Prognostic Value of Pentraxin 3 and Procalcitonin in Late Onset Neonatal Sepsis

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ABSTRACT

Background: High percentage of intensive care unit (ICU) admissions are due to sepsis. Some evidence suggests procalcitonin (PCT) is a useful sepsis prognostic marker. Acute phase protein, which is called pentraxin3 (PTX3) may help in sepsis screening.

Objective: To assess the prognostic value of the PTX3 and PCT in neonatal sepsis in comparison with other screening markers.

Patients and Methods: A prospective study included 40 neonates with sepsis. The study had been conducted in the neonatal ICUs of Ain Shams University, Children's Hospital during the period from January 2020 to May 2022. All neonates had been subjected to clinical examination, anthropometric measurements and sepsis scoring by neonatal sequential organ failure assessment (nSOFA). Laboratory investigations were performed including complete blood count, blood culture, assay of serum levels of C-reactive protein (CRP), PCT and PTX3.

Results: The CRP levels were significantly lower in the deteriorated group compared to the better group, whereas PCT and PTX3 levels were significantly higher with p-value=0.004, 0.016 and 0.019, respectively. After 3 days, CRP, PCT and PTX3 levels increased significantly in deteriorated group than improved group with p-value=0.002, <0.001 and <0.001, respectively. The combination between baseline nSOFA score, CRP and PCT levels had a sensitivity of 84.62%, specificity of 92.59% and AUC 0.906. While combination between baseline nSOFA CRP and PTX3 levels had the highest sensitivity of 100% and AUC of 0.909 in prediction the poor outcome of the studied patients.

Conclusion: Serum levels PCT and PTX3 seem to be promising prognostic markers in neonatal sepsis.

Keywords: C-reactive protein, nSOFA, procalcitonin, pentraxin 3, Late onset neonatal sepsis.

INTRODUCTION

In low and middle-income nations, sepsis continues to be a major contributor to newborn mortality and morbidity. Due to the lack of specificity in the symptoms of neonatal sepsis, testing is required to make a diagnosis. Better clinical outcomes and less unnecessary antibiotic use can be achieved through rapid and precise detection of infection[(1)].

Mild symptoms of neonatal sepsis can quickly deteriorate into life-threatening complications like organ failure and meningitis[(2)]. Subclinical infection can progress to severe local or systemic infection in the clinical setting[(3)]. Therefore, it is crucial to identify reliable early indicators of sepsis to improve diagnosis and prognosis. Several potential biomarkers have been presented recently[(2)].

Procalcitonin (PCT) could be an important prognostic marker for sepsis[(4)]. Following bacterial infection, the PCT level rises in 6 to 12 hours and drops by 50% after 24 hours with the help of appropriate antibiotherapy and the work of the immune system. The level is not affected (does not decrease) by anti-inflammatory drugs[(5)]. PCT appears to be a useful biomarker to differentiate bacterial infections from viral infections with high sensitivity and specificity rates. One of these studies evaluating the rapid diagnosis of sepsis suggested that PCT could be used to differentiate severe clinical situations like sepsis and septic shock, as well as to help determine the type of microbe[(6)].

In response to activation by primary inflammatory signal proteins, the serum concentration of pentraxin 3 (PTX3), an acute phase protein that represents the long pentraxin subfamily, can increase by as much as 100-fold in 6-8 hours. For PTX3, IL-6 is only a marginal inducer [(7)].

Patients with sepsis can have detectable levels of PTX3, PCT in their serum for a long time after the onset of sepsis, whereas other novel proinflammatory cytokines (like and tumour necrosis factor-a as well as interleukin) have a short window of expression, despite showing good prognostic values for mortality. Because of this, multifactor assays are superior to those based on a single factor in identifying sepsis and measuring infection severity[(8)].

There is a lack of neonatal-specific data, but there is an established scoring system similar to the one used to determine sepsis in adults and it can be used in neonates, called the neonatal sequential organ failure assessment (nSOFA) [(9)].

Our study's objective is to evaluate the PTX3, PCT for its predictive significance in newborn sepsis in relation to other sepsis screens. Using a model that incorporates PTX3 and PCT, we can better predict progression in these neonates.

PATIENTS AND METHODS

During the months of January 2020 through May 2022, at Ain Shams University's Children's Hospital, we analyzed data from a prospective study of the NICU there.

