

Estimation of serum amyloid A protein in neonatal sepsis: a prospective study

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Abstract

Background: The diagnosis of neonatal sepsis continues to remain a challenge owing to nonspecific early clinical signs and the nonavailability of a reliable biomarker. The result of blood culture, gold standard test for diagnosis, is available only after 72 h of sampling. Other tests include C-reactive protein (CRP), tumor necrosis factor- α , procalcitonin, serum amyloid A (SAA), and other acute-phase reactants having contradictory outcomes.

Objective: To determine the levels of SAA protein in neonatal sepsis, to correlate SAA levels with CRP, and to evaluate the role of SAA as a marker of neonatal sepsis.

Materials and Methods: This prospective cohort study was done in the neonatal intensive care unit, including 90 neonates ≥ 28 weeks gestational age with clinical signs and symptoms of sepsis. Serum sample was collected at the onset of clinical signs and symptoms of sepsis before the start of antibiotic therapy. CRP was estimated by immunoturbidimetric method, and SAA was estimated by ELISA method.

Result: On the basis of blood culture report, the study subjects were grouped into culture-positive ($n = 40$) and culture-negative ($n = 50$) groups. Mean SAA values were significantly higher in culture-positive group ($47.43 \pm 23.39 \mu\text{g/mL}$) when compared with the culture-negative group ($p < 0.001$). Statistically significant positive correlation was seen between SAA and CRP values ($r = 0.775$, $p < 0.00001$). Using a cut-off of $\geq 10 \mu\text{g/mL}$, SAA showed a sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 82%, 81%, 95%, respectively, when compared with CRP, which gave values of 92.5%, 10%, 45.12%, and 62.5%, respectively.

Conclusion: The results of this study support the use of SAA in the diagnosis of neonatal sepsis.

KEY WORDS: Neonatal sepsis, serum amyloid A protein, serum C-reactive protein, neonates

Introduction

Neonatal sepsis is a systemic infection of neonates during 0–28 days after birth.^[1] The diagnosis of neonatal sepsis is a major challenge, because the clinical signs are subtle, vague, and nonspecific, and there is no single ideal reliable marker

available for the diagnosis. Antimicrobial therapy is often started on clinical suspicion of infection, thus increasing the risk of adverse effects of drugs and the development of drug resistance.^[2,3]

Conventional laboratory tests used for the diagnosis of sepsis are white blood count, absolute neutrophil count, immature/total neutrophil ratio, and C-reactive protein (CRP) estimation.^[3,4] However, these parameters have low sensitivity and are nonspecific.^[3,4] Although blood culture is the gold standard, it has certain drawbacks such as low sensitivity, high incidence of false-negative results, and prolonged time period before reporting.^[3,4]

During severe bacterial infection, CRP rises as part of an early innate immune response. Although an acute-phase reactant, studies have shown that CRP cannot reliably differentiate between systemic inflammatory response and sepsis.^[2,3]

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Therefore, the accurate and prompt diagnosis of neonatal sepsis continues to pose a major diagnostic challenge, making it imperative to find dependable and timely diagnostic biomarkers to enable efficient diagnosis and management of neonatal sepsis.

Serum amyloid A (SAA) are polymorphic apolipoproteins, mainly produced by the liver, and have been proposed as a new sensitive marker of bacterial infection.^[4,5] But, some studies have found conflicting results.^[2,6] The purpose of this study, therefore, was to evaluate the role of SAA in the diagnosis of neonatal sepsis and to correlate SAA levels with serum CRP in neonatal sepsis.

Materials and Methods

Study Design

This prospective cohort study was carried out at the neonatal intensive care unit in our hospital from January 2014 to January 2015. The study group comprised 90 neonates of gestational age ≥ 28 weeks with clinical signs and symptoms of neonatal sepsis. Ethical committee clearance was taken from the institution.

