

EFFECTIVENESS OF SERUM PROCALCITONIN, C-REACTIVE PROTEIN AND HEMATOLOGICAL PARAMETERS VERSUS BLOOD CULTURE IN EARLY DIAGNOSIS OF NEONATAL SEPSIS IN NEONATAL INTENSIVE CARE UNIT

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Abstract

Background: Neonatal septicemia is a clinical condition portrayed by foundational indications of contamination in the primary month of life. It is the main source of neonatal horribleness and mortality in our country. The identification of microorganisms in a patient's blood is very important to know the nature of microorganisms and antibiotic susceptibility; to treat promptly.

Methods: The following tests were done on suspected cases of neonatal sepsis reported to our Institute. Blood culture to isolate the organism. Estimation of Serum Procalcitonin Level, Estimation of serial levels C-Reactive Protein, Estimation of Haematological parameters which included Haemoglobin, Total WBC counts, and Platelet counts. All the samples were collected at the time of admission before starting the antibiotics. 2nd sample of C Reactive Protein for estimation of serial levels is collected after 72 hours of antibiotic administration.

Results: Among the n=36 suspected cases of neonatal sepsis, n=23 were blood culture-positive cases. Among the culture-positive cases, 92.31% showed elevated CRP levels whereas 7.69% showed normal CRP levels. Out of n=13 blood culture-negative cases, 47.82% showed elevated CRP levels and 52.17% showed normal CRP levels. The sensitivity of CRP was 50% and the specificity was noted to be the highest which was 92.30%. The positive and negative predictive values were found to be 92.30% and 52.17% respectively. the sensitivity and specificity of PCT were 69.56% and 53.84% when compared to that of CRP 50% and 92.30%. PCT showed the highest sensitivity and CRP showed the highest specificity in the present study.

Conclusion: The most sensitive test was procalcitonin, which was followed by C-Reactive Protein and Total WBC counts. Out of all the indicators, C-Reactive Protein had the highest positive predictive value and specificity. Compared to other markers, procalcitonin was found to be a sensitive tool for early diagnosis, while C-Reactive Protein and Total WBC count were found to be less effective at predicting the outcome of sepsis.

Keyword: Procalcitonin, C-Reactive Protein, Neonatal sepsis, Blood culture

INTRODUCTION

Disease side effects and signs, either regardless of bacteremia, inside the principal month of life are demonstrative of a clinical sickness called neonatal sepsis.[1] Septicemia, pneumonia, meningitis, joint inflammation, osteomyelitis, and urinary parcel contaminations are among the numerous foundational diseases that fall under this class.

Neonatal sepsis is divided into two categories depending on the Onset namely:

a) Sepsis of early onset, which strikes within the first 72 hours of life. Infants with early-onset sepsis typically present with pneumonia and respiratory distress. The wellspring of contamination here by and large is Maternal genital parcel.

b) Late-Onset Sepsis, which begins 72 hours after death. Children normally present with Septicemia, Meningitis and Pneumonia. The wellspring of contamination here is either medical clinic procured or local area gained. Untimely and Low

Birth Weight children are more inclined for late beginning sepsis.

Neonatal septicemia keeps on being one of the main sources of neonatal dismalness and mortality around the world.^[2] and it has declined to 19 per 1000 live births in 2016 to 2019.^[3] When neonatal sepsis is confirmed by culture, the hospital mortality rate for new-born with the condition climbs to 50%. They require more resources, spend more time in the hospital, and have a higher chance of developing severe neurodevelopmental problems later in life.^[4] Early diagnosis of newborn sepsis is crucial for reducing morbidity and death.