Forty clinically suspected neonates with sepsis, who were clinically free before this age were included in this study. The International Sepsis Definitions from 2001 were used to diagnose sepsis. In neonates, the presence of sepsis can be suspected from the presence of inflammatory symptoms such as hyper or

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hypothermia, tachycardia, and signs of altered organ function such as altered mental status, acute oliguria, hypoxemia, and an elevated serum lactate level, as well as infection (documented or suspected). Leukocytosis, leukopenia, an immature leukocyte count of 10% or more, and elevated CRP levels were indicative of an inflammatory disorder in the lab [(10)].

The clinical and laboratory criteria (leukocyte and thrombocyte counts, CRP) used in the scoring system to diagnose late-onset sepsis. Each worsening metric is assigned as a point value from 0 to 3 depending on the severity of the change. For instance, a score of 0 indicates a normal leukocyte count, a score of 1 indicates leukocytosis, and a score of 3 indicates leukopenia. Patients with scores of 10 or above on this scale will be diagnosed with sepsis [(11)].

Pediatrics with cardiogenic, obstructive and hemorrhagic shock, post cardiac arrest and hypoxic ischemic encephalopathy were excluded.

All patients enrolled in the current study had been subjected to history taking, clinical examination, anthropometric measurements and sepsis scoring by nSOFA[(12)]. Laboratory investigations were collected from all pediatrics including complete blood count, C-reactive protein (CRP), lactate, blood culture. The CRP was assayed by immunoturbidimetric method and was measured using Roche/Hitachi Cobas® c311 System (Roche Diagnostics International Ltd., Switzerland). The assay of serum levels for PTX3 and PCT were performed by Enzyme-Linked Immunosorbant Assay (ELISA) using Sandwich ELISA technique (Bioneovan Co., Ltd).

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient's parent signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

IBM Corp.'s Statistical Package for Social Science (SPSS) was used to analyse the data. Armonk, NY: IBM Corp., 2015, IBM SPSS Statistics for Windows, Version 21.0. Parametric data (i.e., quantitative with normal distribution of data) were presented using mean, standard deviations, and ranges, while median and interquartile range were used to depict the non-parametric data (IQR). The qualitative characteristics were shown in the form of percentages as well as numbers. To compare qualitative data across groups, a chi-square test was used. Independent t-test was used to compare the means of two groups when the data had a normal distribution, whereas the Mann-Whitney U test was used to compare the two groups where the data did not have a normal distribution. The paired t-test was used to compare two paired groups with parametric distributions of quantitative data, whereas the Wilcoxon signed-rank test was used to compare two groups with non-parametric distributions of quantitative data. The optimal cutoff point was determined by calculating the sensitivity, specificity, and area under a receiver operating characteristic (ROC) curve (AUC). The margin of error was set at 5% and the confidence interval was set at 95%. Results were considered significant when the P value was less than 0.05 and highly significant when it was less than 0.001.

RESULTS

Neonatal sepsis with their age from 72 hours to 28 days were included. Twenty-one were females (52.5%) and 19 were males (47.5%). The gestational age ranged between 29-40 weeks with mean age 34.43 ± 3.28 week. Also, 55% of the cases were preterm, 80% of the maternal deliveries were cesarean section. 75% suffered from respiratory distress, 55% didn't need ventilation. The reported duration on mechanical ventilation ranged between 3-12 days with median (IQR) 6 (4 – 10). The duration stay in the NICU ranged from 5 – 90 with median (IQR) 15 (10 – 32), respectively.

Regarding outcome, twenty-seven patients were improved (67.5%), while thirteen patients were deteriorated (32.5%). There was no statistically significant relation found between the outcome of the studied patients and their maternal diseases except the maternal percentage of Covid-19 were (n =2) among the deteriorated group neonates while none of the improved group were Covid-19 (0.0%) with p-value = 0.037.

Both the respiratory and overall baseline scores were significantly higher in the deteriorated group compared to the improved group with p-value = 0.005 and 0.036, respectively. After 3 days, there was statistically significant increase in the hematology score and total score in deteriorated group than improved group with p-value <0.001 and 0.001; respectively (Table **1**).

Table (1): Comparison between the improved group and deteriorated group regarding nSOFA score at baseline and after 3 days

