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Progranulin vs Traditional Sepsis Biomarkers in Diagnosis of Early-Onset Neonatal Sepsis

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Abstract:

Background: Early onset neonatal sepsis (EONS) is associated with significant morbidity and mortality in the neonatal period, so, early diagnosis is crucial and identification of reliable infection biomarkers is necessary. In this study, we aimed to evaluate the diagnostic ability of serum progranulin (PGRN) in EONS and compare its effectiveness with other conventional biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP). **Patients and Methods:** This prospective study was conducted between January 2021 and December 2021 at the Neonatal Intensive Care Unit, Benha University Hospital, Benha, Egypt. The study comprised 80 full-term neonates, categorized into infected and uninfected groups. Blood samples for conventional laboratory tests, blood culture and infection biomarkers were withdrawn on admission. **Results:** serum PGRN level was significantly higher in the infected group than uninfected group (median 89 ng/dl vs 42.95 ng/dl, respectively, p<0.0001). Using receiver operating characteristic curve analysis, the area under the curve (AUC) value of PGRN was higher than other biomarkers, as AUC was 0.836, with a 95% confidence interval (CI) of (0.758-0.979), p<0.0001 for PGRN, 0.756 (95%CI 0.647-0.845), p 0.0008 for PCT, and 0.749 (95%CI 0.639-0.839), p 0.0013 for CRP. Using a cut-off value of 43.2 ng/ml for PGRN, its sensitivity was 97%, and its negative predictive value was 95.2%. Combining PGRN and PCT increased its predictive ability; the odds ratio was 6.479 (95%CI 2.084-24.401), p=0.001. **Conclusion:** PGRN could be used as a promising biomarker for the diagnosis of EONS, and a combination of PGRN and PCT may enhance the diagnosis of sepsis.

Keywords: EONS; neonatal sepsis; Progranulin; Procalcitonin; CRP

Introduction

Neonatal sepsis is a serious and potentially life-threatening condition that arises from a dysregulated host response to a systemic viral, bacterial, or fungal infection within the first 28 days of life in both term and preterm neonates [(1).] Depending on the timing of infection, method of transmission, and causative organisms, there are two main categories of neonatal sepsis: early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS) [(2).] EONS describe a vertically transmitted infection in the first three days (72 hours of life), and LONS is a horizontally transmitted infection (after 72 hours of life) commonly caused by a microorganism in hospital settings [(3)].

EONS is a major health problem in developing countries; its incidence was reported to be 0.62/1000 live births or 4.91/1000 neonatal admissions. Furthermore, it can lead to death in 7% of cases. This renders early diagnosis crucial to decrease morbidity and prevent EONS-related mortality [(4).]

Since most symptoms and signs of neonatal sepsis are ambiguous, diagnosing the condition based just on the clinical background is extremely difficult. Unfortunately, relying solely on blood cultures to validate the clinical suspicion has not been successful because of the low sensitivity of blood cultures in EONS [(4, 5)].

In recent years, hematological and biochemical markers such as total leucocyte count, absolute neutrophil count, C-reactive protein (CRP), procalcitonin (PCT), and various cytokines- have all been suggested as being useful indicators for the early identification of septic neonates [(6).] EONS has traditionally been detected using CRP, produced by the liver in response to several infectious and inflammatory conditions. Nevertheless, results were inconsistent, and its accuracy was debatable [(5, 7)]. PCT has been considered as a sensitive biomarker in neonatal sepsis, particularly in bacterial infection. It is produced by the liver and monocytes to lesser extent. It was found to be of better value in LONS compared to EONS [(5, 7).] Despite being a better indicator of neonatal sepsis than CRP, PCT's sensitivity was still limited, therefore, further research is needed to establish a reliable biomarker that can accurately identify truly and early infected neonates [(4).]