Neonatal sepsis is diagnosed based on the clinical signs and symptoms as well as the results of laboratory tests. The most effective way to diagnose newborn sepsis is by blood culture, which is successful in 25–54% of cases.^[5] In spite of the fact that blood societies are the highest quality level for diagnosing infant sepsis and empowering designated antimicrobial treatment, their discoveries can require as long as 48 hours to be accounted for and they can likewise come out bad in numerous septic shock cases. In developing nations like India, where culture and sensitivity facilities are limited and rapid diagnostic tests like PCR and bacterial rapid antigen tests are prohibitively expensive, the majority of newborns are diagnosed with neonatal sepsis; beginning doubt/determination of neonatal sepsis depends on clinical highlights which are the majority of the times vague, which brings about the inception of exact antimicrobial treatment. Consequently, utilizing quick analytic techniques including lab markers could be helpful for the conclusion of neonatal sepsis. Thus, depending on early indicative markers is vital. C-Reactive Protein and Procalcitonin have the highest sensitivity and specificity rates among the early diagnostic markers that are available.^[6] C-responsive protein (CRP) has been generally utilized as a symptomatic instrument for the ID of contamination. Although several studies demonstrated that a high level of CRP is a sensitive and traditional marker of inflammation, it is unable to distinguish between other infections and bacterial infections. An acute-phase protein known as procalcitonin (PCT) has recently gained attention as a measurable laboratory indicator of sepsis. PCT increments during bacterial, contagious, and parasitic contaminations. Confined bacterial contaminations, extreme viral diseases and fiery responses of non-irresistible beginning don't or just somewhat change the PCT level rather than CRP. While certain examinations announced that PCT is more solid than CRP for the conclusion of neonatal sepsis, others tracked down no benefit of PCT over CRP. This study was carried out because a comparison of these two potential markers yields contradictory information.

MATERIAL AND METHODS

The neonatal intensive care unit of our teaching hospital served as the setting for this cross-sectional study. The research using human subjects received institutional ethical approval. Composed informed assent was taken from the mother.

Sample size calculation: Sample size is calculated by using the formula:

$$= \frac{(Z\alpha)^2 \times \text{sensitivity} \times (100 - \text{sensitivity})}{(\text{Relative error})^2 \times \text{prevalence}}$$

Where, $Z\alpha$ (constant) = 1.96; S = Sensitivity = 81; d = relative error = 5%; p = prevalence = 7%

$$= (2)^2 \times 81 \times (100 - 81) / (5)^2 \times 7$$

$$= 4 \times 81 \times 19 / 25 \times 7$$

$$= 35.17 \cong 36.$$

Inclusion criteria: Neonates who are going to be started on antibiotics with the following criteria.

Neonatal risk factors like Low birth weight, Preterm, Rashness, or Twins giving any of the accompanying clinical signs: Spasms, Respiratory rate >60 breaths/min, Extreme chest indrawing, Nasal erupting, Snorting, Protruding/discouraged fontanelle, Lazy or oblivious (not stimulated by negligible improvement), Decreased developments, Not ready to take care of (not ready to support suck), Not appending to the bosom, No nursing by any means, Crepitations, Cyanosis and Diminished advanced fine top off time, Any of the signs recorded above suggests high doubt of serious bacterial contamination. Or then again with Maternal gamble factors: Premature membrane rupture, prolonged labor (more than 24 hours for both the first and second stages), membrane rupture (more than 24 hours), maternal fever with evidence of bacterial infection within two weeks of delivery, urine that smells bad or is stained with meconium, urinary tract infection, cesarean section, one unclean or more than three sterile vaginal examinations, twin pregnancy, in vitro conception, pre-eclampsia, gestational diabetes mellitus, and insitu cervical stitch.

Exclusion criteria:

- Neonates who had Birth asphyxia, Aspiration syndrome.
- Neonates with Congenital anomalies.
- Referred cases already treated with antibiotics.

Sepsis workup included:

- Blood culture to isolate the organism.
- Estimation of Serum Procalcitonin Level.
- Estimation of serial levels of C-Reactive Protein levels- 1st sample is collected at the time of admission before starting the antibiotics. 2nd sample is collected after 72 hours of antibiotic administration.
- Estimation of Haematological parameters: which included Haemoglobin, Total WBC counts, and Platelet counts.

During the study period, over n=36 neonates with suspected sepsis meeting the inclusion criteria were admitted to the NICU and were recruited into this study.

Blood sample collection: Blood from arterial and venous samples, finger or heel prick-capillary sampling, and newly inserted umbilical catheters can be used. The site of blood collection may also interfere with the blood culture result. Blood collected from the umbilical artery catheter may allow contamination. while blood collected from an umbilicus vein catheter may be unreliable.^[7, 8] A total of 3 ml of blood was collected 1 ml for blood culture to isolate the organism, and the remaining 2 ml for estimation of serum Procalcitonin, 1st CRP level, and Haematological parameters. 0.5 ml of blood was collected after 72 hours of antibiotic administration for estimation of the 2nd CRP level.

