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Serum Ferritin as A Diagnostic and Prognostic Marker of Neonatal Sepsis

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Abstract:
Background*:Sepsis contributes to 17-20% of neonatal deaths.Biomarkers are needed for early diagnosis of sepsis, monitoring response to treatment and predicting outcome.Serum ferritin is one such potential biomarker. This study was planned to evaluate serum ferritin as a diagnostic and prognostic marker of neonatal sepsis.*
Materials and Methods*: After obtaining written informed consent of parent/guardians, neonates admitted in intensive care units were enrolled and divided into three groups:Group I had 20 neonates without sepsis,Group II had 40 septic neonates without Multiple Organ Dysfunction Syndrome (MODS),GroupIII had 17 septic neonates with MODS.The criteria of sepsis and MODS were adopted from International Pediatric Sepsis Consensus conference. Serum ferritin levels were estimated in all these neonates.Comparison of serum ferritin between groups was done by Kruskal-Wallis test. Receiver operating characteristics (ROC) analysis was used to identify cut-offs of serum ferritin for identifying sepsis and predicting poor outcome.*
Results*: The median (Inter-Quartile Range) of serum ferritin in group I, II and III were94.5ng/ml (78.0-104.5); 294.5 ng/ml(156.5-355.0) and 1110.0ng/ml(877.5-1413.2) respectively. The difference of ferritin levels between these groups were statistically significant(p<0.0001). One neonate of group II and four neonates of group III died. ROC curve analysis showed that serum ferritin >116ng/ml predicts the presence of sepsis (94.9% sensitivity; 100%specificity; area under ROC curve 0.95) and serum ferritin>1366 ng/mL predicted mortality (80% sensitivity; 100%specificity; area under ROC curve 0.93).*
Conclusion:*Serum ferritin can be used as a diagnostic and prognostic marker of neonatal sepsis.*
Key Words*: Ferritin,neonatalsepsis,MODS,SIRS*

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I. Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection. The prevalence of neonatal sepsis is estimated to be 2824 cases per 1,00,000 live births worldwide[1]. Sepsis contributes to 17%-20% of neonatal deaths[1]. Various studies have shown that the most important measure in reducingmortality from sepsis is early identification of the condition and prompt initiation of therapy[2,3,4,5].Prognostic scores and biomarkers are commonly used in intensive care units to direct resources, to suggest a more rigorous monitoring or to predict a risk of early deterioration. Variousinflammatory markers like ferritin, C Reactive protein, procalcitonin have attracted attention for theiruse as prognostic markers in neonatal sepsis patients[6,7,8].

Ferritin is an iron storage protein.In inflammatory conditions there is a great production of ferritin which leads to a decrease in serum iron, believed to minimize the availability of iron to microorganisms[9]. For this reason, ferritin in critically ill patients may be elevated, and it is associated with severity in some diseases[10].This study was planned to evaluate serum ferritin as a diagnostic and prognostic marker of neonatal sepsis.

II. Material And Methods

After obtaining institutional ethical clearance, this prospective analytical cross-sectional study was carried out collaboratively by Department of Biochemistry and Department of Pediatrics of S.S.G. Hospital and Medical College Baroda from September to October 2021.Total of 77 neonates admitted in neonatal intensive care units of S.S.G. Hospital were enrolled in this study after obtaining written informed consent of the parents or guardians.

Study Design: Prospective open label observational cross-sectional study
Study Location: This was a tertiary care teaching hospital-based study done in Department of Biochemistry and Department of Pediatrics of S.S.G. Hospital and Medical College Baroda,Vadodara,Gujarat,India.
Study Duration: September to October 2021
Sample size: 77 patients.
Sample size calculation: By applying following formula
$n= Z^2PQ/E^2$.

Here P=Prevalence of neonatal sepsis
Q=1-P
E=Error

Taking P= 2.84 at 95% confidence interval, Q= 90, E=5%We get minimum sample size to be42.

Subjects & selection method: The study population was drawn from neonates admitted in neonatal intensive care units of S.S.G. Hospital.After obtaining written informed consent of the parents or guardians, neonates with clinical suspicion of sepsis fulfilling our inclusion criteria were enrolled in this study.These neonates were divided into three groups based on definitions of sepsis and Multiple Organ Dysfunction Syndrome (MODS)adopted from International Pediatric Sepsis Consensus conference[11].