Progranulin (PGRN) is a novel biomarker that has been previously investigated in studies including adults and children. It is an immunoregulatory protein that has been proposed to be crucial in the body's defense mechanism against bacterial infections. However, PGRN has not been thoroughly investigated in neonatal sepsis [(4).] This study aimed to investigate the role of PGRN as a reliable biomarker in prompt and accurate diagnosis of EONS and compare its sensitivity and specificity with well-established biomarkers, including CRP and PCT.

Patients and methods:

Patients:

This prospective case-control study, that included 80 neonates, was conducted between January 2021 and December 2021, at the Neonatal Intensive Care Unit (NICU), Benha University Hospitals, Benha, Egypt. Neonates ≥37 weeks of gestation and who were presented during the first 72hours of life with clinical suspicion of EONS were eligible for this study, and were subjected to conventional laboratory tests, and blood and cerebrospinal fluid (CSF) cultures. Neonates with congenital malformations, confirmed intrauterine viral infection, confirmed cases with an inborn error of metabolism, hypoxic-ischemic encephalopathy, significant birth trauma, or prior antibiotic therapy- were excluded from this study.

Definition of EONS:

The suspicion of EONS was assessed during the first 72hours of life based on the following criteria [(4)]:

- Maternal risk factors as maternal fever, premature rupture of membrane (PROM)>18 hours, or chorioamnionitis.
- Clinical signs as temperature instability, hemodynamic instability (alterations in heart rate or peripheral perfusion), respiratory dysfunction (apnea or respiratory distress), neurological signs (convulsions, lethargy, or irritability), or feeding problems (intolerance to feeds or abdominal distension).
- Laboratory test results including hematological parameters (white blood cell count (WBC) <5×109/L or >20×109/L, immature/total neutrophil (I/T) ratio>0.12, platelet count <100,000/μl), and positive blood and CSF cultures.

Then, neonates were classified into four groups:

- Proven sepsis: neonates with positive blood or CSF cultures.
- Probable sepsis: neonates with negative cultures + ≥3 clinical signs.
- Possible sepsis: neonates with negative cultures + two clinical signs.
- Unlikely sepsis: neonates with negative cultures + single clinical signs.

Then, neonates were categorized into the two study groups as follows:

- Infected neonates: included neonates with proven or probable sepsis.
- Uninfected neonates: included neonates with possible or unlikely sepsis.

Blood samples and laboratory tests:

At the time of admission, under aseptic conditions, a venous blood sample was obtained by venipuncture for complete blood count (CBC), blood culture, and infection biomarkers (PGRN, PCT, and CRP). For infection biomarkers analysis, plasma was separated by centrifugation and stored in aliquots at -70°C until analysis. Markers enzyme-linked immunosorbent assay kits were used to determine the serum level of markers after all samples were collected as follows: CRP was detected by CRP–latex slide agglutination (Spinreact, Barcelona, Spain). PCT was measured by SunRed kit, Catalogue No. (201–12–0978), Lot (202104), (Hu Tai Road, Baoshan District, Shanghai, China). PGRN was measured using the SunRed kit, Catalogue No. (201–12–0978), Lot (202104), (Hu Tai Road, Baoshan District, Shanghai, China).

Ethical approval and consent to participate

This study was conducted after obtaining informed consent from the parents/guardians of infants, who were fully informed about all study procedures before enrollment. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Research Ethics Committee at Faculty of Medicine, Benha University (MOHP No.:0018122017/ Certificate No.:1017), Study No.: MS.10.12.2020.

Statistical Analysis:

The sample size was calculated using G power software version 3.1.9.2. The total sample size calculated was 80 neonates (40 infected and 40 uninfected). Alpha and power were adjusted at 0.05 and 0.8, respectively. Data were analyzed using Statistical analysis, by using the social science software program (SPSS), V. 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics were as follows, for categorical variables; number and percentage were used, and for quantitative variables; mean, standard deviation (SD), median with interquartile range (IQR) were used. Data were compared using chi square test ($\chi 2$) and fisher exact test for categorical variables, and Mann-Whitney test for quantitative variables. Receiver operating characteristic (ROC) curves were used to assess the performance of each biomarker by MedCalc 12.7 (MedCalc Software, Ostend, Belgium). Optimal cut-off points were determined and the area under the ROC curve (AUC) was calculated by MedCalc 12.7 (MedCalc Software, Ostend, Belgium). P value was

considered statistically significant if less than 0.05.