Blood culture: All the blood samples were directly inoculated onto BD BACTEC Peds Plus/F culture vials and processed for microbial growth in radiometric culture BACTEC 460 TB, which works on the principle of detecting C₁₄ labelled palmitic acid and measures quantitatively the radioactivity on a scale ranging from 0-999 as a growth indicator. Positive cases were exposed to subculture and complete bacteriological ID was finished with the Microscan walkaway framework which is a robotized test framework fit for microbial distinguishing proof, anti-toxin weakness testing, epidemiological moving, and revealing.

Measurable examination: Every one of the accessible pieces of information was transferred to a MS Succeed calculation sheet and examined by SPSS adaptation 20.0 in Windows design.

RESULTS

In the present study, blood culture was positive in 63.89% (n=23) of suspected sepsis cases and was negative in 36.1%(n=1) cases. Hence the blood culture positivity rate in the present study was 63.89%. In this study out of n=36 cases, n=23 were culture-proven sepsis cases, and Neonates who fulfilled the inclusion criteria belonged to the early onset sepsis group. Hence there were no cases of late-onset sepsis. Out of the sepsis cases, n=15 were males and n=8 were females and the male-to-female ratio was 2:1approximately. Out of n=36 suspected sepsis, 2.78% (n=1) was term neonate and 97.22% (n=35) were preterm neonates. Out of n=23 culture-proven sepsis, 4.35% (n=01) was a term, and neonate95.65%(n=22) were preterm (Table 1).

Table 1: Distribution of sepsis according to Gestational age

Gestational age	Suspected sepsis cases (n=36)	Culture-proven sepsis cases (n=23)
Preterm (<37 weeks)	35 (97.22%)	22(95.65%)
Term (>37 weeks)	10 (2.78%)	1(4.35%)
Total	36 (100%)	23 (100%)

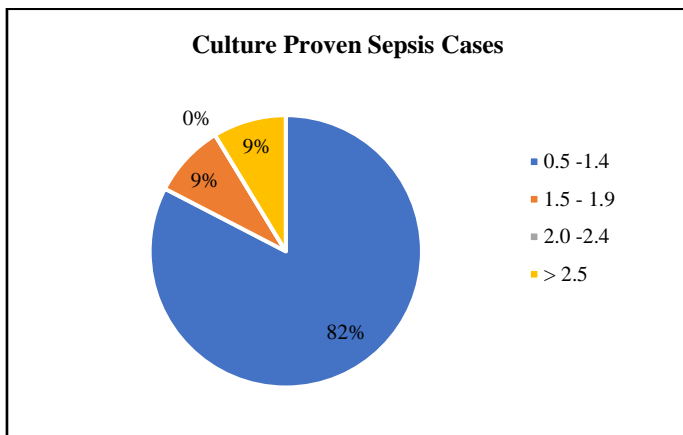


Figure 1: Distribution of Sepsis according to Birth Weight in Kgs

Out of n=36 children with thought sepsis 91.65%(n=33) youngsters were of low birth weight (<2500 gm) and 8.35% (n=03) youngsters were of ordinary birth weight. Out of n=23 youngsters with culture-demonstrated sepsis 91.3%(n=21) children were of low birth weight and 8.70%(n=02) children were of typical birth weight. Culture positivity was highest among low-birth-weight neonates (91.3%, n=21) among the culture-proven sepsis cases. Just 8.70%(n=02) youngsters with ordinary birth weight showed culture energy (Figure 1). In this review, there was no tremendous contrast in the pace of culture seclusion among the children in light of the equality of the mother.

Out of the n=23 culture-proven sepsis cases, the highest number of cases had premature/prolonged rupture of membrane at 21.74% as the maternal risk factor followed by pre-eclampsia at 17.40%, prolonged labor at 4.35%, and maternal pyrexia 4.35%.52.16% of the cases accounted for other risk factors like Twin pregnancy, Invitro conception, Gestational diabetes mellitus,Cervical stitch insitu, home delivery, Cervical cerclage, etc (Table 2).

