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Presepsin as an Early Predictor of Neonatal Sepsis

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Abstract

Background

Pathogens stimulate presepsin (P-SEP) shedding from immune cells such as macrophages, monocytes, and neutrophils. Although its function is still unclear, P-SEP is believed to interact with B and T cells to modulate specific immune responses. We aimed to evaluate the accuracy of P-SEP as a novel biomarker for the diagnosis of bacterial infection and correlate its level with blood culture, C-reactive protein (CRP), and procalcitonin (PCT) levels.

Materials and Methods: This is a prospective comparative study conducted at Minia University Hospital, Egypt, including eighty neonates. They were divided into two groups: Group *I*: Twenty full term neonates; infants ≥ 37 weeks. Group II: Sixty preterm neonates <37 weeks, it was classified into three subgroups; *Group II A:* 20 Low birth weight neonates: 1501- 2500 gr, *Group II B:* 20 Very low birth weight neonates: 1001-1500 gr, *Group II C:* 20 Extremely low birth weight neonates: 500-1000 gr. Cord presepsin (presepsin 1) was measured at birth. CBC, CRP, Blood culture, Procalcitonin and presepsin 2 were measured after the onset of sepsis.

Results: No significant difference in levels of P-SEP 1 was found between the two groups. P-SEP 2 levels were higher in sepsis group than in non-sepsis group. Presepsin showed more diagnostic accuracy than PCT in diagnosis of sepsis. The best cut-off value for Presepsin was 485 pg/ml, with 97.8% sensitivity, and 94.1% specificity.

Conclusion

Presepsin as a biomarker is not only suitable for early diagnosis of sepsis but it is also more accurate than both PCT and CRP.

Key Words: Prespsin, Procalcitonin, Sepsis, Neonates.

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1- INTRODUCTION

Neonatal sepsis is the most common cause of morbidity and mortality during the neonatal period (1, 2). Neonatal sepsis is classified as early-onset sepsis (EOS; ≤72 hours after birth), and late-onset sepsis (LOS; >72 hours after birth**)** (3). Neonatal sepsis is defined as the presence of a positive blood culture constituting the "gold standard" for the presence of neonatal sepsis (4). Neonatal sepsis can be presented with subtle signs, but it can rapidly progress into multisystem organ failure carrying high mortality and morbidity rates (5). When blood cultures are negative while the infants manifest signs of infection, this may be considered "clinical" sepsis. Interpretation of CRP in the diagnosis of EOS may be hindered by several non-infectious causes that influence CRP during the first days of life (6, 7). Procalcitonin (PCT) is the precursor of calcitonin, normally synthesized in the C-cells of the thyroid gland. Systemic inflammation and sepsis induce PCT production by various cells; hepatocytes, nephrons and monocytes (8). Presepsin (P-SEP) is a truncated variant of soluble CD14. Pathogens stimulate P-SEP shedding from the surface of immune cells such as macrophages, monocytes, and neutrophils. Although its function is still unclear, P-SEP is believed to interact with B and T cells to modulate specific immune responses (9). The aim of our study is to evaluate the accuracy of presepsin (P-SEP) as a novel biomarker for the diagnosis of bacterial infection and correlate its level with blood culture, C-reactive protein (CRP), and procalcitonin (PCT) levels.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a prospective comparative study conducted on neonates in the neonatal intensive care unit (NICU), Minia Children and Maternity University Hospital, from July 2018 to June 2019. This study included eighty neonates admitted to NICU. They were divided into two major groups:

Group I*:* included twenty full term neonates; infants who were born after 37 weeks of gestation.

Group II: included sixty preterm neonates; infants who were (<37 weeks of gestation), they were further classified into three subgroups:

- *Group II A:* Twenty low birth weight neonates: 1500- 2500 gr.
- *Group II B:* Twenty very low birth weight neonates: 1000-1500 gr.
- *Group II C:* Twenty extremely low birth weight neonates: 500-1000 gr (10).

All neonates were subjected to the following: history taking; obstetric history (previous sibling death or previous admission to NICU), prenatal history (diabetes mellitus, maternal fever, maternal antibiotic and maternal urinary tract infection). Natal history (premature rupture of membranes (PROM) >18 hours, maternal fever >38 ^{0}C, and prolonged second stage of labor) (11). Postnatal history (prolonged resuscitation, respiratory distress, cyanosis, fever and jaundice), and Present history (common symptoms of sepsis).

