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Presepsin as an Early Diagnostic Marker of Neonatal Sepsis in Preterm Neonate

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Abstract: Sepsis remains a major challenge in clinical practice with considerable morbidity and mortality despite modern treatments. In the era of multi-drug resistance, definite and early diagnosis of neonatal sepsis is important for avoiding its fatal outcomes and improving the prognosis of patients especially because symptoms and signs are non-specific. Recently, presepsin has been shown to be beneficial as sepsis marker**. Objectives:** This study is to evaluate the diagnostic accuracy of presepsin as an early diagnostic marker of sepsis in preterm new born in comparison with CRP. **Methods:** Comparing clinical and lab results regarding demographic data, measuring the sepsis work up including (CRP level and presepsin level) in 90 preterm infants 30 diagnosed as early onset sepsis,30 diagnosed as late onset sepsis and 30 control. **Conclusion:** Serum P-Sep level was significantly elevated in preterm with neonatal sepsis either early or late onset sepsis, positively correlated with CRP, TLC, ANC and I/T ratio, at cut of value of >799 pg./dL serum P-Sep yielded a sensitivity of 93.33 %, specificity 90.0 %, positive predictive value 94.9 % and negative predictive value 87.1 so Serum P-Sep was superior than CRP as an early diagnostic marker of neonatal sepsis with more sensitivity and specificity.

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1. Introduction

Sepsis remains a major challenge in clinical practice with considerable morbidity and mortality despite modern treatments.[1]In the era of multi-drug resistance, definite and early diagnosis of neonatal sepsis is important for avoiding its fatal outcomes and improving the prognosis of patients especially because symptoms and signs are non-specific[3]. About 178 sepsis markers have been found, most of which are intermediate inflammatory products and pro-inflammatory cytokines as (CRP, procalcitonin, interleukin-6, etc.).[2] Recently, presepsin has been shown to be beneficial as sepsis marker. Presepsin seems to have a better sensitivity and specificity in the diagnosis of sepsis.[3]

Aim of the work

The aim of our work was to evaluate the diagnostic accuracy of presepsin as an early diagnostic marker of sepsis in preterm newborn in comparison with CRP.

2. Subject and Methods

90 preterm infants that fulfilled the inclusion criteria were recruited from Neonatal intensive care unit (NICU) of Tanta University Hospital. The studied infants were classified into 3 Groups:

i. **Group 1:** Includes thirty (30) preterm new-borns diagnosed as early onset sepsis.

ii. **Group 2:** Includes thirty (30) preterm new-borns diagnosed as late onset sepsis.

The diagnosis of sepsis is done by Griffin's neonatal sepsis score [4].

iii. **Group 3:** Includes thirty (30) healthy preterm newborns with same age and sex were served as the control group, those newborn were generally doing well healthy preterm newborn who did not show any clinical, radiographic, or laboratory findings attributable to sepsis were included as controls.

Duration of the Study:

12 months from January 2018 to January 2019.

Inclusion criteria:

- For the septic group:

1) Preterm newborn with clinical criteria of sepsis including:

Convulsions, Respiratory distress, Bulging fontanelle, Pus draining from the ear, Redness around umbilicus extending to the skin, hypothermia or hyperthermia, Lethargic or unconscious (not aroused by minimal stimulus), Reduced movements (change in activity), weak suckling, Crepitations and Reduced digital capillary refill time.

2) Preterm with Rodwell's criteria of sepsis including: leukocytosis, thrombocytopenia, increased I/T ratio and rising CRP.

3) preterm with diagnosed neonatal sepsis by blood culture.

For the control group: Healthy preterm newborn who did not show any clinical, radiographic, or laboratory findings attributable to sepsis were included as controls.

Methods of the study:

The pervious groups admitted to our NICU will undergo **Complete history taking:**

Antenatal: for any congenital infection, PROM, IUFD or other pregnancy complications.

Natal: including mode of delivery, place of delivery, gestational age and exposure to any complications.

Post-natal: once the baby arrives to postnatal ward the baby should have –

complete

Clinical examination: including his.

Vitals: as temperature, pulse, respiratory record and weight.

Systemic examination: as skin rash, fontanels, ear and eye discharge, rooting reflex, chest examination, and umbilicus for redness, pus or foul.