Method of Collection of Data

Inclusion Criteria

Inclusion criteria for the neonates were preterm birth (37.70°C), lethargy and poor cry, poor perfusion (capillary refill time > 2 s), respiratory distress (respiratory rate $> 60/\text{min}$), hypoglycemia (< 40 mg/dL) or hyperglycemia (> 125 mg/dL), vomiting, diarrhea, and abdominal distension.^[1] All the above mentioned conditions are clinical signs and symptoms of sepsis.^[1]

The maternal criteria were intrapartum fever, foul smelling, and/or meconium-stained liquor amnii, prolonged rupture of membrane (> 24 h), and more than three vaginal examinations during labor. Presence of more than or equal to two risk factors were investigated with sepsis screen.^[1]

Exclusion Criteria

The neonates with traumatic tissue injury, inborn errors of metabolism, congenital anomalies, history of perinatal and postnatal asphyxia, and neonates who were on antibiotics or those who developed the signs of sepsis within 72 h of discontinuation of antibiotics were excluded from the study.^[1]

Sample Collection

At the onset of clinical signs and symptoms of sepsis before the start of antibiotic therapy, serum sample was drawn for sepsis screen panel. After written informed consent was taken from either of the parents/guardians, blood sample sent to the Biochemistry Laboratory for CRP was aliquoted, labeled, and stored at -20°C for assay of SAA. CRP estimation was done on the samples on Roche Cobas 6000 c501 fully automated analyzer by immunoturbidimetric method.^[7] The blood culture reports of neonates chosen to be a part of the study were

recorded. SAA assay was measured by Human SAA ELISA KIT quantitative sandwich enzyme immunoassay technique.^[8]

Statistical Analysis of Data

All the quantitative parameters were described in terms of descriptive statistics, mean, and standard deviation. Qualitative parameters were expressed as proportions. Comparison of quantitative variables between the study groups was done using Student's *t*-test for independent samples. The level of significance was taken as $p < 0.05$. The correlation between SAA and CRP was estimated through Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve was plotted using MedCalc statistical software version, 15.10.0 for Windows (MedCalc Software bvba; Ostend, Belgium).

Result

The baseline characteristics of the neonates are shown in Table 1. Male babies formed 57.7% of the study subjects and female babies formed 42.3%. The mean \pm SD of age in days at the time of presentation was 4.06 ± 6.9 . The mean gestational age (weeks) was 34.45 ± 3.61 . Prematurity (< 37 weeks gestational age) was seen in 63.3% of the subjects, and 36.7% were term (gestational age ≥ 37 weeks) babies. The mean \pm SD of birth weight (g) was $2,161 \pm 920$. The number of neonates who were of low birth weight (LBW) ($< 2,500$ g) in the study population were 51 (56.7%), whereas 39 (43.3%) of the neonates were of normal birth weight.

On the basis of blood culture report that was obtained 72 h after sampling, the neonates were divided into two groups. Group I: culture positive, consisting of 40 neonates and group II: culture negative, consisting of 50 neonates. A comparison between the two groups is shown in Table 2. No significant difference was found between the groups regarding age, gender, and mode of delivery. When birth weight, gestational age, duration of admission, and number of deaths in hospital were considered, there were significant differences between the two groups. In group I, 70% neonates were born preterm (gestational age < 37 weeks), and, in group II, 58% of neonates were born preterm ($p = 0.24$).

Table 3 and Figure 1 show a comparison of the CRP and SAA levels between the groups I and II. The mean \pm SD of serum CRP (mg/dL) and SAA ($\mu\text{g/mL}$) values were significantly higher in culture-positive group (13.0 ± 7.4 , 47.4 ± 23.4 , respectively) when compared with the culture-negative group (4.6 ± 3.13 , 7.2 ± 3.9 , respectively) ($p < 0.05$).

Figure 2 shows the microorganisms that were isolated on blood culture in the culture-positive group. The common organisms isolated were *Klebsiella* sp. in 35%, followed by *Staphylococcus aureus* in 16%, and *Acinetobacter* sp. in 12% of the culture-positive neonates.

No statistically significant differences were found in the mean \pm SD for SAA and CRP among the neonates where gram-positive, gram-negative, and fungal organisms were isolated [Table 4 and Figure 3].

There was a statistically significant strong positive correlation between SAA and CRP values of all the study subjects ($r = 0.775, p < 0.00001$) [Figure 4].

The laboratory investigations in the study groups were compared as shown in Table 5 and Figure 5-6. Among the culture-positive group, 92.5% of neonates showed serum CRP levels ≥ 1 mg/L, whereas 90% of neonates with blood culture negative showed serum CRP levels ≥ 1 mg/dL. Ninety-five percentage of the neonates with blood culture positive, and only 18% of the culture-negative neonates showed SAA levels ≥ 10 μ g/mL.