2-2. Inclusion and exclusion criteria

Infants with maternal diseases, congenital anomalies, or features suggestive of metabolic disease were excluded from our study, otherwise, all other neonates were included in our study.

2-3. Clinical examination

Weight, length and head circumference, gestational age according to new Ballard Score, vital signs (pulse, temperature, blood pressure and respiratory rate), neonatal reflexes. All neonates were followed up with complete clinical examination to detect clinical signs of

sepsis (temperature instability, respiratory, circulatory, GIT or neurological dysfunction) (3, 12). Once clinical signs of sepsis were detected, laboratory investigations (CBC, CRP, Blood culture, PCT and Serum human presepsin) were drawn.

2-4. Laboratory investigations

3 ml of venous blood was collected under complete aseptic conditions; 2 ml in EDTA tubes tested by sysmex KX-2IN automated hematology analyzer for Complete blood count study and 1 ml for C-reactive protein estimation by latex agglutination assay using the AVITEX CRP kit (13). Another one ml of venous blood was collected for the blood culture. Examination of the blood culture bottle was done every day for detection of any growth and any bacterial growth was identified by Gram-stained film for bacterial morphology. Bacterial subculture was done on MacConkey agar plate, blood agar plate and Sabouraud Dextrose Agar. Bacteria were identified by biochemical reaction (14).

2-5. Serum human presepsin assay

Two samples were collected for assessment of human presepsin: a) First sample, two ml were collected from cord blood at birth as a basal level. b) Second sample, another two ml of venous blood were collected after the onset sepsis; either clinically or by laboratory investigations. Both samples were collected in plain tubes and incubated for 10-20 minutes at room temperature, centrifuged (at 2000-3000 RPM) for 20 minutes. This kit uses enzyme-linked immune sorbent assay (ELISA) (15).

2-6. Ethical consideration

Our study was approved by the local ethics committee. Informed consents were obtained from families of the neonates included in the study.

2-7. Statistical analysis

The description of data was in the form of mean (±) SD for quantitative data, and frequency and proportion for qualitative data. SPSS software version 16.0 was used for statistical analysis. Student-t test was used for comparison between the two groups as regards normally distributed (parametric) quantitative data. Mann-Whitney test (Z) was used for the comparison between two groups as regards non-parametric quantitative data. Chi-Square Test (X2) was used for comparison between two groups as regards qualitative data. Pearson correlation coefficient test (r): was used to test a positive or negative relationship between two variables. A receiver operating characteristic (ROC) analysis was performed to define a cutoff value of serum presepsin for the risk of neonatal sepsis and the associated specificity and sensitivity levels. Results were considered significant if $P \leq 0.05$, highly significant if $P \leq 0.01$.

3- RESULTS

This study included 80 neonates divided into two major groups:

- **Group I**: 20 full term neonates; (37≥ weeks) (10 males and 10 females)**,** 6 neonates (30%) of them developed sepsis (2 males and 4 females), (4 EOS and 2 LOS).
- **Group II**: 60 preterm neonates; (<37 weeks), they were further classified into three subgroups:

Group II A: 20 low birth weight neonates (LBW): 1501- 2500 gr, (10 males and 10 females) 8 neonates (40%) of them developed sepsis (5 males and 3 females), (5 EOS and 3 LOS).

Group II B: 20 very low birth weight neonates (VLBW): 1001-1500 gr (11 males and 9 females) 13 neonates (65%) of them developed sepsis (6 males and 7 females), (9 EOS and 4 LOS).

Group II C: 20 extremely low birth weight neonates (ELBW): 500-1000 gr (11

males and 9 females) 19 neonates (95%) of them developed sepsis (10 males and 9 females), (13 EOS and 6 LOS).