nSOFA		Improved group No. = 27	Deteriorated group No. = 13	Test value	P-value	Sig.
Baseline						
Respiratory	Median (IQR) Range	0 (0 – 2) 0 – 4	2 (2 – 3) 0 – 4	2.832	0.005	HS
Cardiovascular	Median (IQR) Range	2 (0 – 3) 0 – 3	2 (2 – 3) 0 – 3	-1.565	0.118	NS
Hematology	Median (IQR) Range	1 (0 – 2) 0 – 3	0 (0 – 2) 0 – 3	-0.435	0.664	NS
Total score	Median (IQR) Range	3 (2 – 4) 0 – 8	5 (4 – 7) 2 – 9	2.100	0.036	S
After 3 days						
Respiratory	Median (IQR) Range	0 (0 – 2) 0 – 3	2 (0 – 2) 0 – 4	1.029≠	0.303	NS
Cardiovascular	Median (IQR) Range	2 (0 – 2) 0 – 3	2 (2 – 3) 0 – 3	1.874≠	0.061	NS
Hematology	Median (IQR) Range	0 (0 – 1) 0 – 2	2 (1 – 3) 0 – 3	3.604≠	0.000	HS
Total score	Median (IQR) Range	2 (2 – 4) 0 – 6	5 (4 – 7) 2 – 8	3.450≠	0.001	HS

HS: Highly significant (P-value < 0.01), NS: Non significant (P-value > 0.05), S: Significant (P-value < 0.05).
•: Independent t-test; ≠: Mann-Whitney test.

Baseline CRP levels in the deteriorated group were lower than those of the improved group (p = 0.004), whereas PCT and PTX3 levels were higher in the deteriorated group as compared to improved group (p = 0.016 and 0.019, respectively). Also, after 3 days, there was statistically significant increase in CRP, PCT and PTX3 levels in deteriorated group than improved group after 3 days with p-value = 0.002, <0.001 and <0.001, respectively (Table **2**).

Table (2): Comparison between the improved group and deteriorated group regarding their laboratory results at baseline and after 3 days among the studied patients

		Improved group n = 27	Deteriorated group n = 13	Test value	P-value	Sig.
Baseline						
CRP (mg\L)	Mean ± SD	72.5 ± 15.46	11.5 ± 2.34	-2.852≠	0.004	HS
Procalcitonin (ng\mL)	Mean ± SD	3.3 ± 0.61	8.96 ± 1.82	2.411≠	0.016	S
Pentraxin 3 (ng\mL)	Mean ± SD	3.78 ± 0.72	5.66 ± 1.10	2.339≠	0.019	S
hemoglobin (g\dl)	Mean ± SD	13.66 ± 3.33	13.99 ± 3.67	0.209•	0.002	HS
TLC (10^9/L)	Mean ± SD	11.2 ± 2.31	11.1 ± 2.21	-0.043≠	0.000	HS
Platelets (10^9/L)	Mean ± SD	192 ± 41.52	129 ± 31.32	-2.1085≠	0.000	HS
After 3 days						
CRP (mg\L)	Mean ± SD	24 ± 5.21	75 ± 6.41	3.091≠	0.002	HS
Procalcitonin (ng\mL)	Mean ± SD	1.94 ± 0.34	11.65 ± 2.51	4.433≠	0.000	HS
Pentraxin 3 (ng\mL)	Mean ± SD	2.47 ± 0.33	7.12 ± 1.12	3.885≠	0.000	HS
hemoglobin (g\dl)	Mean ± SD	14.22 ± 3.25	12.18 ± 2.31	-0.523•	0.604	NS
TLC (10^9/L)	Mean ± SD	12.6 ± 2.52	12.2 ± 2.41	-1.083≠	0.279	NS
Platelets (10^9/L)	Mean ± SD	195 ± 38.62	86 ± 18.64	-3.437≠	0.001	HS

HS: Highly significant (P-value < 0.01), NS: Non significant (P-value > 0.05), S: Significant (P-value < 0.05).
•: Independent t-test; ≠: Mann-Whitney test.

Table **3** & **4** showed the comparison between different studied parameters at baseline and after 3 days among the different studied groups.

The ROC curve showed that nSOFA score can predict the poor outcome of the studied patients at baseline at the level of > 3 with sensitivity 76.92%, specificity of 62.96% and AUC of 0.704. Regarding the CRP at the level of ≤ 30 mg/L at baseline had a sensitivity of 76.92%, specificity of 81.48% and AUC of

0.781. the PCT level can also predict the poor outcome of the studied patients at the level of >6.81 ng\mL with sensitivity 69.23%, specificity of 92.59% and AUC of 0.738 while the baseline PTX3 at the level of > 5.04 ng\mL showed sensitivity of 61.54%, specificity of 88.89% and AUC of 0.731. The combination between nSOFA score, CRP and PCT levels had a sensitivity of 84.62%, specificity of 92.59% and AUC of 0.909 while the combination between nSOFA score, CRP and PTX3 levels have a sensitivity of 100.0%, specificity of 70.37% and AUC of 0.909. The combination between PCT and PTX3 levels had a sensitivity of 76.92%, specificity of 81.48% and AUC of 0.846 while the combination between nSOFA score, CRP, PCT and PTX3 levels had a sensitivity of 100.0%, specificity of 77.78% and AUC of 0.929 (Figure **1**).