Tables 6 and 7 show a comparison of SAA values and CRP values in culture-positive and culture-negative groups. A statistically significant association was seen between the SAA results and the blood culture results ($p < 0.001$). There was no statistically significant association seen between the CRP results and the blood culture results ($p > 0.05$).

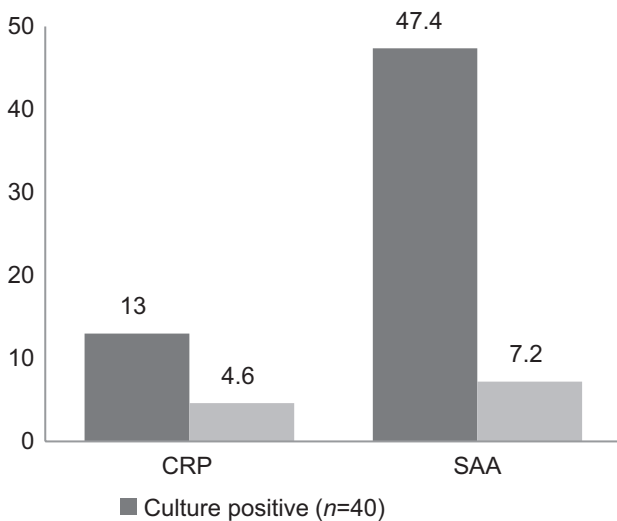


Figure 1: Mean values of serum amyloid A and CRP in the groups.

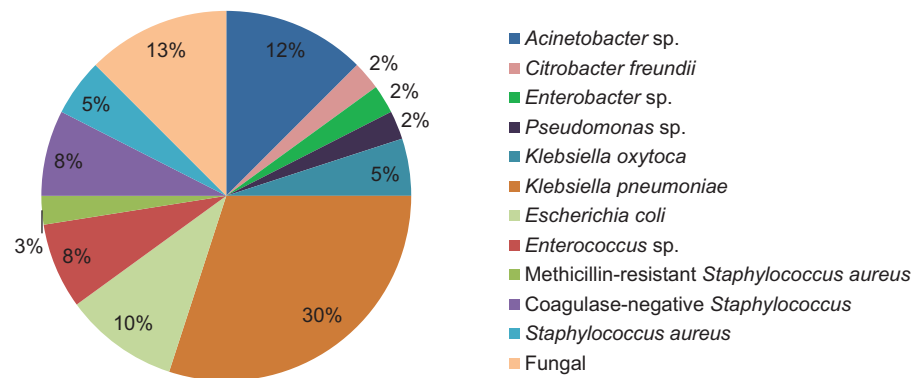


Figure 2: Causative microorganisms in the culture-positive group.

The study subjects were 90, but there were three neonates (one in culture-positive group and two in the culture-negative group), who took a voluntary discharge against medical advice. Among the 87 neonates that were followed up till discharge, 18 neonates (12 in culture-positive group and six in the culture-negative group), died. Among the nonsurvivors, CRP was elevated ≥ 1 mg/dL in 94.4% of the nonsurvivors, and SAA was above ≥ 10 μ g/mL in 72.2% of the nonsurvivors [Table 8]. Among the survivors, 53.62% showed normal SAA levels.

Sensitivity of SAA at a cutoff of ≥ 10 μ g/mL was 95%, and, for CRP, at cutoff of ≥ 1 mg/dL was 92.5%. At the same cutoffs, the specificity for SAA and CRP were 82% and 10%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) for SAA were 81% and 95.3%, while for CRP, PPV and NPV were only 45.1% and 62.5%, respectively [Table 9]. In the culture-positive group, the number of neonates with normal CRP and raised SAA was three, and there were two neonates with normal SAA and raised CRP in the same group.

In order to study the diagnostic accuracy of the laboratory tests for the diagnosis of neonatal sepsis, ROC curves were plotted [Figure 7]. The area under the ROC curve (AUC) was 0.9683 for SAA compared with serum CRP AUC that was 0.868, with a difference of 0.37 in AUC and the difference being statistically significant ($p = 0.039$). From the ROC curves, the optimal cutoff points obtained for SAA and serum CRP was ≥ 12 μ g/mL and ≥ 7.5 mg/dL, respectively in this study.