Results

This study included 80 full-term neonates; 40 were classified as infected (two with proven sepsis and 38 with probable sepsis), and 40 were classified as uninfected (28 with possible sepsis and 12 with unlikely sepsis)- both groups were matched in gestational age, birth weight, and sex. Vaginal delivery, chorioamnionitis, PROM>18 hours, and maternal fever were significant risk factors for neonatal sepsis (p 0.02, 0.001, <0.001, and <0.001 respectively). Apgar score at one minute was significantly different between the two groups (p <0.001), and feeding intolerance was the commonest presenting symptom among the infected neonates (97.5% versus 64.9% in the uninfected group). Regarding the primary outcome, the infected group had a significantly longer duration of NICU admission and oxygenation (p <0.001, and <0.001, respectively). Regarding the secondary outcome, the survival rate was significantly lower in the infected group compared to the uninfected group, 75% compared to 100%, p <0.001 (Table 1).

On initial laboratory tests, the infected group had significantly higher levels of WBCs, I/T ratio, and a significantly lower platelet count (p 0.002, <0.001, and <0.001, respectively). Comparing the infected group to the uninfected group, the infected group had statistically higher serum levels of CRP, PCT, and PGRN (Figure 1, 2, 3). The serum PGRN level was significantly higher in the infected group (median 89 ng/dl, range 65.3-115.6 ng/dl) than the uninfected group (median 42.95 ng/dl, range 25.3-70.3 ng/dl), p<0.0001. The serum PCT level was significantly higher in the infected group (median 0.668 ng/dl, range 0.421-3.724 ng/dl) than the uninfected group (median 0.443 ng/dl, range 0.056-3.005 ng/dl), p 0.0007.

The serum CRP level was significantly higher in the infected group (median 10 mg/L, range 3-96 mg/L) than the uninfected group (median 6 mg/L, range 4-30 mg/L), p 0.0013 (Table 2).

Using the ROC curve analysis to evaluate the diagnostic usefulness of each infection biomarker, PGRN demonstrated the highest AUC value, as evident on comparing PGRN to PCT and CRP; the AUC values were 0.836 (95% confidence interval (CI) 0.758-0.979, p <0.0001), 0.756 (95%CI 0.647-0.845, p 0.0008), and 0.749 (95%CI 0.639-0.839, p 0.0013), respectively. The cut-off level for each biomarker was determined based on the ROC curve analysis, with a cut-off level of PGRN at 43.2 ng/ml; it had a sensitivity of 97%, specificity of 50%, PPV of 66.1%, and NPV of 95.2%. Combinations of infection biomarkers were tested using ROC curve analysis. Analysis showed that the combination of PGRN and PCT together had a strong association with EONS, as the addition of PGRN to PCT resulted in increased AUC values (from 0.836 to 0.987, p <0.001), with a specificity of 91% and a PPV of 87.7%. Additionally, on combining the three biomarkers, CRP, PCT, and PGRN, the AUC value increased further to 0.996 (p <0.001) (Table 3, Figure 4).

On performing a multivariate logistic regression model, two biomarkers, PGRN and PCT- were found to be significant independent predictors of Sepsis.

Moreover, PCT showed a higher correlation with EONS than PGRN (odds ratio (OR) 5.203, 95% CI 1.072-17.721, p 0.001 for PCT) and (OR 1.818, 95% CI 1.016-3.255, p 0.0001 for PGRN), while CRP, when considering its effect alongside PGRN and PCT, did not provide valuable information in predicting the likelihood of Sepsis (OR 1.018, 95% CI 0.825-1.184, p 0.471). Combinations were also analyzed; the combination of PGRN and PCT showed the highest OR value of 6.479 (95% CI 2.084-24.401, p 0.001). This was followed by the three-biomarker combination, showing an OR value of4.150 (95% CI 2.722- 8.827, p <0.0001)

Table 1: Clinical characteristics of the study groups.