Group I had 20 neonates without sepsis

Group II had 40 septic neonates without MODS

Group III had 17 septic neonates with MODS

Inclusion criteria:

1. Age less than 30 days

2. A neonate with any of the following symptoms:

i) Core temperature of more than 38.5°Cor less than 36°C
ii)Tachycardia, defined as a mean heart rate more than 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli.
iii)Mean respiratory rate more than 2 SD above normal for age or neonate on mechanical ventilation.
iv) Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or more than 10% immature neutrophils.
iv)A suspected or proven infection (by positive culture, tissue stain, or polymerase chain reaction test).Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpureal rash).

Exclusion criteria:
1. Conditions with iron overload whether primary, e.g., hereditary hemochromatosis or secondary, e.g., transfusion overload, porphyria cutanea tarda.
2. Ineffective erythropoiesis (in sideroblastic anemia or thalassemia)
3. Hematological malignancy.

Procedure methodology

After written informed consent from the parents or guardians,77 neonates with clinical suspicion of sepsis were enrolled in this study.These neonates were screened for sepsis according to the criteria of sepsis and Multiple Organ Dysfunction Syndrome (MODS)defined by International Pediatric Sepsis Consensus conference[11].

A neonate having at least two of the four SIRS(systemic inflammatory response syndrome) criteria plus evidence of infection would be defined to have sepsis. SIRS criteria were i) Core temperature of more than 38.5°C or less than 36° C, ii)Tachycardia, defined as a mean heart rate more than 2 SD above normal for age in

the absence of external stimulus, chronic drugs, or painful stimuli, iii)Mean respiratory rate more than 2 SD above normal for age or neonate on mechanical ventilation, iv) Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or more than 10% immature neutrophils.

A neonate having Multiple organ dysfunctionsyndrome(MODS) was defined as a neonate having sepsis plus cardiovascular organ dysfunction OR a neonate having sepsis plus acute respiratory distress syndrome (ARDS) OR a neonate having two or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic).

These neonates were then divided into three groups: Group I had 20 neonates without sepsis; Group II had 40 septic neonates without MODS and Group III had 17 septic neonates with MODS. In all these patients, serum ferritin levels were estimated along with blood culture. Serum ferritin level was estimated by latex immunoturbidimetric[12]method on fully automated biochemistry analyzer, Mindray BS-430.All assays were carried out by the same team of laboratory technicians using the same method, throughout the study period.

Statistical analysis

All statistical calculations were done using software MEDCAL. Shapiro-Wilk test was applied to find whether data on ferritin levels was parametric or non-parametric.Serum ferritin levels were found to be not normally distributed within the groups. Comparison of serum ferritin between the groups was done by Kruskal Wallis test. Thep level< 0.05 was considered as the cutoff value for significance.Receiver operating characteristics (ROC) analysis was used to identify cut-offs of serum ferritin level for determining the presence of sepsis and predicting poor outcome.

III. Result

77 neonates were enrolled in this study which included 38 males and 39 females. Mean age of these neonates was 2.1± 1.8 days.Neonates were divided into three groups after applying criteria of International Pediatric Sepsis Consensus conference. The number of neonates in each group is shown in Table 1.

Table 1: Shows number of neonates in the three groups

I. Neonates without sepsis	20 neonates
II. Septic neonates without MODS	40 neonates
III.Septic neonates with MODS	17 neonates

The blood culture reports were positive in all cases of Group II(septic neonates without MODS)& Group III(septic neonates with MODS).Culture positivity rate of 74% was seen.Culture was positive in 31 out of 38 males(81.57%) and 26 out of 39 females(66.66%). The commonly isolated organisms in decreasing order of frequency were Staphylococcus(38.96%),Klebsiella(15.58%),E.coli(5.19%),Acetinobacter(3.80%),Candida(1.29%), Psuedomonas(1.29%).