Demographic data, risk factors and outcome of the studied groups are shown in **(Table.1)**. Results of blood culture were positive in 100% of septic neonates. As regards the causative organisms in sepsis group, they included: Methicillin resistant staphylococcus aureus (MRSA) (28%), group B streptococcus (GBS) (18%), Escherichia coli (15%), Pseudomonus (11%), Streptococcus agalactiae (9%), Klebsiella Pn (7%), Klebsiella oxytoca (4%), and Enterococus Fecalis (4%). Sepsis group expressed general features of sepsis, e.g., (skin mottling, sclerema, edema, temperature instability and petechiae), also they expressed specific features of sepsis; neurological manifestations (weak reflexes, lethargy, irritability and convulsions), respiratory manifestations (RD and apnea), cardiovascular manifestations (tachycardia, hypotension and HR instability), and GIT manifestations (jaundice, feeding intolerance, vomiting, abdominal distension and hepatomegaly). Comparison between the studied groups revealed that, the lower the weight of the neonate the more the affected levels of Hb, PLT, TLC and CRP (P=0.002, 0.010, 0.035 and 0.005, respectively) **(Table.2)**. Regarding procalcitonin levels, the lower the weight of the neonate the higher the level of PCT (P=0.004) **(Table.2)**. Regarding P-SEP 1, there was no statistical difference between the studied groups (P=0.126), while results of P-SEP 2 revealed that the lower the weight of the neonate the higher the presepsin levels (P=0.002) **(Table.2)**.

Table-1: Comparison between the studied groups as regards demographic data, risk factors and outcome.

Variables	(Group I) Full term, (n=20)	(Group II A) LBW, (n=20)	(Group II B) VLBW, (n=20)	(Group II C) ELBW, (n=20)	P- value
Gender					
Male	10 (50%)	10 (50%)	11 (55%)	11 (55%)	0.978
Female	10 (50%)	10 (50%)	9 (45%)	9 (45%)	
Mode of delivery					
NVD	8 (40%)	9 (45%)	8 (40%)	10 (50%)	0.906
CS	12 (60%)	11 (55%)	12 (60%)	10 (50%)	
Gestational age, (week)	38.7±1.26	35.2±1.36	32.80±1.40	28.80±1.15	<0.001*
Birth weight (gm)	2821.5±621.82	1993.5±272.67	1298.50±100.49	878.00±77.16	<0.001*
Onset of sepsis	5.83±3.31	4.75±2.82	2.92±1.80	2.47±1.02	0.002*
Sepsis					
Yes	6 (30%) 2M 4F	8 (40%) 5M 3F	13 (65%) 6M 7F	19 (95%) 10M 9F	<0.001*
No	14 (70%)	12 (60%)	7 (35%)	1 (5%)	
Type of sepsis					
EOS	4 (66.7%)	5 (62.5%)	10 (76.9%)	17 (89.5%)	0.303
LOS	2 (33.3%)	3 (37.5%)	3 (23.1%)	2 (10.5%)	
Outcome					
Survived	15 (75%)	12 (60%)	8 (40%)	6 (30%)	0.021*
Died	5 (25%)	8 (40%)	12 (60%)	14 (70%)	
Risk factors					
No	15 (75%)	11 (55%)	10 (50%)	2 (10%)	0.001*
Maternal fever	1 (5%)	0 (0%)	2 (15%)	2 (10%)	
Mechanical ventilation	0 (0%)	3 (15%)	1 (5%)	4 (20%)	
PROM	0 (0%)	0 (0%)	0 (0%)	3 (15%)	

NVD: Normal vaginal delivery, CS: Caesarean section, EOS: Early-onset sepsis, LOS: Late-onset sepsis, LBW: Low birth weight, VLBW: Very low birth weight, ELBW: Extremely low birth weight, PROM: Premature Rupture of Membrane.

Table-2: Comparison between the studied groups regarding laboratory data.