Discussion

Neonatal sepsis remains a major cause of neonatal morbidity and mortality in spite of advanced and improved management strategies.^[9]

Currently, the most reliable test for diagnosing sepsis is a blood culture, but that too could give erroneous results owing to contamination or inadequate sampling, and reports are available only 72 h later.^[3,4] Adjuvant laboratory tests in

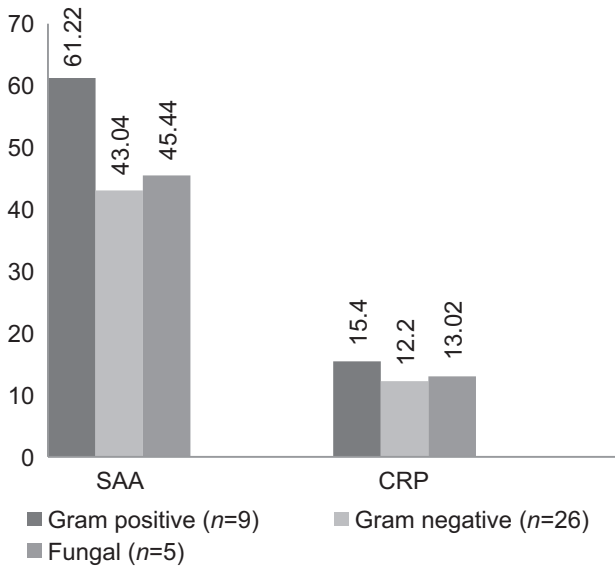


Figure 3: SAA and CRP distribution in the groups.

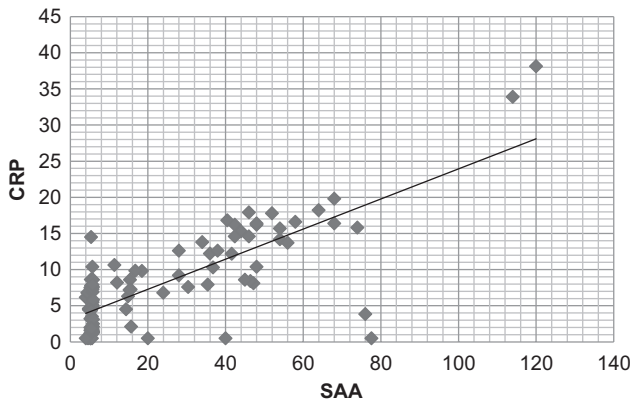


Figure 4: Correlation between SAA and CRP.

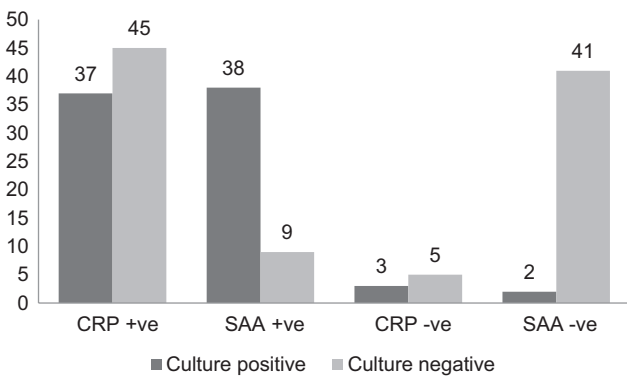


Figure 5: Comparison of SAA and CRP levels among culture-positive and culture-negative groups.

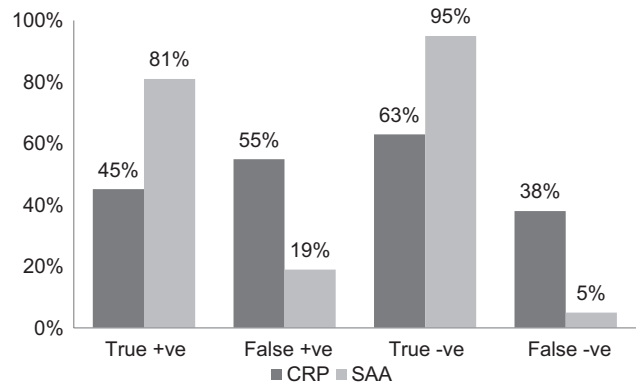


Figure 6: A comparison of serum CRP and SAA protein using blood culture as gold standard.