When we reassessed the performance of theses biomarkers after 3 days, SOFA score at the level of > 2 showed a sensitivity 92.31%, specificity of 59.26% and AUC of 0.835. While, CRP at the level of >30 mg/L at 3 days had a sensitivity of 76.92%, specificity of 74.07% and AUC of 0.805. Regarding the PCT at the level of >3.13 ng\mL showed a sensitivity 92.31%, specificity of 81.48% and AUC of 0.937 while the PTX3 at the level of > 3.15 ng\mL had a sensitivity of 84.62%, specificity of 88.89% and AUC of 0.883 (Figure 2). Also, the combination between all studied parameters with their performance are illustrated in Figures **1** & **2**.

Table (3): Comparison between nSOFA at baseline and after 3 days among the different studied groups

nSOFA		Baseline	After 3 days	Test value	P-value	Sig.
Improved group (n = 27)						
Respiratory	Median (IQR) Range	0 (0 – 2) 0 – 4	0 (0 – 2) 0 – 3	-0.707≠	0.480	NS
Cardiovascular	Median (IQR) Range	2 (0 – 3) 0 – 3	2 (0 – 2) 0 – 3	-1.350≠	0.177	NS
Hematology	Median (IQR) Range	1 (0 – 2) 0 – 3	0 (0 – 1) 0 – 2	-2.923≠	0.003	HS
Total Score	Median (IQR) Range	3 (2 – 4) 0 – 8	2 (2 – 4) 0 – 6	-2.344≠	0.019	S
Deteriorated group (n = 13)						
Respiratory	Median (IQR) Range	2 (2 – 3) 0 – 4	2 (0 – 2) 0 – 4	-1.473≠	0.141	NS
Cardiovascular	Median (IQR) Range	2 (2 – 3) 0 – 3	2 (2 – 3) 0 – 3	-0.577≠	0.564	NS
Hematology	Median (IQR) Range	0 (0 – 2) 0 – 3	2 (1 – 3) 0 – 3	1.606≠	0.108	NS
Total Score	Median (IQR) Range	5 (4 – 7) 2 – 9	5 (4 – 7) 2 – 8	-0.474≠	0.636	NS

HS: Highly significant (P-value < 0.01), NS: Non significant (P-value > 0.05), S: Significant (P-value < 0.05). ≠: Wilcoxon signed rank test

Table (4): Comparison between the laboratory results at baseline and after 3 days among the different studied groups

		Baseline	After 3 days	Test value	P-value	Sig.
Improved group (n = 27)						
Hemoglobin (g\dl)	Mean ± SD	13.66 ± 3.33	12.14 ± 3.01	-4.187•	0.000	HS
TLC (10^9/L)	Mean ± SD	11.2 ± 2.51	12.6 ± 2.72	0.264≠	0.792	NS
Platelets (10^9/L)	Mean ± SD	192 ± 44.21	195 ± 6.52	3.200≠	0.004	HS
CRP (mg\L)	Mean ± SD	72.5 ± 6.11	24 ± 5.21	-3.412≠	0.001	HS
Procalcitonin (ng\mL)	Mean ± SD	3.3 ± 0.61	1.94 ± 0.31	-3.580≠	0.000	HS
Pentraxin 3 (ng\mL)	Mean ± SD	3.78 ± 0.52	2.47 ± 0.32	-3.340≠	0.001	HS
Deteriorated group (n = 13)						
hemoglobin (g\dl)	Mean ± SD	13.99 ± 3.67	12.18 ± 2.31	-1.711•	0.113	NS
TLC (10^9/L)	Mean ± SD	11.1 ± 2.53	12.2 ± 2.61	0.699≠	0.485	NS
Platelets (10^9/L)	Mean ± SD	129 ± 30.31	86 ± 18.31	-2.481≠	0.013	S
CRP (mg\L)	Mean ± SD	11.5 ± 2.33	75 ± 6.21	3.110≠	0.002	HS
Procalcitonin (ng\mL)	Mean ± SD	8.96 ± 2.10	11.65 ± 2.33	1.433≠	0.152	NS
Pentraxin 3 (ng\mL)	Mean ± SD	5.66 ± 1.11	7.12 ± 1.61	2.342≠	0.019	S

HS: Highly significant (P-value < 0.01), NS: Nonsignificant (P-value > 0.05), S: Significant (P-value < 0.05).
•: Paired t-test; ≠: Wilcoxon signed rank test