Demographic data		Infected N=40	Uninfected N=40	P value
Demographic Data				
Gestational age (weeks), mean (±SD)		38.25 (±0.93)	38.13 (±0.88)	0.5
Birth weight (kg), mean (±SD)		3.25 (±0.32)	3.27 (±0.41)	0.75
Sex, N (%)	Male	23 (57.5)	24 (60.0)	0.9
	Female	17 (42.5)	16 (40.0)	
Delivery method, N (%)	CS	24 (60.0)	34 (85.0)	0.02*
	NVD	16 (40.0)	6 (15.0)	
Apgar Score, mean (±SD)	at 1minute	5.88 (±1.86)	7.30 (±0.65)	<0.001*
	at 5minutes	8.34 (±0.52)	8.88 (±0.42)	0.07
Maternal risk factors, N (%)				
UTI		16 (40)	10 (25)	0.2
Chorioamnionitis		9 (22.5)	0 (0)	0.001*
PROM>18 h		25 (62.5)	4 (10)	<0.001*
GDM		10 (25)	20 (50)	0.320
Fever		21 (52.5)	0 (0)	<0.001*
Outcome				
Primary, mean (±SD)	**Duration of NICU admission (days)**	12.75 (±6.89)	4.8 (±1.26)	<0.001*
	Duration of oxygenation (days)	7.95 (±4.51)	0.28 (±0.99)	<0.001*
Secondary, N (%)	**Non-survival**	10 (25.0)	0 (0.0)	<0.001*
	Survival	30 (75.0)	40 (100.0)	

Abbreviations, SD: standard deviation; CS: cesarean section; NVD: normal vaginal delivery; UTI: urinary tract infection; PROM: premature rupture of membrane; GDM: gestational diabetes mellites; NICU: neonatal intensive care unit, *statistically significant p value.

Table 2: Laboratory parameters of the study groups.

Laboratory test		Infected N=40		Uninfected N=40		P-value
Complete blood picture, mean (± SD)	Hb (g/dl)	15.23	1.53	14.76	1.37	0.1
	TLC ($\times 10^3/\mu l$)	17.01	5.75	13.71	3.11	0.002*
	Platelet ($\times 10^3/\mu l$)	161.28	109.85	285.71	33.50	<0.001*
	I/T ratio	0.08	0.03	0.06	0.01	<0.001*
Positive Blood Culture, N (%)		4	10%	0	0%	0.1
Sepsis biomarkers, median (IQR)	CRP mg/dl	10	3-96	6	4-30	0.0013*
	PCT ng/dl	0.668	0.421-3.724	0.443	0.056-3.005	0.0007*
	PGRN ng/dl	89	65.3-115.6	42.95	25.3-70.3	<0.0001*

Abbreviations, SD: standard deviation; Hb: hemoglobin; TLC: total leucocytic count; I/T ratio: immature/total neutrophil ratio; IQR: interquartile range; CRP: C-reactive protein; PCT: procalcitonin; PGRN: progranulin, *statistically significant p value.

