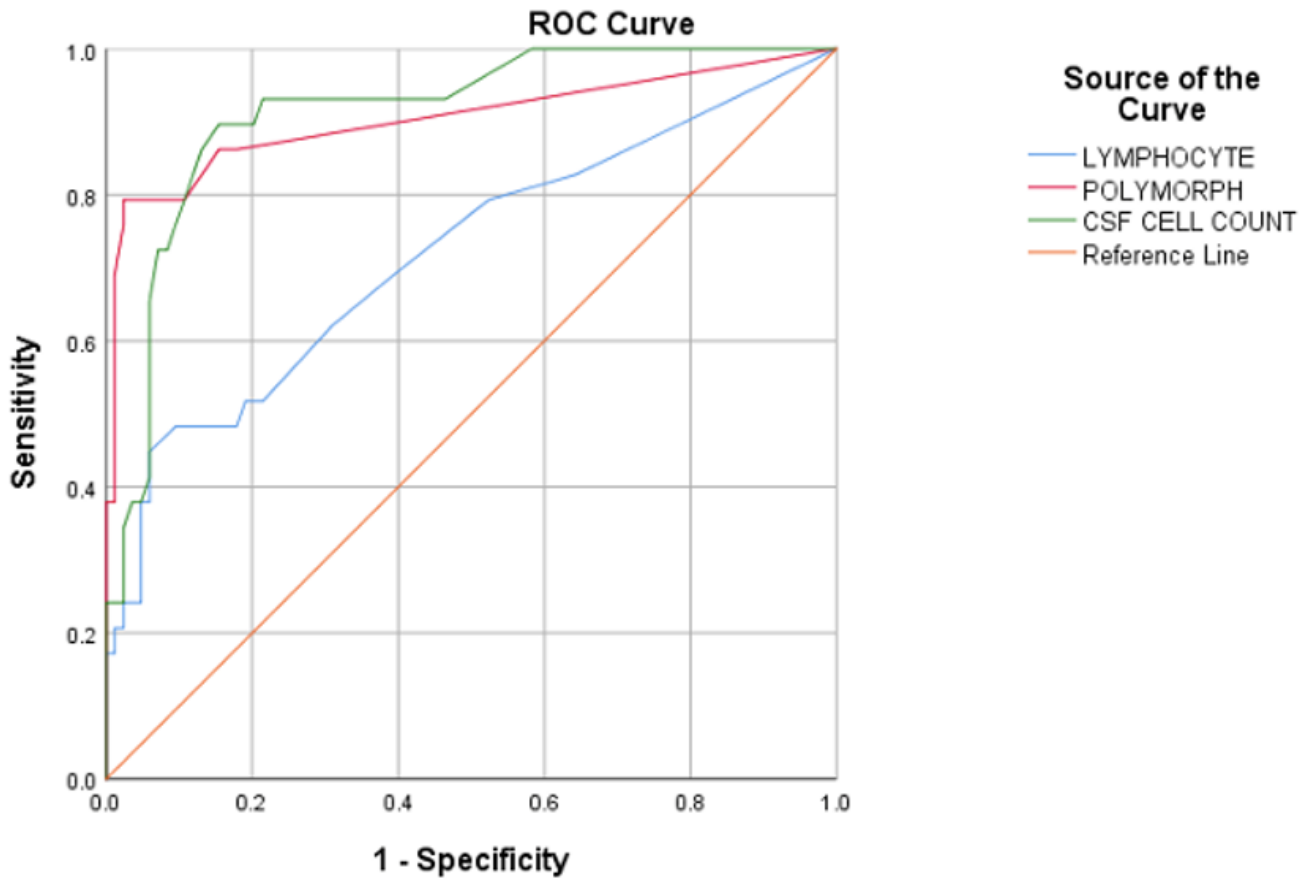


Figure 2

ROC curve of CSF cell count, polymorph and lymphocyte count. (ROC: Receiver operating characteristic)

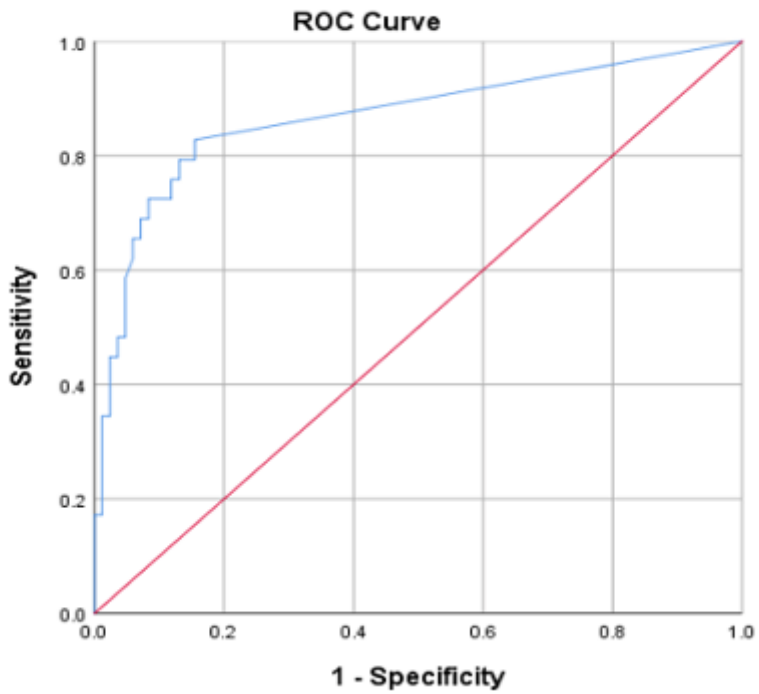


Figure 3

ROC curve of procalcitonin. (ROC: Receiver operating characteristic)