Table 2: Sepsis Concerning Maternal Risk Factors

Maternal Risk factors	Suspected sepsis cases(n=36)	Culture-proven sepsis cases(n=23)
Premature/prolonged rupture of membranes	7 (19.44%)	21.74%(n=05)
Prolonged labor	2 (5.56%)	1 (4.35%)
Preeclampsia	7 (19.44%)	4 (17.40%)
Maternal pyrexia	2(5.56%)	1 (4.35%)
Maternal UTI	0 (00%)	0 (00%)
Unclean vaginal examinations	0 (00%)	0 (00%)
Others	18 (50%)	12 (52.16%)

Among the n=36 suspected cases of neonatal sepsis, 16.67% (n=06) were delivered by normal vaginal delivery (NVD), and 83.33% (n=30) by lower-section cesarean section (LSCS). Among the n=23 culture-positive cases of neonatal sepsis,17.39% (n=04) were delivered by NVD, and 82.60%(n=19) by lower-section cesarean section. About four-fold rise in culture positivity was noticed among the neonates delivered by LSCS (82.60%) in comparison to those delivered by NVD (17.39%). Out of n=23 culture-proven sepsis cases, 30.44%(n=07) were bacterial isolates and 69.44%(n=16) were fungal isolates. Among the bacterial isolates *Klebsiella pneumoniae* constituted majority of isolates n=2(8.09%) followed by *Pseudomonas aeruginosa* n=1(4.35%), *Escherichia coli* n=1(4.35%), *Enterobacter cloacae* n=1(4.35%), *Staphylococcus epidermidis* n=1(4.35%), *Staphylococcus hemolyticus* n=1(4.35%).

In the present study, out of n=23 blood culture-positive cases, 92.31% showed elevated CRP levels whereas 7.69% showed normal CRP levels. Out of 13 blood culture-negative cases 47.82% showed elevated CRP levels and 52.17% showed normal CRP levels. In the present study, there was a persistent increase in the C-Reactive Protein (CRP) seen in all the suspected and culture-proven cases of neonatal sepsis which was done after 72 hours of antibiotic administration. Out of 23 blood culture-positive cases, elevated Procalcitonin (PCT) levels were seen in 72.72% of cases and showed normal levels in 27.27%.out of 13 blood culture-negative cases, 50% showed elevated PCT levels and 50% showed normal PCT levels.

In the n=23 culture-proven sepsis cases, elevated CRP levels were noted in 52.17% of cases whereas elevated PCT levels were noted in 73.91% of cases. Among all the markers of sepsis in the present study, procalcitonin showed the highest sensitivity of 69.56% and C-Reactive Protein showed the highest specificity of 92.30%.CRP showed the highest positive predictive value of 92.30% followed by PCT which is 72.72%. The total WBC counts showed the least negative predictive value of 36.84% (Table 3).

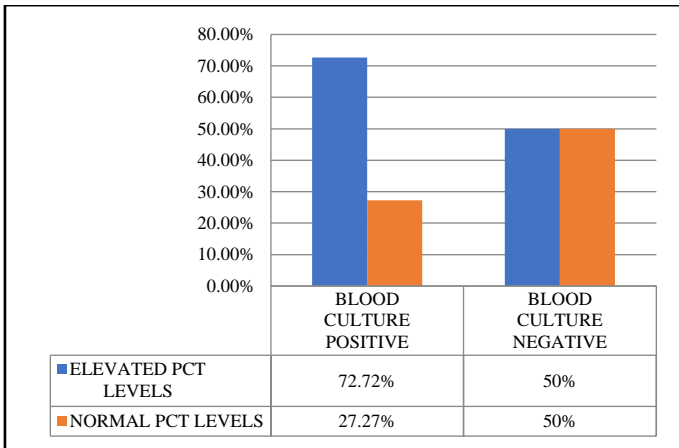


Figure 2: Sensitivity, Specificity, PPV, and NPV of Procalcitonin

Table 3: Comparison of all markers of Sepsis

Markers	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Hemoglobin percentage	26.06%	84.16%	75.00%	39.28%
Total WBC counts	61.11%	53.84%	64.70%	36.84%
Platelet counts	47.05%	69.25%	66.66%	37.5%
1 st CRP	50.00%	92.30%	92.30%	52.17%
Procalcitonin	69.56%	53.84%	72.72%	50.00%

DISCUSSION

The present study was undertaken to effectively diagnose neonatal sepsis at the earliest and evaluate the same and to assess the efficacy of limited rapid diagnostic tests in comparison with the blood culture. Most of the similar studies in this field reported male predominance Sharma et al.,^[9] reported 62.08%, and Basavaraj Pet al.,^[10] reported 65.5%. The rate of culture positivity in this study was 63.88%. Other similar studies have reported positivity rates ranging from 41.6% to 65.2% as depicted in Table 4.