Table 3: Diagnostic performance of infection biomarkers in diagnosis of EONS

Biomarker	AUC	95%CI		P value	Cut off point	Sensitivity	specificity	PLR	NLR	PPV	NPV
PGRN	0.836	0.758	0.979	<0.0001*	43.2	97	50	1.95	0.05	66.1	95.2
PCT	0.756	0.647	0.845	0.0008*	0.49	62.5	70	2.08	0.67	67.6	65.1
CRP	0.749	0.639	0.839	0.0013*	7	60	70	2	0.57	66.7	63.6
PGRN+ PCT	0.987	0.948	1.000	<0.001*	≥1 positive	97.5	42.5	1.68	0.07	62.7	93.4
					=2 positive	64	91	7.11	0.4	87.7	71.7
PGRN+ CRP	0.898	0.875	0.975	<0.001*	≥1 positive	96.5	41.1	2.8	0.03	62.1	92.2
					=2 positive	57.5	90	5.75	0.47	85.2	67.9
PCT+ CRP	0.763	0.654	0.851	0.00053*	≥1 positive	75	60	1.87	0.42	65.2	70.6
					=2 positive	35	95	7.00	0.68	87.5	59.4
PCT+ CRP+ PGRP	0.996	0.948	1.000	<0.001*	≥1 positive	98	65	1.63	0.085	73.7	97
					=2 positive	75.3	86.8	5.62	0.29	85.1	77.9
					=3 positive	86.8	95.5	19.29	0.14	95	87.1

Abbreviations, CRP: C-reactive protein; PCT: procalcitonin; PGRN: progranulin; AUC: area under the curve; 95% CI: 95% confidence interval; PLR: positive likelihood ratio; NLR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value, *statistically significant p value.

Table 4: Multivariate logistic regression models to assess the ability of infection biomarkers to predict EONS

Biomarker	p-value	Odds	95% CI	
PGRN	0.0001*	1.818	1.016	3.255
PCT	0.001*	5.203	1.072	17.721
CRP	0.471	1.018	0.825	1.184
PGRN+PCT	0.001*	6.479	2.084	24.401
PGRN+CRP	0.033*	2.561	0.848	4.789
PCT+CRP	0.498	0.662	0.231	1.837
PCT+CRP+PGRP	<0.0001*	4.150	2.722	8.827

Abbreviations, CRP: C-reactive protein; PCT: procalcitonin; PGRN: progranulin; 95% CI: 95% confidence interval, *statistically significant p value.