Figure 1: Shows culture positivity rate in male neonates

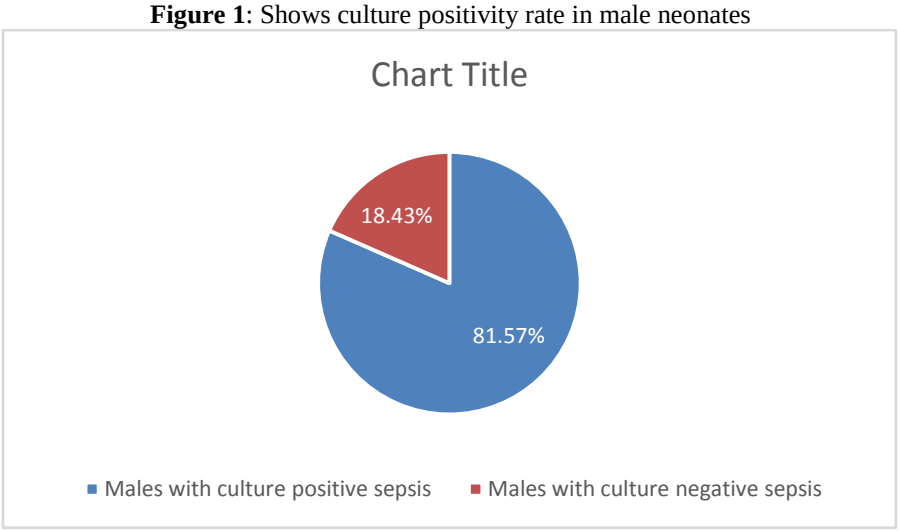
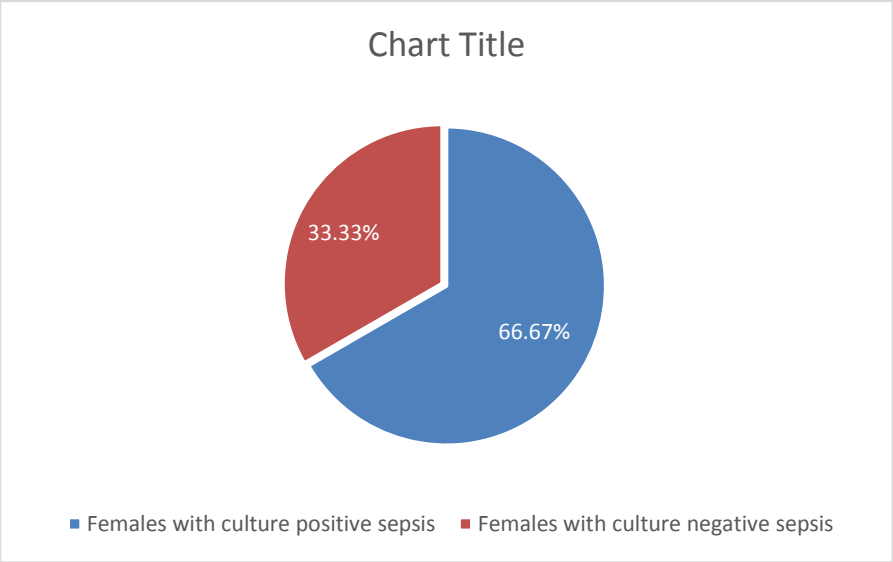


Figure 2: Shows culture positivity rate in female neonates



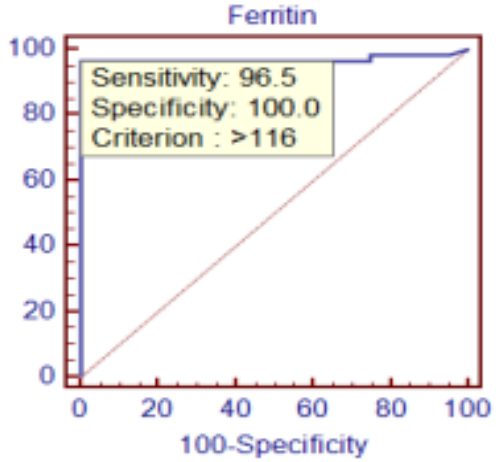
Ferritin levels were not normally distributed in these groups, so median (Inter-Quartile range) were calculated for all the three groups as shown in Table 2.

Table 2 : Showsmedian (Inter-Quartile range) of serum ferritin levels in the three groups. Reference range of serum ferritin in neonates is 25 to 200 ng/ml.