Table 4: Blood Culture Positivity Rate in Neonatal Sepsis by Various Other Studies

Author	Place of Study	Percentage Positivity
Swati Karad et al., ^[11]	Maharashtra	36.11%
Gosalia et al., ^[12]	Rajkot	62.00%
Jadhav et al., ^[13]	Pune	65.20%
Mahmoud M. Zahran ^[14]	Saudi Arabia	36.11%
Present study	Belagavi	63.88%

The positivity rate of the present study is comparable with that of Jadhav et al.,^[13] 65.2% and Gosalia et al.,^[12] 62%. The variety in the pace of detachment in various examinations can be credited to the way that the occurrence of neonatal sepsis shifts from one spot to another affected by different variables like gestational age, birth weight of the youngster, maternal nourishment, perinatal consideration, medical services offices, and so on. The site of blood collection may also interfere with the blood culture result.^[7, 8] To avoid these negative factors blood for culture was obtained from a peripheral vein in all the neonates with the help of trained staff in the present study. The incidence of early-onset sepsis was significantly high i.e., 100%

in both suspected and culture-proven sepsis cases as compared to late-onset sepsis in our study in contrast with the studies done by Rasul C.H et al.,^[15] and Movahedian AH et al.,^[16] The period of early onset ranged from 0 to 72 hours in the present study. The lower occurrence of LOS in this study can't be made sense of by a solitary variable. Different changes that have happened lately notwithstanding the expanded mindfulness in the counteraction of sepsis like better hand cleanliness works on, keeping up with standard conventions in taking care of intravenous catheters, and more limited span of obtrusive ventilation because of the utilization of surfactants might have added to the diminished frequency of LOS. In the current review, culture demonstrated sepsis was more normal among preterm and low birth weight children. Comparable discoveries were accounted for by Vergnano et al.,^[17] A extremely impressive relationship of culture-demonstrated sepsis (94%) with rashness was accounted for by Rathod SD et al.,^[18] LBW and preterm youngsters are at high gamble of creating sepsis in contrast with a term child as they are helpless against sepsis because of their natural weakness to contamination attributable to the juvenile safe system, in expansion to different variables like lacking IgG levels delayed emergency clinic stay, total parenteral nourishment and openness to obtrusive methods. Out of the n=23 culture-proven sepsis cases, the highest number of cases had premature/prolonged rupture of membrane at 21.74% as the maternal risk factor followed by preeclampsia at 17.40%, prolonged labor at 4.35% and maternal pyrexia at 4.35%. Similar findings were observed in studies done by Chacko et al.,^[19] In the present study, Candida species constituted the majority of isolates (69.56%) followed by bacterial isolates (30.44%). Studies conducted by Mane et al.,^[20] also showed candida species as a majority of isolates in suspected neonatal sepsis. Environmental sources, such as ventilation systems and storage shelves have been implicated.^[21]

In the present study, CoNS constituted 8.70% of the total isolates. The CoNS that were isolated are *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*. Neonatal sepsis may present with nonspecific subtle symptoms and signs, which may intrigue even the most astute clinician. Definite diagnosis of neonatal septicemia depends on positive blood culture which takes around 48-72 hours. Various hematological parameters have been utilized to screen for sepsis, with doubtful sensitivity and specificity. In the present study, limited parameters were evaluated in assisting the diagnosis of neonatal septicemia. These included PCT levels, CRP levels, Haemoglobin percentage, Total WBC counts, and Platelet counts. Blood culture was considered a gold standard. C-Receptive Protein goes about as a scrounger causing the opsonization of microscopic organisms and initiation of the supplement framework in this way working with phagocytosis during a provocative reaction. CRP examine, the most dissected boundary for a really long time has a higher probability of anticipating sepsis than most different boundaries. CRP had a sensitivity of 50% and a specificity of 92.30% that were found to be the highest in this study. The positive and negative prescient qualities were viewed as 92.30 % and 52.17 % individually.

Table 5: Correlation of Responsiveness, Particularity, Positive Prescient Worth, and Negative Prescient Worth done by various examinations:

Author	Place of study	Sensitivity	Specificity	PPV	NPV
Amposah et al.,[22]	Ghana	50.00%	72.20%	37.50%	83.10%
Mohammed et al.,[23]	Saudi Arabia	70.00%	60.00%	28.00%	80.00%
Hakeem Abdel Mohsen et al.,[24]	Mangalore, Karnataka	50.00%	52.90%	33.33%	100.0%
Suchitalingam et al.,[1]	Tamil Nadu, India	55.60%	89.50%	58.80%	88.60%
Present study	Belagavi, Karnataka	50.00%	92.30%	92.30%	52.17%