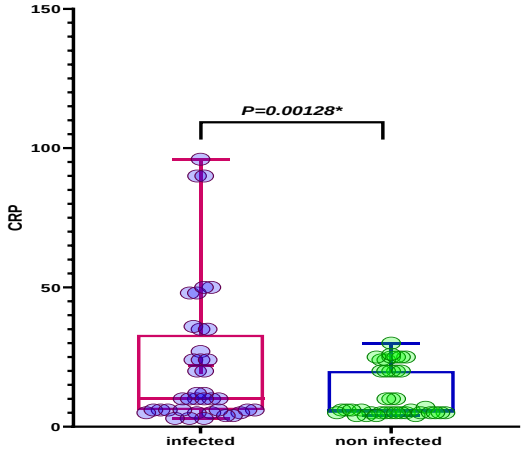

Figure 1: CRP serum concentration in the study groups

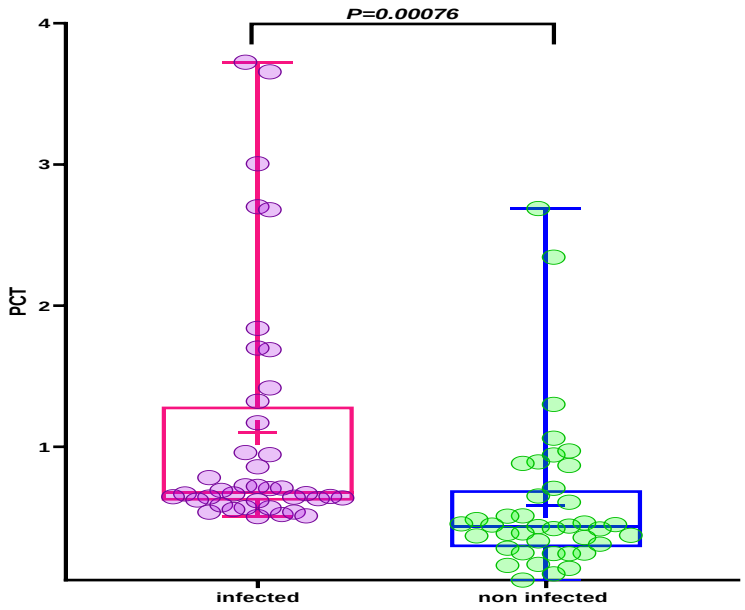

Figure 2: Procalcitonin serum concentration in the study groups

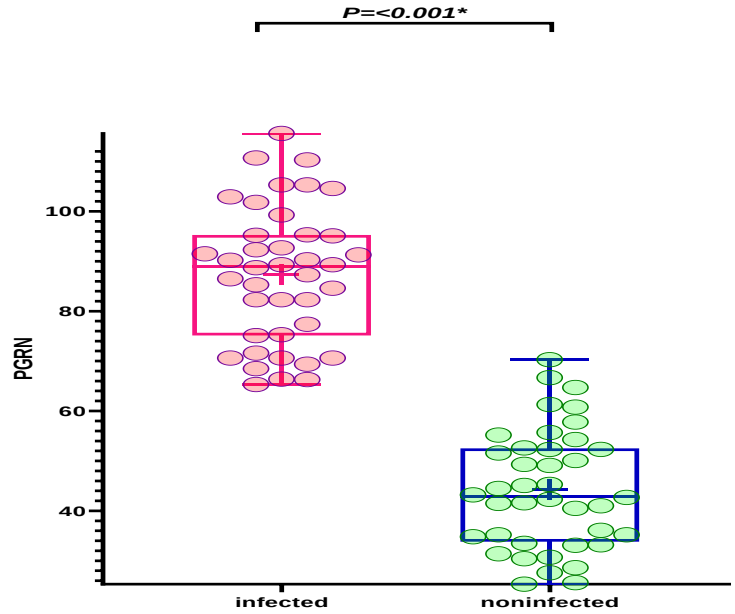

Figure 3: Progranulin serum concentration in the study groups

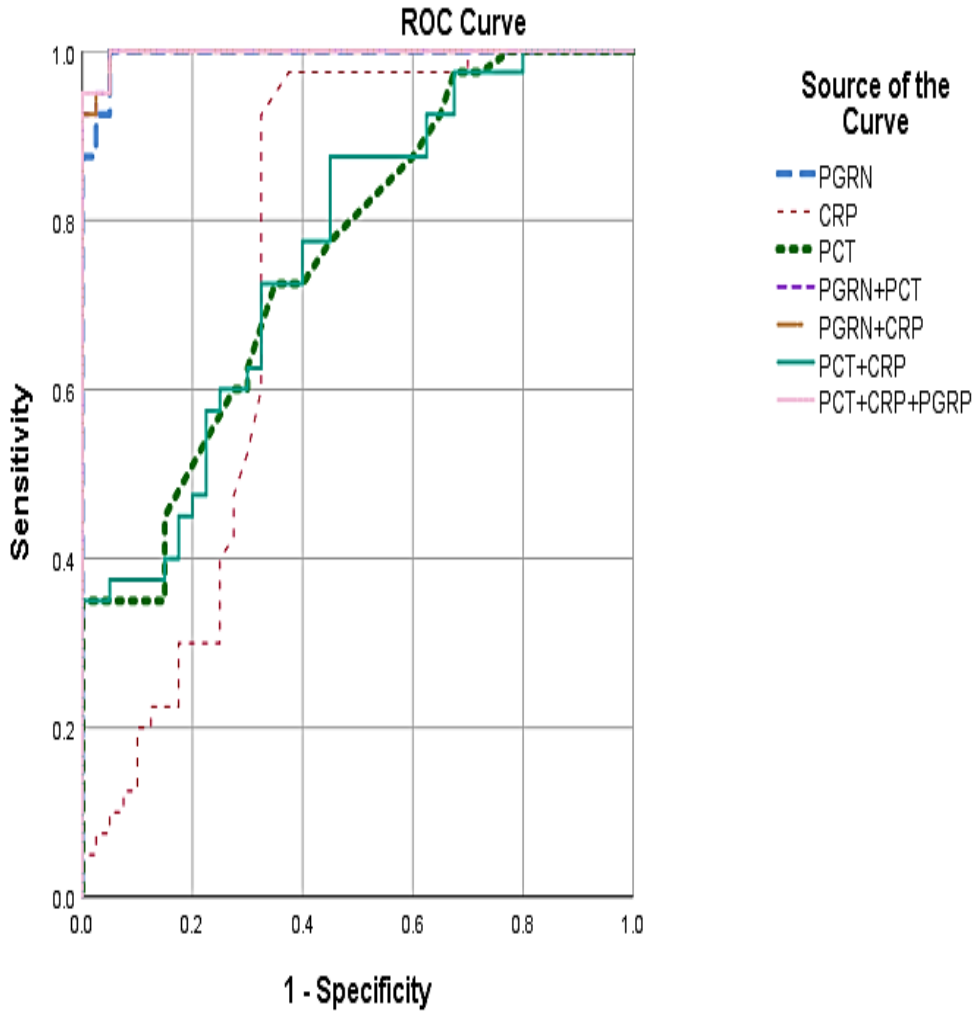

Figure 4: ROC curve analysis of performance of sepsis biomarkers in detection of EONS

Discussion

This prospective case-control study was conducted on 80 full-term neonates with suspected EONS. Our results found that PGRN was the most predictive inflammatory biomarker of EONS, followed by PCT. The combination of both and the combination of the three biomarkers- PGRN, PCT, and CRP- added to the predictive value of the PGRN.

The most reliable method for diagnosing neonatal sepsis is still blood culture. Nonetheless, a variety of factors contribute to its low positive rate [8]. The diagnostic yield of neonatal sepsis has improved with the use of inflammatory biomarkers that can predict EONS; however, the optimal biomarker with a high sensitivity and specificity is still lacking [4].

In the current study, CRP was significantly higher in the infected group than in the uninfected group, as previously reported [4, 9,11]. It had a sensitivity of 60% and a specificity of 70% in this study. While other previous studies indicated that CRP's sensitivity and/or specificity were sufficient for detecting EONS, others revealed that CRP's accuracy was appalling [4,5,11]. Due to its various limitations; short half-life, and delayed response following infection, a single test

of CR-P has a limited sensitivity for diagnosing EONS [11-14].