Groups	Median(ng/ml)	Interquartile range(ng/ml)
I. Neonates without sepsis	94.5	78.0-104.5
II.Septic neonates without MODS	294.5	156.5-355.0
III.Septic neonates with MODS	1110.0	877.5-1413.2

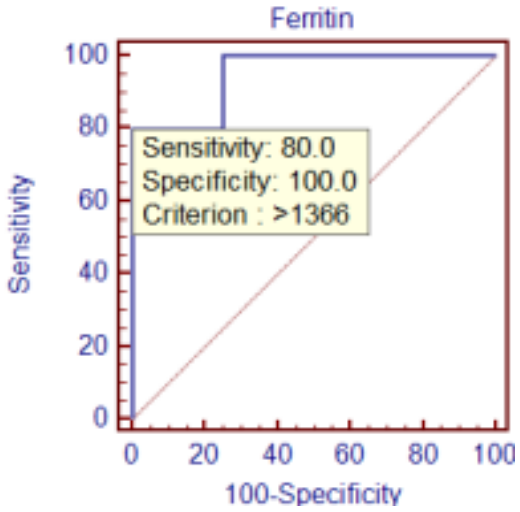
Applying Kruskal Wallis test, we found a statistically significant difference in serum ferritin levels between the three groups. (H=58.32, p<0.0001, df=2). ROC curve analysis showed that serum ferritin >116ng/ml predicted the presence of neonatal sepsis (94.9% sensitivity; 100%specifcity; area under ROC curve 0.95) as shown in Figure 3.

Figure 3: Shows ROC curve analysis for predicting the presence of neonatal sepsis by serum ferritin levels



During the study period total of five neonates died. Mortality in group II was 1 out of 40 neonates (2.5%) and mortality group III was 4 out of 17neonates (23%).ROC curve analysis showed that serum ferritin >1366 ng/mL predicted mortality (80% sensitivity; 100%specifcity;area under ROC curve 0.93) in neonatal sepsis patients as shown in Figure 4.

Figure 4: Shows ROC curve analysis for predicting mortality by serum ferritin levels in neonatal sepsis



IV. Discussion

In the present study, 77 neonates suspected of having sepsis were investigated. A culture positivity rate of 74% was observed. The study of Arora et al[13] obtained a culture positive rate of 46.8% and Roy et al[14] observed a culture positive rate of 47.5%. Out of 77 cases in our study, 49.35% were males and 50.65% were females. S.P.Khatua et al[15] reported that culture positivity is more common in males ranging from 59-82%. The male infants with positive culture in our study constituted 81.57% as compared to positive culture in 66.67% females. Piyush Gupta et al[16] and Anitha Sharma et al[17] reported a male predominance of culture positivity to be 64.7% and 74% respectively.

In the present study Staphylococcus aureus(38.96%) and Klebsiella pneumoniae(15.58%) were the predominant organisms causing septicemia. Karthikeyan et al[18] reported that Staphylococcus aureus was the predominant pathogen followed by Klebsiella pneumoniae which correlates well with our present study.

Assessment of severity of sepsis at time of admission is important for effective patient management, prognostication, and optimum utilization of resources. Simple interventions such as early rapid fluid administration, early antibiotics therapy, oxygen supplementation, and early use of inotropes have shown to improve the outcome of neonatal sepsis[19]. Biomarkers commonly used for diagnosis and prognosis of neonatal sepsis include leukocyte count, C-reactive protein (CRP),procalcitonin and ferritin levels, but limited studies have been done which correlate serumferritin levels with severity of neonatal sepsis.

Various authors have reported association of high levels of ferritin with severity of sepsis and mortality. Arnab Nandy*et al.*[20] reportedserum ferritin >1994 ng/ml and Sarkar M et al[21] reported serum ferritin >2375 ng/ml as a predictor of mortality. Garcia et al.[6] found that level > 500 ng/mL was associated with 58% mortality.In our study the highest values of serum ferritin occurred in the MODS stage of neonatal sepsis and a cut-off value of serum ferritin >1366 ng/ml was identified to predict mortality(80% sensitivity; 100%specifcity; area under ROC curve 0.93).Our study is in agreement with previous studies that high ferritin levels are associated with poor outcome.

Limitations of present study was that it was a single-centered study. Multicentric large sample studies are recommended.

V. Conclusion

In neonates, high mortality is seen in sepsis with MODS and serum ferritin can be used as a diagnostic and prognostic marker for neonatal sepsis.

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