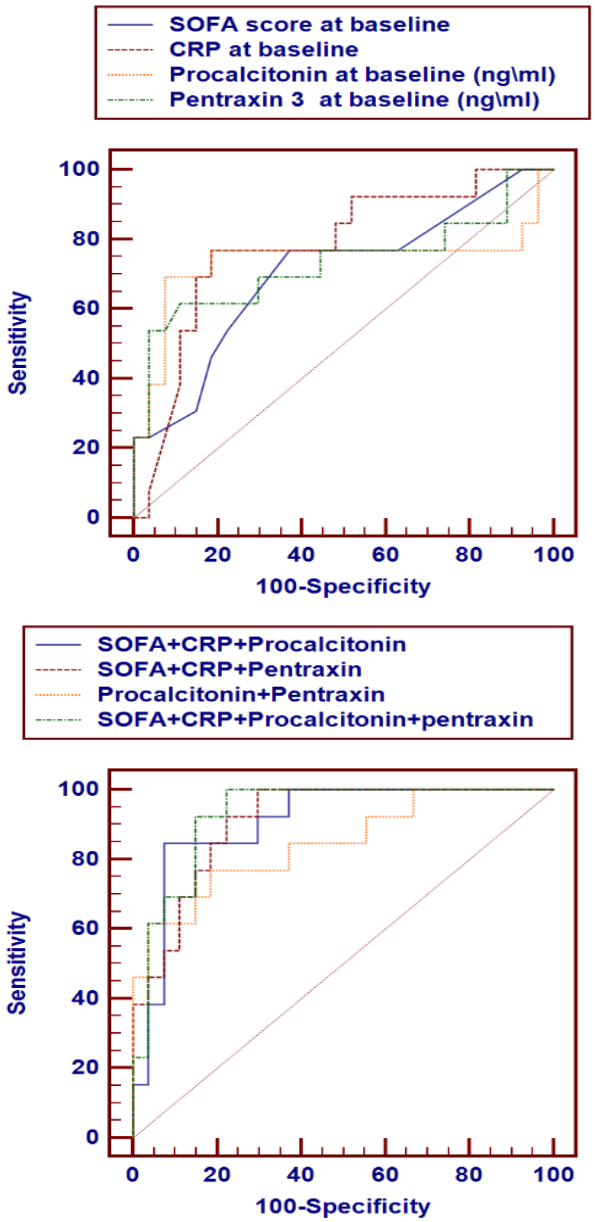

Figure (1): ROC curve for SOFA score, CRP, procalcitonin (ng\mL) and pentraxin 3 (ng\mL) levels and combination between them at the baseline as prognostic markers to predict the poor outcome of the studied patients