In this study, the infected group had significantly higher serum levels of PCT compared to the uninfected group, as previously mentioned in other studies [4, 15]. In this study, PCT demonstrated a 62.5% sensitivity and a 70% specificity. Results from previous studies showed that the sensitivity varied from 58.4 to 72.4%, and the specificity ranged from 71.1 to 81.2% [4, 12]. PCT was considered to be a more promising biomarker than CRP in the systematic review done by Gopal et al. because of its higher sensitivity, specificity, and accuracy despite being more expensive [16]. However, because of the typical rise in its level in the first few days following delivery, Yang et al. claimed that its diagnostic accuracy in LONS is more profound than in EONS [12]. Both CRP and PCT, who are considered the conventional sepsis biomarkers that are most commonly used in most laboratories for prediction of EONS, could be influenced by various non-infectious perinatal variables, resulting in limited specificity, and their levels varies with different gestational and postnatal ages [17]. Furthermore, it has been recommended to have serial measurements of CRP or PCT to enhance their accuracy [5, 16].

In the present study, the infected group had statistically higher serum levels of PGRN compared to the uninfected group; our results were in agreement with other studies [4, 12, 18, 19]. The cut-off point for PGRN was defined by ROC curve analysis as 43.2ng/ml.

The PGRN cut-off point was slightly lower in the Rao et al. study**,** at >37.89ng/ml [4]. The authors concluded that there is no need to adjust the optimal PGRN cut-off value within the first 72 hours of life to diagnose EONS. PGRN was shown to have a steady level during the first few days of life in the systematic review conducted by Gopal et al., [16].