Parameters	(Group I) Full term, (n=20)	(Group II A) LBW, (n=20)	(Group II B) VLBW, (n=20)	(Group II C) ELBW, (n=20)	P- value
Hb (gm/dl) Mean ± SD	13.58±2.94	13.03±3.05	12.45±3.14	10.37±1.29	0.002*
PLT (x10^3/mm3) Mean ± SD	199.55±151.32	196.50±159.94	152.55±121.49	68.80±87.24	0.010*
TLC (x10^3/mm3) Mean ± SD	15.31±10.74	17.79±12.93	19.12±11.59	25.90±11.21	0.035*
CRP (ng/ml) Mean ± SD	16.8±25.1	24.4±21.3	39.9±45.8	48.6±41.3	0.005*
PCT (microg/L) Median (IQR)	0.7 (0.06-2.54)	1.19 (0.1-2.6)	1.49 (0.13-3.9)	2.9 (1.46-5)	0.004*
P-SEP 1 (pg/ml) Median (IQR)	120 (90-140)	110 (80-150)	140 (120-170)	135 (90-170)	0.126
P-SEP 2 (pg/ml) Median (IQR)	315 (120-495)	390 (120-600)	520 (135-750)	650 (490-1030)	0.002*

*Significant difference. Hb: Hemoglobin, PLT: Platelet count, TLC: Total Leukocyte count, CRP: C-reactive protein, PCT: Procalcitonin, P-SEP 1: Presepsin in cord blood, P-SEP 2: Presepsin after onset of sepsis, IQR: Inter quartile range, SD: Standard deviation.

TLC, CRP and procalcitonin levels were higher in the sepsis group (26.88±9.35, 49.30±39.13 and 3.79±2.53 versus 9.59±7.29 3.71±3.91, and 0.16±0.25 respectively), P<0.001; while Hb and PLT levels were lower in the sepsis group (10.62±1.97 and 69.04±50.90 versus 14.70±2.33 and 266.82±143.45, respectively), P<0.01. Results showed significantly higher levels of toxic granulations and shift to the left in sepsis groups (**Table.3)**. There was no statistically significant difference between the 2 groups regarding the cord presepsin (P-SEP 1) levels, while there was a significant increase in P-SEP 2 levels in the sepsis group in comparison with the non-sepsis group [650(490-860), and 120(100-170), respectively], P<0.001 **(Table.3)**.

Table-3: Comparison between sepsis and non-sepsis groups as regards laboratory data.

Parameters		Sepsis, (n=46)	Non sepsis (n=34)	P-value
Hb, Mean ± SD (gm/dl)		10.62±1.97	14.70±2.33	<0.001*
PLT, (x10^3/mm3)		69.04±50.90	266.82±143.45	<0.001*
TLC, (x10^3/mm3)		26.88±9.35	9.59±7.29	<0.001*
Shift to left	Yes	41 (89.1%)	0 (0%)	<0.001*
	No	5 (10.9%)	34 (100%)	
Toxic granulations	Yes	16 (34.8%)	0 (0%)	<0.001*
	No	30 (65.2%)	34 (100%)	
CRP, Mean ± SD (ng/ml)		49.30±39.13	3.71±3.91	<0.001*
Procalcitonin, Mean ± SD (microg/L)		3.79±2.53	0.16±0.25	<0.001*
P-SEP 1, (pg/ml) Median (IQR)		125 (80-170)	120 (100-150)	0.674
P-SEP 2, (pg/ml) Median (IQR)		650 (490-860)	120 (100-170)	<0.001*

SD: Standard deviation, Hb: Hemoglobin, TLC: Telephone-Linked Communications, CRP: C-reactive protein, P-SEP 1: Presepsin in cord blood, P-SEP 2: Presepsin after onset of sepsis, IQR: Inter quartile range.

ROC Curve has revealed that the cut-off point for P-SEP 2 was >485pg/ml with 97.8% sensitivity and 94.1% specificity (P<0.001) **(Table.4)**. ROC curve has revealed that the cut-off point for PCT was <0.7 microg/L with 93.5% sensitivity and 79.4% specificity (P<0.001) **(Table.5)**. There were positive correlations between P-SEP 2 and both PCT and CRP (r=0.655 and r=0.734, P<0.001, respectively), while there was a negative correlation between P-SEP2 and PLT (r = -0.459) P<0.001 **(Table.6)**. Finally, our results revealed a positive correlation between PCT and CRP (r=0.815) P<0.001, but a negative correlation between PCT and PLT (r = -0.549, P<0.001) **(Table.7)**.

Table-4: Diagnostic accuracy of serum P-SEP 2.