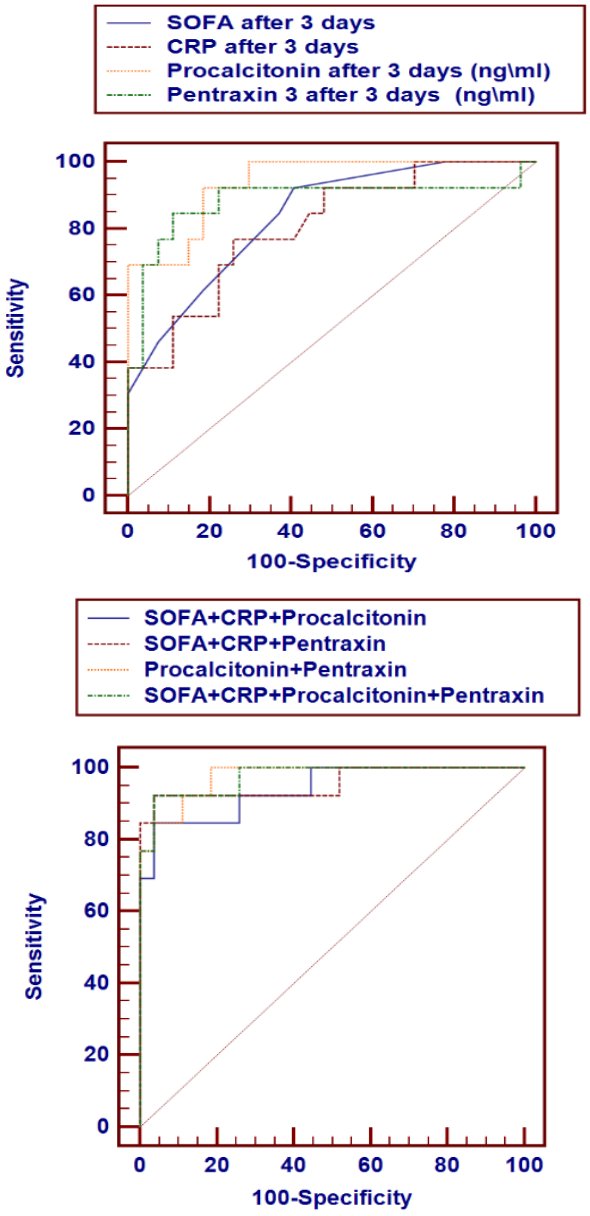

Figure (2): ROC curve for SOFA score, CRP, procalcitonin (ng\mL) and pentraxin 3 (ng\mL) levels and combination between them after 3 days as prognostic markers to predict the poor outcome of the studied patients.

DISCUSSION

The mortality and morbidity rates associated with neonatal sepsis remain high. About 1–10 out of every 1,000 are born with neonatal sepsis. While antibiotherapy for neonatal sepsis has improved, significant challenges remain for both full-term and preterm infants [13].

The gold standard for diagnosing sepsis is the growth of one or more microbial agents in blood culture. However, there are situations where this is simply impossible. Some of the most useful ancillary diagnostic techniques are inflammatory markers including TLC and CRP, PCT, fibrinogen, ceruloplasmin, haptoglobin, IL-6, serum amyloid-A, and PTX3[14].

Although the diagnostic efficacy of PCT and PTX3 is well established, yet studies regarding their prognostic role are very limited and needs further exploration. Therefore our study aimed at evaluation the prognostic value of these biomarkers in patients with late onset sepsis and severe infections requiring NICU admission, For the purpose of better mortality prediction, it would be beneficial to combine severity scores with biomarkers, and a viable model for doing so is currently being developed and validated.

Our findings showed that 65% of the blood cultures had positive results with Klebsiella pneumoniae and staphylococcus aureus being the most common organisms (12.5% each), **Morad *et al.*** [15] agreed with our results as Most of the bacteria found in these samples belong to the gram-negative bacillus genus Klebsiella (61.3%).

On the other hand, **Charles *et al.*** [16] found that Escherichia coli, Pseudomonas aeruginosa, and

Candida albicans all accounted for 22.2% of the organisms isolated from their positive culture, with Klebsiella pneumoniae coming up at a distant third (11.1%). Furthermore, 36% of our samples had no growth on the blood culture, similar negative cultures were found by **Atay *et al.*** [17] who recorded 16% from the enrolled 49 patients had no growth on their blood culture. They noted there could be a number of reasons for the slow growth rates in the culture, including mistakes made during specimen collection and addition to culture, a lack of blood sample material, or the administration of antibiotics prior to taking the culture.

No statistically significant association was found between the outcome of our patients and their maternal illnesses or other clinical features like hypertension, anemia, diabetes, rheumatic heart, hypothyroidism, accidental hemorrhage, thyroidectomy, sever preeclampsia, or epilepsy except the maternal percentage of Covid 19 were 15.4% (n= 2) among the deteriorated group neonates while none of the improved group had Covid 19 (0.0%) with p-value = 0.037.

This could be explained by **Zgutka *et al.*** [18] who reported that preterm patients with maternal COVID-19 have a considerably greater rate of admission to the neonatal critical care unit, need for respiratory support, suspected sepsis, hyperbilirubinemia, feeding intolerance, and longer length of stay (LOS).

Platelet counts were found to be significantly higher in the worsened group compared to the improved group with p-value = 0.010, while hemoglobin and TLC levels did not differ significantly between the two groups. Deteriorated patients developed thrombocytopenia during the follow-up period after 3 days, as we noticed a statistically significant decrease in platelet level in deteriorated group than improved group with p-value = 0.002. While levels of hemoglobin and TLC were not significantly different between the two groups.

This change in the platelet levels was previously suggested by **Ree *et al.*** [19] who noticed that thrombocytopenia in neonatal sepsis is more prominent in patients gram negative bacteria and its related to the released endotoxins in neonatal sepsis. Because of this, thrombocytopenia may be used as an indicator of the severity of sepsis. However, it is unclear what causes thrombocytopenia in the newborn with sepsis.

In addition, neonates who develop sepsis often experience a reduction in hemoglobin levels, which can lead to anemia and, perhaps, ischemia and hypoxic damage due to inadequate oxygen delivery to the tissues. As the oxygen-carrying capacity of the blood drops below what is needed for tissue growth, anaerobic metabolism and an increase in byproducts become prevalent (e.g., lactic acid) [20].