In this study, using the ROC curve analysis to evaluate how well test biomarkers performed in the prediction of EONS. Our results indicated that elevated serum PGRN level was strongly correlated with EONS, the AUC for PGRN was 0.836, with a good sensitivity of 97%, and a high NPV of 95.2%, representing a promising biomarker in EONS prediction. A multivariate logistic regression model was conducted to identify independent predictors of EONS among the tested biomarkers; PGRN and PCT were statistically independent predictors of sepsis, and PCT exhibited even higher correlation than PGRN (OR 5.203, p 0.0·1 for PCT) and (OR 1.818, p 0.00·1 for PGRN). In contrast, CRP was not significant (OR 1.018, p 0.471).

This has been illustrated previously in Rao et al. study, as PGRN was shown to be the best predictive biomarker in EONS, independent of age-adjusted PCT and CRP, and to have a substantial correlation with bloodstream infection [4].

The AUC for PGRN to detect infection was found to be higher than that for age-adjusted PCT, which was in turn higher than that for CRP; AUC values were as follows: 0.786, 0.699 and 0.673, respectively. PGRN diagnostic sensitivity and NPV were high at 94.34% and 91.7%, respectively. Moreover, using the multivariate logistic regression model, only PGRN and age-adjusted PCT qualified for the model, while CRP was insignificant**.**

In Yang et al. study**,** PGRN appears to be as effective as, if not better than, the other two conventional markers- PCT and CRP- in predicting EONS at the early stage of the disease with an AUC of 0.760, 0.717, and 0.714, respectively [12]. PGRN demonstrated a high specificity of 80.3%, with a NPV of 67.6%, however, its sensitivity was unsatisfactory at 67.1%, but with a high PPV at 76.5%. Applying stepwise multivariate logistic regression analysis, PGRN, interleukin (IL) -33, and PCT- were identified as independent predictive factors for EONS, with PCT

showing the highest correlation with EONS (OR 4.557, p <0.001).

In our study, PCT had a better diagnostic performance than CRP. Both showed reasonable specificity but low sensitivity. Rao et al. also stated that PCT was more predictive for EONS than CRP, both had high specificity (81.25% and 82.81%, respectively) but low sensitivity (58.49% and 49.06%, respectively) [4]. Similarly, Yang et al. reported that the conventional EONS markers PCT and CRP showed a sensitivity of 72.4% and 73.7%, and a specificity of 71.1% and 57.9%, respectively [12].

Generally, PCT demonstrated a better prediction for EONS compared to CRP. It rises rapidly as a consequence of bacterial or fungal infections. PCT also drops appropriately in response to treatment. It can also discriminate a truly positive blood culture from a contaminated one [5, 16].

We experimented with combinations, combining two of these biomarkers. When PCT was added to PGRN, this represented the best combination of two biomarkers, as the AUC was increased to 0.987, followed by combined PGRN and CRP. Moreover, adding PGRN to PCT increased the predictive value of both as the odds ratio increased, OR 6.479, p 0.001. Our results were comparable to previous studies [4, 12].

Combining the three biomarkers, PGRN, PCT and CRP- the AUC was the highest at 0.996. Combined biomarkers had a sensitivity of 86.6%, with the highest PPV of 95% and specificity of 95.5%. This constitutes the best indicator test for EONS with OR value of 4.150, p <0.0001. Similar results were found in previous studies [4, 12].

Our study has some limitations- though our sample size was satisfactory based on sample size calculation- further larger studies are required to confirm the findings. There was a single measurement of the inflammatory biomarkers from each patient. Serial measurements may add further value to the predictive and prognostic ability of such biomarkers.

Conclusion

In conclusion, PGRN is a promising biomarker for prompt and accurate diagnosis of EONS. Combining PGRN with PCT- showed the most predictive biomarker combination for prediction of EONS.

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