Investigations:

Blood samples were obtained to determine the laboratory data of the studied group including:

-Routine: as CBC, serial CRP, renal functions, liver functions, ESR and CSF if needed.

-study investigation:

presepsin.

Random blood samples of the studied groups were collected. Blood samples were allowed to clot then centrifuged and the serum obtained and collected into clean dry tubes and stored it -70 ^{0} C for the time of assay.

Statistical method

The analysis was calculated by SPSS version 25. Furthermore, the qualitative parameters were described by number of frequency and percentage while the quantitative variables were described by mean, standard deviation and range. In addition, comparison of qualitative variables between the three groups were calculated by Chi Square, Fisher's Exact Test or Monte Carlo test according to the expected count in the table cells.

3. Results

Table (1): Demographic data/anthropometric measures of the studied group.

		Groups						Chi-Square or ANOVA	
		Control		Early onset sepsis		Late onset sepsis			
		N	%	N	%	N	%	X^2 or F	P-value
Sex	Male	15	50.00	14	46.67	17	56.67	0.623	0.733
	Female	15	50.00	16	53.33	13	43.33		
Mode of Delivery	CS	25	83.33	19	63.33	22	73.33	3.068	0.216
	NVD	5	16.67	11	36.67	8	26.67		
Gestational Age (wks)	Range	25 - 36		26 - 36		26 - 36		0.942	0.394
	Mean ±SD	32.833 ± 3.086		31.867 ± 3.037		32.067 ± 2.477			
Birth weight (kg)	Range	0.75 - 2.75		0.78 - 2.55		0.8 - 2.65		0.874	0.421
	Mean ±SD	1.959 ± 0.576		1.784 ± 0.564		1.817 ± 0.494			
Length (cm)	Range	32.5 - 48.5		32.8 - 47		32.5 - 47.5		1.342	0.267
	Mean ±SD	43.217 ± 4.312		41.670 ± 3.878		41.947 ± 3.463			
HC (cm)	Range	22.7 - 32		22 - 33		23 - 33		0.018	0.982
	Mean ±SD	29.580 ± 2.587		29.450 ± 3.000		29.523 ± 2.426			
APGAR at 1 min	Range	7 - 9		6 - 9		6 - 8		7.642	0.001*
	Mean ±SD	7.867 ± 0.776		7.067 ± 0.907		7.267 ± 0.785			
APGAR at 5 min	Range	9 - 10		8 - 10		8 - 10		3.178	0.047*
	Mean ±SD	9.567 ± 0.504		9.100 ± 0.845		9.267 ± 0.785			

There was no significant difference between all the studied groups as regard the sex, gestational age, birth weight and head circumference.

Although there was higher incidence of cesarean section as mode of delivery in comparison to the normal vaginal delivery in all the studied groups.

As regard the Apgar score there was significant decrease at (1 min and 5 min) among the sepsis group in comparison with the control group.

Table (2): Clinical maternal and neonatal characteristics of studied group.

Clinical maternal and neonatal characteristics of studied group	Early onset sepsis		Late onset sepsis	
	N	%	N	%
Premature rupture of membranes (PROM)	12	40.00	-	-
Chorioamnionitis	6	20.00	-	-
Mechanical ventilation (M.V)	-	-	0	0.00
Umblicalvanous catheter (UVC)	-	-	6	20.00
Central vanous line (CVL)	-	-	3	10.00
Preeclampsia	7	23.33	5	16.67
Antenatal steroids	5	16.67	-	-
Mortality	8	26.67	4	13.33

As regard EOS group: PROM was the major finding in 12 patients (40%), pre eclampsia in 7 patients (23.33%), chorioamnionitis in 6 patients (20%)., 5 patients were on MV and 5 of them were with UVC and 2 of then were with CVL.

As regard LOS group: umbilical venous catheter (UVC) and Antenatal steroids in 6 patients (20%), pre eclampsia in 5 patients (16.67%), Central venous line (CVL) in 3 patients (10%).

Respiratory distress was the most frequent clinical finding 56% followed by hypotonia 53%, poor reflexes 43%, feeding intolerance 33%, temperature instability 30%, lethargy 26% mottling 23%, pallor 20% followed by apnea, cyanosis 16% followed by jaundice and hepatosplenomegaly 10%.

Table (3): Clinical Presentation of the septic groups.