CRP levels were found to be significantly lower in the deteriorated group than in the improved group, whereas PCT and PTX3 levels were found to be significantly higher with p-value = 0.004, 0.016 and 0.019; respectively. All patients were followed up with reassessment of levels of CRP, PCT and PTX3 at 3 days, during this time, CRP, PCT, and PTX-3 levels were significantly higher in the worsened group compared to the improved group with p-value= 0.002, <0.001 and <0.001; respectively.

This comes in line with **Fahmey *et al.*** [20] who showed that newborns whose sepsis did not resolve had greater serum levels of PTX3 than those who did, suggesting that PTX3 could be utilized as a predictive diagnostic for neonatal sepsis.

Another study by **Atay *et al.*** [17] collecting three measurements over the course of their trial to determine how PTX3 factors into the diagnosis and subsequent monitoring of newborn sepsis. Both PTX3 and CRP levels were significantly different in the experimental and control groups ($p<0.05$).

Our ROC curve showed that the baseline nSOFA at the cut-off score >3 can predict the deteriorated outcome of our studied patients, with sensitivity of 76.92%, specificity of 62.96%, and AUC of 70.4%. When nSOFA score was reassessed at 3 days, the best cut-off score was >2 with a sensitivity of 92.31%, specificity of 59.26%, and AUC of 83.5%. Regarding the baseline CRP at the level of ≤ 30 mg/L had a sensitivity of 76.92%, specificity of 81.48%, and AUC of 78.1%.

This was compared to **Berka *et al.*** [21] who performed a ROC curve to predict future mortality or serious illness (more than 48 hours after delivery). Sensitivity was 67%, specificity was 80%, and AUC was 0.795 for a nSOFA >2 cutoff (95% CI = 0.763–0.827).

Interestingly, our study detected that the best cut-off levels for differentiating deteriorated patients from improved patients early at the baseline as follow; the baseline PCT level of >6.81 ng\mL can predict the poor outcome with a sensitivity 69.23%, specificity of 92.59%, and AUC of 73.8%. Regarding the baseline PTX3 at the level of >5.04 ng\mL can poor outcome with a sensitivity of 61.54%, specificity of 88.89%, and AUC of 73.1%,

We reassessed the ROC performance during the follow up after 3 days, the best cut-off level for PCT was >3.13 ng\mL for differentiating the deteriorated patients from improved patients, with a sensitivity of 92.31%, specificity of 81.48%, and AUC of 93.7%. Regarding the PTX3 at 3 days, the best cut-off level of > 3.15 ng\mL had a sensitivity of 84.62%, specificity of 88.89%, and AUC of 88.3%. According to **Ruetsch *et al.*** [22] A PCT value >8.9 g/L was shown to be linked with 60-day mortality in the study of preterm infants with late-onset sepsis. Between 0.70 and 0.82, the AUC of PCT was found to be useful for prognosis. They also found that PCT values increased significantly in deceased patients between the time of diagnosis and 48 hours later, which suggests that PCT sample would be most useful at the time of diagnosis and 24 hours afterwards. For patients whose PCT value at sepsis diagnosis was less than 8.9 g/L, the estimated chance of

survival at day 60 was greater than 95% and less than 45% if higher (p0.0001). The AUC was 0.8276 (p = 0.0361) across a time period of 24-48 hours, and a cutoff value of 6.74 g/L was found to have 75% sensitivity and 79% specificity. The researchers determined that a PCT value >8.92 g/L at the time of LONS diagnostic suspicion is a promising prognostic marker.

In addition, the combination between the different studied biomarkers were more valuable. From our findings, we recommend to add PCT and PTX3 to the routinely profile for early prediction the poor outcome as we noticed that the baseline nSOFA score, CRP and PCT levels had a higher sensitivity of 84.62%, specificity of 92.59% and AUC 0.906. Moreover, combination between baseline nSOFA CRP and PTX3 had the highest sensitivity (100%) and AUC of 0.909 with specificity of 70.37%. Regarding their performance at 3 days, the combination between PCT and PTX3 had the best sensitivity of 100%, and AUC of 0.974 with specificity of 81.48%.

CONCLUSION

Serum pentraxin 3 and procalcitonin levels seem to be promising prognostic markers in neonatal sepsis with higher sensitivity and specificity for procalcitonin than pentraxin at 3 days. The combination between baseline nSOFA score, CRP and PCT levels had a sensitivity of 84.62%, specificity of 92.59% and AUC 0.906. While, combination between baseline nSOFA CRP and PTX3 levels had the highest sensitivity (100%) and AUC of 0.909 in prediction the poor outcome of the studied patients. More informative than CRP, PCT and PTX3 could direct individualized intense monitoring, raise alarms for impending clinical deterioration, and facilitate early action.