Parameter	AUC	P-value	Cut-off point	Sensitivity	Specificity
P-SEP 2 (pg/ml)	0.97	<0.001*	>485	97.8%	94.1%

P-SEP 2: Presepsin after onset of sepsis.

Table-5: Diagnostic accuracy of serum PCT.

Parameter	AUC	P-value	Cut-off point	Sensitivity	Specificity
PCT (microg/L)	0.95	<0.001*	>0.7	93.5%	79.4%

PCT: Procalcitonin.

Table-6: Correlation of P-SEP2 with PLT, CRP and PCT among sepsis group.

Parameter		R	P-value
P-SEP 2 (pg/ml)	PCT (microg/L)	0.655	<0.001*
	CRP (ng/ml)	0.734	<0.001*
	PLT (x103/mm3)	-0.549	<0.001*

P-SEP 2: Presepsin after onset of sepsis, PCT: Procalcitonin, CRP: C-reactive protein, PLT: Platelet.

Table-7: Correlation of PCT with CRP and PLT among sepsis group.

Parameter		R	P-value
PCT (microg/L)	CRP (ng/ml)	0.815	<0.001
	PLT (x103/mm3)	-0.549	<0.001

PCT: Procalcitonin, CRP: C-reactive protein, PLT: Platelet.

4- DISCUSSION

Despite the improved neonatal care over the past decades, infections remain common and life-threatening in neonates admitted to the neonatal intensive care unit (NICU) (16). Early recognition and diagnosis of neonatal sepsis are not easy because of variable and non-specific clinical presentations (17). It is important to make an early diagnosis of sepsis as a prompt introduction of antimicrobial therapy improves outcomes (18). Diagnosis and management of sepsis are considered a great challenge facing neonatologists; while the clinical diagnosis is difficult due to nonspecific signs and symptoms, and laboratory diagnosis is

time consuming, initiation of empirical antibiotic therapy is necessary. Increased multidrug-resistant organisms make the treatment hard and delay its effect (19). In this study, we evaluated the role and accuracy of presepsin (P-SEP) as a novel biomarker for sepsis and correlate its level with blood culture, CRP and procalcitonin (PCT) levels. This study included 80 neonates, 20 full-term neonates (group I), and 60 preterm neonates (group II) which were further subdivided into three equal subgroups with each of them including 20 neonates according to their birth weight; LBW group (group II A), VLBW group (group II B) and ELBW group (group II C). Cord blood samples were withdrawn from all 80 neonates for detection of basal serum presepsin levels (P-SEP 1).

All 80 neonates were followed- up for the development of sepsis. According to both clinical manifestations and lab results, all included neonates were classified into sepsis and non-sepsis groups. Once sepsis developed, another blood sample was withdrawn for detection of serum presepsin levels (P-SEP 2). According to the demographic data, this study included 80 neonates (42 males and 38 females), 46 (54.3%) of these neonates developed sepsis, with mean gestational age (33.87±1.3 weeks), and birth weight (1,747.5±267.5 gr). Thirty-six neonates (78.3%) of the sepsis group developed EOS, while10 neonates (21.7%) developed LOS. In accordance with our results, Miyosawa et al. revealed that there were insignificant differences between the study and control groups regarding gender, gestational age and birth weight (20).

Our patients were diagnosed as sepsis depending on the clinical findings of neonatal sepsis including general signs (temperature instability, skin mottling, sclerema and edema), neurological manifestations (poor reflexes, lethargy, irritability and convulsions), respiratory and cardiovascular manifestations respiratory distress, apnea, tachycardia and hypotension), and gastrointestinal manifestations (feeding intolerance, vomiting, hepatomegaly and jaundice). These data agree with Aliefendioglu et al. (21), and Morven (22) who described them as main clinical manifestations of neonatal sepsis. In our study, CRP levels were significantly higher in septic group than in non-sepsis group (49.30 ± 39.13 mg/dL, and 3.71 ± 3.91 mg/dL, respectively, P <0.001), this is in agreement with Adu (23) who found that CRP levels in septic neonates were significantly higher than in control group (22.18±8.1 mg/dL and 13.08 mg/dL respectively) (p <0.001).