The distinctions in these examinations might be because of the variety concerning the planning of CRP test after the clinical beginning of contamination notwithstanding the way that this large number of review estimated CRP quantitatively with various limits. A sound clinical judgment joined with a quantitative CRP examine could give an objective premise to treatment choices in the administration of neonatal sepsis. Such a system could presumably diminish pointless antimicrobial treatment and the ensuing rise of safe types of the creatures. Siddaiah et al., [25] examinations the job of CRP in concluding the span of anti-toxin treatment in neonatal sepsis and reasoned that babies with thought sepsis having raised CRP levels required a more extended length of anti-microbial treatment of over 7 days. Sequential CRP levels are helpful in the symptomatic assessment of children with thought contamination. Two CRP levels <1 mg/dL got 24 hours separated, 8 to 48 hours after show, demonstrate that bacterial contamination is impossible. At the initial evaluation, the sensitivity of a normal CRP is insufficient to justify discontinuing antibiotic therapy. In this study, there was a persistent increase in the CRP seen in all of the suspected and culture-proven cases of neonatal sepsis that was done after 72 hours of antibiotic administration. This was because elevated CRP levels have a low positive predictive value, especially for early-onset infections that have been culture-proven.[26] This can be because of different iatrogenic causes like IV Catheters, Endotracheal tubes [27]. Among the n=36 youngsters of thought sepsis, PCT was raised in 24 children while CRP was raised in 13. Out of 23 culture-demonstrated sepsis raised serum PCT was found in 17 cases while raised CRP was seen in 12 cases. In our review, the responsiveness and explicitness of PCT were 69.56% and 53.84% when contrasted with that of CRP half and 92.30%. PCT showed the most noteworthy awareness and CRP showed the most elevated particularity in the current review. Comparable discoveries were accounted for by Sucilathangam G et al., [25] As indicated by a review that was done by Polling form DE et al., [26] likewise revealed a higher responsiveness of PCT and high explicitness for CRP in identifying sepsis in connection with CRP. [28] Despite the way that PCT can't be depended upon as the sole marker of sepsis, it is a fundamental part of the sepsis workup and, because of its high awareness and lower levels, rejects sepsis. An enormous part of the examinations including those of Rathod et al., [18] and Abdalla et al., [29] underscored the scientific occupation of PCT in diagnosing neonatal sepsis rather than CRP and contemplated that PCT was more fragile stood out from CRP which compares with our survey. During the initial 48 hours of contamination, CRP's responsiveness is nullified due to a sluggish ascent. It has been discovered that elevated CRP fixations in conditions other

than sepsis, such as PROM and meconium desire, also influence its explicitness. The hemoglobin rate was found to have the least responsiveness of all the sepsis markers examined, in spite of having a high particularity when contrasted with blood culture in this review. All out WBC counts showed the second-most elevated awareness and the most un-Negative Prescient Worth contrasted with any remaining markers of sepsis. When compared to other markers, it was discovered that thrombocytopenia and the percentage of hemoglobin were not specific indicators. PCT had the greatest sensitivity, followed by CRP and total WBC counts. CRP showed the most elevated explicitness and positive prescient worth among any remaining markers. Thus, Procalcitonin can be utilized as a touchy device in diagnosing sepsis. Because it is specific for bacterial and fungal sepsis, it can be used to distinguish between viral and bacterial infections. Additionally, it prevents the accidental use of antibiotics and aids in the early diagnosis of sepsis on the day of admission, thereby reducing the spread of drug-resistant strains. Despite its numerous benefits, Procalcitonin cannot be used solely as a marker, despite its crucial role in sepsis. A mix of WBC counts, C-Reactive Protein, and Procalcitonin levels is suggested as it shows an expansion in its responsiveness and explicitness in early finding of Neonatal sepsis.

CONCLUSION

In the current review, we found the gamble factors normally connected with neonatal sepsis were viewed as Prematurity, Low Birth Weight, LSCS, and untimely/drawn outbreak of layers. Compared to Late Onset Sepsis, Early Onset Sepsis was more common. Procalcitonin showed the most noteworthy responsiveness followed by Absolute WBC counts and C-Receptive Protein. C-Receptive Protein showed the most elevated particularity and positive prescient worth among any remaining markers. When compared to other markers, Procalcitonin was found to be a sensitive tool for early diagnosis, whereas C-Reactive Protein and Total WBC count were found to be more accurate for predicting the outcome of sepsis.

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