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REFERENCES

1. **Celik I, Hanna M, Canpolat F *et al.* (2022):** Diagnosis of neonatal sepsis: the past, present and future. Pediatr Res., 91(2):337-50.
2. **Kim F, Polin R, Hooven T (2020):** Neonatal sepsis. BMJ., 371. doi: 10.1136/bmj.m3672.
3. **Odabasi I, Bulbul A (2020):** Neonatal sepsis. Sisli Etfal Hastan Tip Bul., 54(2): 142-58.
4. **Tan M, Lu Y, Jiang H *et al.* (2019):** The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. J Cell Biochem., 120(4): 5852-9.
5. **Schuetz P, Chiappa V, Briel M *et al.* (2011):** Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med., 171(15):1322-31.
6. **Brodská H, Malíčková K, Adámková V *et al.* (2013):** Significantly higher procalcitonin levels could differentiate Gram-negative sepsis from Gram-positive and fungal sepsis. Clin Exper Med., 13(3):165-70.
7. **Garnacho-Montero J, Huici-Moreno M, Gutiérrez-Pizarraya A *et al.* (2014):** Prognostic and diagnostic value of eosinopenia, C-reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis. Crit Care, 18(3):1-9.
8. **Hu C, Zhou Y, Liu C *et al.* (2018):** Pentraxin-3, procalcitonin and lactate as prognostic markers in patients with sepsis and septic shock. Oncotarget., 9(4):5125-36.
9. **Singer M (2016):** The new sepsis consensus definitions (Sepsis-3): the good, the not-so-bad, and the actually-quite-pretty. Intens Care Med., 42(12):2027-9.
10. **Levy M, Fink M, Marshall J *et al.* (2003):** 2001 sccm/esicm/accp/ats/sis international sepsis definitions conference. Intens Care Med., 29(4):530-8.
11. **Töllner U (1982):** Early diagnosis of septicemia in the newborn. Eur J Pediatr., 138(4):331-7.
12. **Wynn J, Kelly M, Benjamin D *et al.* (2017):** Timing of multiorgan dysfunction among hospitalized infants with fatal fulminant sepsis. Am J Perinatol., 34(07):633-9.
13. **Zou H, Jia X, He X *et al.* (2021):** Emerging threat of multidrug resistant pathogens from neonatal sepsis. Front Cell Infec Microbiol., 11: 694093. doi: 10.3389/fcimb.2021.694093
14. **Battal F, Bulut Ö, Yıldırım Ş *et al.* (2019):** Serum pentraxin 3 concentration in neonatal sepsis. J Pediatr Infec Dis., 14(05):219-22.
15. **Morad E, Rabie R, Almalky M *et al.* (2020):** Evaluation of procalcitonin, C-reactive protein, and interleukin-6 as early markers for diagnosis of neonatal sepsis. https://doi.org/10.1155/2020/8889086
16. **Charles M, Kalaivani R, Venkatesh S *et al.* (2018):** Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis. Indian J Pathol Microbiol., 61(1):81-84.
17. **Atay T, Sahin K, Elevli M *et al.* (2022):** A Comparative Study of the Effectiveness of Serum C-reactive Protein and Serum Pentraxin-3 Levels in the Diagnosis and Follow-up of Neonatal Sepsis. Med Bull Haseki/Haseki Tip Bulteni., 60(1): 33-39.
18. **Zgutka K, Prasanth K, Pinero-Bernardo S *et al.* (2021):** Infant outcomes and maternal COVID-19 status at delivery. J Perinat Med., 49(6):691-6.
19. **Ree I, Fustolo-Gunnink S, Bekker V *et al.* (2017):** Thrombocytopenia in neonatal sepsis: Incidence, severity and risk factors. PloS One, 12(10):e0185581. https://doi.org/10.1371/journal.pone.0185581
20. **Fahmey S, Mostafa N (2019):** Pentraxin 3 as a novel diagnostic marker in neonatal sepsis. J Neonat Perinat Med., 12(4):437-42.
21. **Berka I, Korček P, Janota J *et al.* (2022):** Neonatal Sequential Organ Failure Assessment (nSOFA) Score within 72 Hours after Birth Reliably Predicts Mortality and Serious Morbidity in Very Preterm Infants. Diagnostics, 12(6):1342. doi: 10.3390/diagnostics12061342.
22. **Ruetsch V, Barreault S, Le Sache N *et al.* (2022):** Procalcitonin is a Prognosis Biomarker in Late Onset Neonatal Sepsis: A Pilot Study. Eur J Pediatr., 181(4):1459-1464.