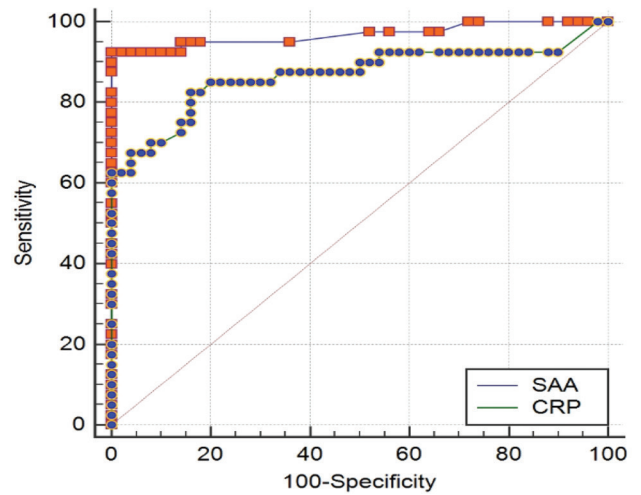


Figure 7: ROC curve for SAA and CRP in neonatal sepsis.

the screening and diagnosis of neonatal sepsis include total leukocyte count (TLC), band to total polymorphonuclear cells ratio, absolute neutrophil count, micro-erythrocyte sedimentation rate, platelet counts, and CRP levels—each one of them having varied performance characteristics and differing in terms of sensitivity and specificity.^[3,4]

In our study, male neonates formed a majority of the study subjects (57.7%) [Table 1]. Similar results were seen in the study done by Mohsen *et al.*^[4] and Sriram,^[10] in which male subjects were commonly affected compared with females with a ratio of 1.5:1. The male preponderance in neonatal septicemia may be linked to the X-linked immunoregulatory gene factor contributing to the host's susceptibility to infections in male subjects.^[11]

The mean gestational age (weeks) was 34.45 ± 3.61 [Table 1] and prematurity (<37 weeks gestational age) was seen in 63% of the subjects. Only 36% were term (gestational age ≥ 37 weeks) babies [Table 1]. This is in agreement with the study done by Labib *et al.*,^[12] which showed that majority

Table 1: Baseline characteristics of the study subjects

Characteristics	n = 90
Gender	
Male (n, %)	52 (57.7)
Female (n, %)	38 (42.3)
Mean ± SD of age (in days) at sampling	4.06 ± 6.9
Gestational age (weeks) (mean ± SD)	34.45 ± 3.61
No. of preterm (<37 weeks gestational age) (n, %)	57 (63.3)
No. of full term (37–42 weeks gestational age) (n, %)	33 (36.7)
Birth weight (g) (mean ± SD)	2161 ± 920
No. of normal birth weight (≥2,500 g) (n, %)	39 (43.3)
No. of low birth weight (<2,500 g) (n, %)	51 (56.7)

Table 2: Comparison of demographic data in group I and II

	Group I, culture positive, n = 40 (%)	Group II, culture negative, n = 50 (%)	p
Mean ± SD of age in days	3.3 ± 6.7	4.68 ± 7.10	0.35
Gender			
No. of male neonates (%)	20 (50)	32 (64)	0.181
No. of female neonates (%)	20 (50)	18 (36)	
Birth weight (g) (mean ± SD)	1800 ± 930	2450 ± 800	0.0005
No. of normal birth weight (≥2,500 g) neonates (%)	12 (30)	27 (54)	0.022
No. of low birth weight (<2,500 g) neonates (%)	28 (70)	23 (46)	
Gestational age in weeks (mean ± SD)	33.3 ± 4.09	35.38 ± 2.9	0.005
No. of preterm (<37 weeks gestational age) neonates (%)	28 (70)	29 (58)	0.24
No. of full term (37–42 weeks gestational age) neonates (%)	12 (30)	21 (42)	
Mode of delivery			
No. of normal delivery (%)	15 (37.5)	18 (36)	0.88
No. of lower segment cesarian section (%)	25 (62.5)	32 (64)	
Duration of admission in days (mean ± SD)	28.675 ± 19.47	14.72 ± 13.09	0.001
No. of deaths (%)	12 (30)	6 (12)	0.033