Miyosawa et al. has also found that there were significant differences in CRP levels between study and control groups (39.9±8 mg/dL and 1.1±1.7 mg/dL, respectively) (p= 0.01) (20). CRP has been shown to be the best diagnostic marker of neonatal sepsis, with high sensitivity and specificity, it can be widely used to diagnose sepsis and monitor the response to antibiotic treatment in newborns, but it has low sensitivity during the early phases of infection, as time is needed for its release; its peak values are reached 2 to 3 days after the infective stimulus (7).

Interpretation of CRP in the diagnosis of EOS may be hindered by several non-infectious conditions that influence CRP during the first days after birth (24). In our study, the causative organisms in sepsis group included MRSA (28%), GBS (18%), E.Coli (15%), Pseudomonus (11%), Streptococcus agalactiae (9%), Klebsiella Pn (7%), Klebsiella oxytoca (4%) and Enterococus Fecalis (4%). Near to our results, Adu (2017) stated that Staphylococcus spp. were the major causative agents of bacterial sepsis among the study population, accounting for about 57% of blood culture results (23), while Singh et al. stated that Klebsiella pneumoniae was the most common (44.8%), Pseudomonas spp. was the

second most common (24.8%), and E. coli was the third most common isolated micro-organism (13.3%) (25). Current study revealed that Hb levels were lower, while TLC levels were higher in sepsis group. Results showed significantly higher levels of toxic granulations and shift to left in sepsis groups. Similarly, Adu has found that the mean Hb level was significantly lower in cases than in controls (p=0.0062), while TLC was significantly higher in sepsis group (p<0.001) (23).

Also, a review performed by Bhat et al. based on 17 studies, showed that a TLC count < 5000 cells/mm^3 or > 20.000 cells/mm^3 suggests EOS with sensitivity that ranges between 15.6 and 81%. Leukopenia was found to be a better predictor for neonatal sepsis compared to leukocytosis and is more common in infections with gram negative germs (26). TLC increases in severe neonatal infections (both mature and immature cells), secondary to the release of growth factors and cytokine that stimulate the bone marrow production (27). Regarding PLT levels, our study revealed that PLT levels were lower in sepsis than in non-sepsis group. Similarly, Singh et al.'s study showed that thrombocytopenia was present in 100 neonates out of 105 culture positive neonates (95.2%) (25).

Thrombocytopenia is due to increased destruction (secondary to infection), failed platelet production (secondary to reduced megakaryocytes), or damaging effect of endotoxins which is frequently associated with neonatal sepsis but is usually a late sign of infection. This indicates a poor prognosis and cannot be used to guide antibiotic therapy since thrombocytopenia may persist even weeks after an infectious episode (27). In our study, comparison between sepsis and non- sepsis groups revealed significant differences in procalcitonin (PCT) levels; being higher in sepsis group than in non-sepsis group (p<0.001); cut-off value on ROC curve was (<0.7 microg/L) with 85.16% specificity and 60.4 % sensitivity. This comes in agreement with Adu who found the same results with 86.96% specificity, and 57.14% sensitivity for PCT (23). PCT is a better predictive marker for neonatal sepsis than CRP within the first 12 hours of life (28). Poggi et al. stated that PCT shows earlier peak values than CRP, occurring 10 to 12 hours after infection, and has recently been demonstrated to be accurate for the diagnosis of nosocomial sepsis in VLBW neonates (7, 29). In our study, there was no difference between sepsis and non-sepsis groups regarding P-SEP 1 levels. In contrast, P-SEP 2 levels were higher in sepsis group than in non-sepsis group (650 pg/ml and 120 pg/ml, respectively) (p<0.001). Similarly, Adu found that serum presepsin level was significantly higher in septic cases than in healthy ones; 25.46 (19.20-66.23) pg/ml and 18.09 (13.82-20.98) pg/ml, respectively, (p<0.001) (23).

Also, Miyosawa et al., reported the same results (20). Comparison between full-term and preterm groups, revealed significant increase of serum P-SEP 2 in preterm groups; being lowest in full-term group (295±301.30 pg/mL), and highest in ELBW group (846.50±367.41 pg/mL), so the lower the weight of the neonate the more elevated the levels of P-SEP 2. In accordance with our results, Pugni et al. evaluated 684 neonates (484 full term and 200 preterm); in full term neonates, median P-SEP was 603.5 pg/mL while in preterm infants, median P-SEP was higher at 620 pg/mL (30).