	N	%
Poor reflexes	13	43
Lethargy	8	26
Temperature instability	9	30
Respiratory distress	17	56
Hypotonia	16	53
Pallor	6	20
Jaundice	3	10
Cyanosis	5	16
Feeding intolerance	10	33
Apnea	5	16
Mottling	7	23
Hepatosplenomegaly	3	10

Table (4): Vital signs of the studied groups.

		Groups								
		Control			Early onset sepsis			Late onset sepsis		
Temperature	Range	36.4	-	38	35.8	-	39	36	-	38.4
	Mean ±SD	36.920	±	0.409	37.300	±	0.997	37.410	±	0.652
Respiratory rate (cycle/min)	Range	50	-	62	55	-	90	56	-	85
	Mean ±SD	54.000	±	3.620	63.900	±	9.974	63.900	±	6.337
Heart rate (beat/min)	Range	117	-	180	100	-	210	123	-	240
	Mean ±SD	140.533	±	16.128	143.967	±	27.834	152.300	±	27.152
Systolic blood pressure (mmhg)	Range	65	-	96	30	-	70	40	-	80
	Mean ±SD	75.233	±	9.145	65.267	±	7.952	69.800	±	9.629
Diastolic blood pressure (mmhg)	Range	30	-	60	10	-	40	15	-	46
	Mean ±SD	40.367	±	8.075	34.700	±	6.221	33.200	±	5.653

As regard vital signs, there was statically significant difference in temperature, respiratory rate, blood pressure, in septic groups compared to control group while; there was no statically significant deference as regard heart rate between two groups.

Table (5): Routine laboratory investigations of the studied groups.

		Groups								
		Control			Early onset sepsis			Late onset sepsis		
Alanine transaminase	**Range**	10	-	45	80	-	215	65	-	220
	Mean ±SD	28.667	±	13.126	155.000	±	41.854	142.333	±	42.745
Aspartate transaminase	**Range**	15	-	53	55	-	200	55	-	160
	Mean ±SD	34.733	±	11.194	145.333	±	33.629	116.167	±	32.766
Blood urea	**Range**	13	-	72	17	-	77	20	-	72
	Mean ±SD	31.420	±	16.904	51.067	±	15.220	53.167	±	16.674
Blood creatinine	**Range**	0.2	-	0.8	0.4	-	2	0.9	-	1.8
	Mean ±SD	0.521	±	0.164	1.184	±	0.316	1.295	±	0.283
Serum albumin	**Range**	3.6	-	5.5	2.7	-	3.7	3.1	-	3.9
	Mean ±SD	4.903	±	0.347	3.377	±	0.288	3.447	±	0.274
Serum sodium (NA)	**Range**	133	-	147.7	132	-	147	132	-	145
	Mean ±SD	140.320	±	4.004	138.567	±	4.561	138.500	±	3.422
Serum potassium (K+)	**Range**	3.5	-	5.4	2.6	-	5.4	2.6	-	4.9
	Mean ±SD	4.396	±	0.499	4.427	±	0.615	4.073	±	0.792
PH	**Range**	7.34	-	7.48	7	-	7.25	6.8	-	7.3
	Mean ±SD	7.402	±	0.046	7.127	±	0.089	7.115	±	0.133
CO2	**Range**	30	-	45	32	-	70	32	-	80
	Mean ±SD	38.640	±	4.173	47.413	±	9.823	45.737	±	12.742
HCO3	**Range**	17.3	-	32	6	-	23.8	7	-	26.9
	Mean ±SD	23.687	±	2.643	13.760	±	4.320	14.423	±	4.560

There was statistically significant elevation in septic group than control group as regard, ALT, AST, urea and creatinine. while there was no statistically significant difference between both groups as regard NA and K. As regard arterial blood gas (ABG) there was metabolic, respiratory or mixed acidosis among sepsis group.

Table (6): Hematological data in the studied groups.