Table 3: CRP and SAA levels in study subjects

Quantitative Variables (mean ± SD)	Group I, culture positive, (n = 40)	Group II, culture negative, (n = 50)	p (Student's t-test)
CRP (mg/dL)	13.0 ± 7.4	4.6 ± 3.13	<0.05
SAA (µg/mL)	47.4 ± 23.4	7.2 ± 3.9	<0.05

Table 4: A comparison of CRP and SAA levels according to the microorganism isolated

Mean ± SD	Gram positive (n = 9)	Gram negative (n = 26)	Fungal (n = 5)	p
SAA(µg/mL)	61.22 ± 38.20	43.04 ± 16.61	45.44 ± 11.60	0.130
CRP (mg/dL)	15.40 ± 12.93	12.20 ± 5.13	13.02 ± 13.56	0.633

Table 5: Comparison of laboratory investigations among culture-positive and culture-negative groups

Parameters	Cutoffs	Study subjects, n = 90, n (%)	Culture positive, n = 40, n (%)	Culture negative, n = 50, n (%)
CRP in mg/dL	Above ≥1	82 (91.1)	37 (92.5)	45 (90)
	Normal <1	8 (8.9)	3 (7.5)	5 (10)
SAA in µg/mL	Above ≥10	47 (52.2)	38 (95)	9 (18)
	Normal <10	43 (47.8)	2 (5)	41 (82)

Table 6: Comparison of SAA values in culture-positive and culture-negative groups

SAA in µg/mL	Culture negative		Culture positive		χ^2	P
	n	%	n	%		
≥10	9	18	38	95		
<10	41	82	2	5	38.455	<0.001
Total	50	100	40	100		

Table 7: Comparison of CRP values in culture-positive and culture-negative groups

CRP in mg/dL	Culture negative		Culture positive		χ^2	P
	n	%	n	%		
≥1	45	90	37	93		
<1	5	10	3	8	2.679	0.102
Total	50	100	40	100		

Table 8: Comparison of laboratory investigations in survivors and nonsurvivors

Parameters	Cutoffs	Survivors, n = 69, n (%)	Nonsurvivors, n = 18, n (%)
CRP in mg/dL	Above ≥1	62 (89.8)	17 (94.4)
	Normal <1	7 (10.1)	1 (5.55)
SAA in µg/mL	Above ≥10	32 (46.37)	13 (72.2)
	Normal <10	37 (53.62)	5 (27.7)

Table 9: Sensitivity, specificity, positive predictive value, and negative predictive value of laboratory investigations in neonatal sepsis

Tests with cutoff values	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CRP ≥ 1 mg/dL	92.5	10	45.1	62.5
SAA ≥ 10 µg/mL	95	82	81	95.3

of sepsis occurred in LBW and premature infants (68.6% each). Immature humoral and cellular defense mechanisms and invasive life support systems make the premature neonate, particularly susceptible to overwhelming infection.^[13] It has been suggested that with decrease in gestational age of the neonates the incidence of septicemia increases,^[13] thereby making preterms more vulnerable to infection.

On the basis of blood culture report that was obtained 72 h after sampling, the neonates were divided into two groups. Group I: culture positive (40 neonates) and group II: culture negative (50 neonates). A comparison between the two groups is shown in Table 2. The birth weight (g) of neonates in culture-positive group was 1,800 ± 930 and in culture-negative group was 2,450 ± 800. Significant difference was seen in the birth weight between culture-positive (2,388 ± 670) and culture-negative group (2,728 ± 673) in the study done by Prashant *et al.*^[14] Few other studies do not show any significant difference between birth weights between the groups.^[4,12]

When a comparison of the laboratory investigations between the culture-positive group I and culture-negative

group II were done, it was found that there was a statistically significant difference between groups I and II in mean ± SD of serum CRP and SAA. In agreement to our results, Labib *et al.*^[12] in their study, found that the mean CRP level was significantly higher in patients (32.91 ± 25.42) than in control subjects (7.50 ± 2.12), and Mohsen *et al.*^[4] found a significant difference in SAA levels in both groups [40.16 ± 35.17 (µg/mL) and 6.45 ± 2.42 (µg/mL), respectively].