On the other hand, Mussap et al. evaluated 26 non-septic preterm newborns having gestational age between 26 and 36 weeks with various severe diseases, there was no correlation between gestational age and P-SEP (31). In our study, a positive correlation was observed between serum P-SEP 2, PCT and CRP levels, this is in agreement with Miyosawa et al. who

found the same results (20). In our study, presepsin showed more diagnostic accuracy than PCT in diagnosis of sepsis, the AUC for P-SEP 2 was 0.97 with cut-off value by ROC curve (485 pg/ml), 97.8% sensitivity, and 94.1% specificity, while the AUC for PCT was 0.95 with cut-off value by ROC curve (<0.7 microg/L) with 85.16% specificity and 60.4 % sensitivity. This is in agreement with studies done by Topucuoglu et al., and Montaldo et al., who found the same results (32, 33). On the other hand, Adu stated that PCT showed a better accuracy for blood culture diagnosed sepsis followed by CRP and presepsin, respectively (7, 23). Our study revealed that serum P-SEP 2 had high diagnostic accuracy to detect sepsis; (AUC= 0.97), cut-off value on ROC curve (485 pg/ml) with 97.8% sensitivity, and 94.1% specificity ($p<0.001$). Similarly, several reports demonstrated the efficacy of P-SEP for diagnosis of both LOS and EOS; Zou et al, 2014 reported that 399 pg/ml of presepsin as a cut-off value, the sensitivity of diagnosis of sepsis was 80.3% and the specificity was 78.5% (34).

Also, Topcuoglu et al. reported that P-SEP was significantly elevated in preterm neonates with LOS and that cut-off value for P-SEP was 800.5 pg/mL, with 67% sensitivity and 100% specificity (32). Then Montaldo et al. evaluated 32 preterm newborns with EOS and compared them with non-sepsis preterm newborns: the AUC for P-SEP was 0.97 and the cut-off value was 788 pg/mL, with 93% sensitivity and 100% specificity (33). Miyosawa et al. found that 795 pg/mL was established as the cut-off for P-SEP, with 85% sensitivity and 89% specificity (20).

4-1. Study Limitations

Limitations of our study are the small size of our study population. Follow up samples for presepsin should be considered.

5- CONCLUSION

Based on the results, Presepsin as a biomarker is not only suitable for early diagnosis of sepsis, but it is also more accurate than both PCT and CRP.

6- ABBREVIATIONS

P-SEP: Presepsin.
CRP: C Reactive Protein.
PCT: Procalcitonin.
CBC: Complete Blood Count.
P-SEP 1: Cord Blood Presepsin.
P-SEP 2: Presepsin after the onset of sepsis.
EOS: Early Onset Sepsis.
LOS: Late Onset Sepsis.
CD14: Cluster of Differentiation 14.
B- Cells: B Lymphocytes.
T- Cells: T Lymphocytes.
NICU: Neonatal Intensive Care Unit.
PROM: Premature Rupture of Membrane.
GIT: Gastrointestinal Tract.
ELISA: Enzyme Linked Immune Sorbent Assay.
RD: Respiratory Distress.
HR: Heart Rate.
Hb: Hemoglobin.
PLT: Platelets.
TLC: Total Leucocytic Count.
ROC Curve: receiver operating characteristic curve.
LBW: Low Birth Weight.
VLBW: Very Low Birth Weight.
ELBW: Extremely Low Birth Weight.
AUC: Area under the Curve.

7- AUTHORS' CONTRIBUTIONS

Reem A. Abdel Aziz, Hossam Fathey Abd-ullah and Magdy Mostafa Kamel conceived the study, carried out its designing, coordinated the implementation, helped to perform the statistical analysis and drafted the manuscript. RA designed the study, participated in the analysis and interpretation of data and revised the statistics and final draft of the manuscript. Mostafa Ahmed El Sayed was responsible for interpretation of laboratory data of patients and revision of the manuscript. All

authors read and approved the final manuscript.

8- CONFLICT OF INTEREST: None.

9- ACKNOWLEDGMENTS

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