		Groups								
		Control			Early onset sepsis			Late onset sepsis		
Hemoglobin (gm/dl)	Range	11	-	19.3	6.5	-	9.8	7.7	-	10.4
	Mean ±SD	13.893	±	1.965	8.353	±	0.764	9.003	±	0.695
Blood platelets count (-/cmm)	Range	102	-	340	68	-	133	10	-	123
	Mean ±SD	208.450	±	76.640	101.800	±	16.908	69.700	±	33.717
Total Leucocyte count (-/cmm)	Range	2.6	-	14.8	25	-	84.3	25	-	73
	Mean ±SD	7.919	±	3.411	42.180	±	18.382	35.980	±	10.693
Absolute neutrophil count	Range	1	-	5.5	14	-	45	14	-	40
	Mean ±SD	3.073	±	1.322	23.800	±	9.647	21.300	±	5.802
I/T Ratio	Range	0.06	-	0.15	0.2	-	0.37	0.2	-	0.38
	Mean ±SD	0.117	±	0.024	0.296	±	0.048	0.323	±	0.040

There was a statically significant reduction in values of HB and PLT among patients group both early and late onset sepsis in comparison with control group while there was a significant increase in values of total Leucocyte count, absolute neutrophil count and I/T ratio among patients group both early and late onset sepsis in comparison with control group.

Table (7): comparison between CRP level in control group and patient groups.

CRP	**Groups**									**ANOVA**	
	Control			**Early onset sepsis**			**Late onset sepsis**			**F**	**P-value**
Range	1	-	5	6	-	157	7	-	135	24.247	<0.001*
Mean ±SD	3.567	±	1.104	56.200	±	45.379	56.000	±	36.799		

There was significant increase in CRP level in EOS group in comparison with the control group, there was significant increase in CRP level in LOS group in comparison with the control group and little higher CRP level in EOS in comparison with LOS group.

Table (8): comparison between PSPN level in all studied groups.

PSPN (pg/dl)	Groups									ANOVA	
	Control			Early onset sepsis			Late onset sepsis			F	P-value
Range	321	-	1188	700	-	6888	650	-	8150	38.339	<0.001*
Mean ±SD	545.833	±	239.966	3474.967	±	2335.006	4994.667	±	2548.384		
TUKEY'S Test											
Control and Early onset sepsis (P1)				Control and Late onset sepsis (P2)			-				
<0.001*				<0.001*			-				

There was a significant increase in PSPN level in EOS group in comparison with the control group (P1 <0.001), there was a significant increase in PSPN level in LOS group in comparison with the control group (P2 <0.001).

Table (9): comparison between PSPN level in sepsis group and control group.

PSPN (pg/dl)	Groups						T-Test	
	Control			Sepsis			t	P-value
Range	321	-	1188	650	-	8150	-7.910	<0.001*
Mean ±SD	545.833	±	239.966	4234.817	±	2541.490		

There was a significant increase in PSPN level in sepsis groups (EOS & LOS) in comparison with the control group (P3 <0.001).

Table (10) Blood cultures result in patient groups.

No Growth	4	13.33	12	40.00	16	26.67
Pseudomonous	2	6.67	0	0.00	2	3.33
Klebsiella	12	40.00	5	16.67	17	28.33
Klebsiella + Psudomonous	1	3.33	0	0.00	1	1.67
Staphylococcus Haemolyticus	8	26.67	7	23.33	15	25.00
Enterococci	2	6.67	2	6.67	4	6.67
Streptococci	1	3.33	4	13.33	5	8.33
Total	30	100.00	30	100.00	60	100.00

Among culture positive groups: As regard EOS group klebsiella was the most prevelantorganism (40%) followed by: Staphylococcus Haemolyticus, Enterococci, Pseudomonous, mix of Klebsiella and Psudomonous then Streptococci.

As regard LOS group klebsiella was also the most prevelantorganism (28%) followed by: Staphylococcus Haemolyticus, Streptococci, Enterococci, Psudomonous then mix of Klebsiella and Psudomonous.

Table (11):multivariate logistic regression

	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	Std. Error	Beta		
Mode of Delivery	-1148.815	931.924	-0.212	-1.233	0.223
Sex	1126.300	647.645	0.223	1.739	0.088
Birth weight (kg)	1937.780	2528.190	0.401	0.766	0.447
Gestational Age (wks)	-384.366	504.143	-0.416	-0.762	0.449
Dependent Variable: PSPN (pg/dl)					

There was no significant correlation between mode of delivery, sex, birth weight and gestational age and presepsin.

Table (12) correlation between serum PSPN level and CRP in patient groups.

Correlations		
	PSPN (pg/dl)	
	r	P-value
CRP	0.328	0.010*

There was a positive correlation between serum PSPN and serum CRP in sepsis groups.