On comparing laboratory investigations according to the microorganism isolated on culture and application of analysis of variance (ANOVA) test, the mean ± SD of serum CRP and SAA were highest in gram-positive infections. This was contradictory to the study done by Mohsen *et al.*^[4] who found that the gram-negative sepsis produced a more pronounced elevation of SAA levels than what occurred with gram-positive sepsis.

There was a statistically significant strong positive correlation between SAA and CRP values of all the study subjects ($r = 0.775$, $p < 0.00001$) [Figure 4]. This was in agreement with Mohsen *et al.*^[4] ($r = 0.483$, $p < 0.01$). A higher proportion of the neonates with sepsis showed raised SAA levels

(95% vs. 18%) than those without sepsis, similar to as seen in the study done by Mohsen *et al.*^[4] Raised CRP levels were seen in those with sepsis (92.5%) and those without sepsis (90%). A statistically significant association was seen between the SAA results and the blood culture results ($p < 0.001$), while a comparison of CRP values in culture-positive and culture-negative groups did not show any statistically significant association ($p > 0.05$) [Tables 6 and 7].

Sensitivity for SAA at a cutoff of 10 $\mu\text{g/mL}$ was 95% and was 92.5% for CRP at a cutoff of $\geq 1 \text{ mg/dL}$. This implies that the ability of SAA to correctly provide a diagnosis of neonatal sepsis in a neonate with signs and symptoms of sepsis is better than serum CRP. There is a high probability of SAA being raised above the cutoff when neonatal sepsis is present. It is also very unlikely that neonates with SAA levels $< 10 \mu\text{g/mL}$, but with signs and symptoms of sepsis will have blood culture-positive neonatal sepsis. Franz *et al.*^[15] showed that there is generally a delay of up to 24 h between onset of symptoms of infection and a rise in serum CRP. Sensitivity of the test at presentation is only 40%, that is, 60% of subsequently proven sepsis episodes will have a normal initial CRP.

Specificity was 10% for CRP and 82% for SAA [Table 8]. This signifies that there is a high probability of neonates with normal SAA levels when there is no neonatal sepsis. It is also very likely that the neonate with signs and symptoms of sepsis will have blood culture-positive neonatal sepsis if SAA levels is $\geq 10 \mu\text{g/mL}$.

PPV is the probability that subjects with a positive test truly have the disease. In this study, PPV [Table 12] for SAA was 81%, whereas, for Serum CRP, it was 45.1%, which indicates that, among the neonates who showed SAA levels $\geq 10 \mu\text{g/mL}$, the probability of sepsis was 81%. The PPV of SAA in this study was higher than that of CRP and TLC. NPV is the probability that subjects with a negative test truly do not have the disease. NPV [Table 12] for SAA was 95.3%, whereas, for serum CRP, it was 62.5%. This signifies that, among the neonates who showed SAA levels $< 10 \mu\text{g/mL}$, the probability of being disease-free was 95.3%. These results came in agreement with Arnon *et al.*,^[16] who showed a high PPV of SAA compared with that of CRP (86%).

In order to study the diagnostic accuracy of the laboratory tests for the diagnosis of neonatal sepsis, ROC curves were plotted [Figure 7], which showed that AUC for SAA (0.986) was significantly higher than serum CRP (0.868). From the ROC curves, SAA and serum CRP showed optimal cutoffs of $\geq 12 \mu\text{g/mL}$ and $\geq 7.5 \text{ mg/dL}$, respectively in this study.

A small sample size, a single sample without serial measurement, not including healthy neonates as control subjects among study subjects are some of the limitations of this study.

Conclusion

We conclude that a higher proportion of the neonates with sepsis showed raised SAA levels than those without sepsis,

and the level correlated well to the severity of the condition. SAA protein levels were significantly higher in the neonates with a positive blood culture than in the neonates with clinical signs of sepsis but with a negative blood culture. The findings of this study suggest that SAA can be used both as diagnostic and as a prognostic marker of neonatal sepsis as it has a high specificity and a high PPV compared with serum CRP. The role of SAA should be further evaluated and considered as a potential neonatal sepsis biomarker in routine clinical settings.

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