Table (13): ROC curve (specificity and sensitivity) of serum CRP for sepsis.

ROC curve between Control and Patient				
Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**
>6	**92.0**	**86.1**	**93.4**	**86.1**

At cut off value of >6 mg/L serum CRP yielded a sensitivity of 92.0 %, specificity 86.1 %,positive predictive value 93.4 % and negative predictive value 86.1 %.

Table (14): ROC curve (specificity and sensitivity) of serum PSPN for sepsis.

ROC curve between Control and Patient				
Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**
>799	**93.33**	**90.0**	**94.9**	**87.1**

At cut off value of >799 pg/dL serum PSPN yielded a sensitivity of 93.33 %, specificity 90.0 %, positive predictive value 94.9 % and negative predictive value 87.1 %.

4. Discussion

Premature babies in the NICU are at a much greater risk for systemic infections. They have immature immune systems, and can't fight off infections very well. Also many of them have invasive procedures while they are in the NICU. Central IV lines like umbilical venous catheters or PICC lines, mechanical ventilation, and surgeries can all introduce infection into the body[5].

The diagnosis of "suspected sepsis" in neonates in the NICU is challenging due to the nonspecific signs of sepsis, the poor diagnostic performance of currently used laboratory markers and the unfortunate delay in bacterial culture data [5] and although sepsis screening panels and scoring systems that include multiple laboratory values may help exclude neonatal sepsis, their positive predictive value is very poor.

So it is important to identify a marker of "high likelihood" of sepsis in neonates who require antimicrobial agents soon after birth, in short, a marker with a useful positive predictive value. [6].

Traditionally, clinicians been dependent on using the complete blood count in their diagnosis, in spite of studies have reported unreliability of traditional laboratory diagnostic tools in diagnosis of EOS such as platelet count, total white blood cell count, ANC, and I: T ratio. Assessment of the human P-SPN level started to emerge as a diagnostic tool for early and late onset sepsis as wide range been investigated for their potential benefits such as acute-phase reactants and cytokines.

In our study the P-SPN level was significantly higher in serum of newborn infants who developed sepsis, giving it the advantage of being an early tool of diagnosis.

In this study, patients groups, composed of 60 preterm: 30 with EOS (14 were males and 16 preterm were females) and 30 with LOS (17 were males and 13 preterm were females) with male to female ratio almost 1:1, and this comes in agreement with **Mike Smertka et al; De Benedetti et al** [7].

In the present study, we found that newborns with EOS were more likely to have low Apgar score in the first and in the fifth minute in comparison to infants without sepsis with mean APGAR score for the patients at 1minute: EOS group (7.067±0.907), LOS group (7.267±0.785) and at 5 minutes: EOS group (9.100±0.845), LOS group (9.267±0.785) and for controls was (7.867±0.776) at 1minute, and at 5 minutes was (9.567±0.504); as we excluded patients with asphyxia, and this agrees with **Lorenza Pugn., et al.** who found that among the variables analyzed in their study, only Apgar score at 1 min was < 8)

Mike Smertka et al, 2014 found that There is no significant difference between patients and controls as regard APGAR score at 1,5 minute [7].

In this study, mechanical ventilator (MV) was the main neonatal risk factor as 55% of infected cases were ventilated.

This agrees with **Leal et al,** and **Krajcinovic et al,** who found that 82.5% of preterm infants with sepsis was mechanically ventilated, and even 38.1% of them were diagnosed with pneumonia.

Also, in our study PROM and chorioamnionitis were the most common maternal risk factor for neonatal sepsis present in 18.33% of infected cases. This come in accordance with **Selimovic et al**; **Leal et al**; who worked on 340 preterm neonates and found that PROM was the main risk factor in 95 % of EOS group [210].

In a study done by **Boseila et al,** 40% of the neonates with sepsis and 45% of suspected had PROM. **Khair et al,** reported that PROM occurred in 75%of his cases [211].

Bizzarro et al, found that PROM was present in 46% of EOS cases. This higher incidence of PROM may be due to low socioeconomic state and lack of antenatal care of the mothers as mentioned by **Ali,** [8].

In the present study, TLC was significantly higher in the sepsis group than in control group. This agrees with **Mike Smertka et al,**[9].

Boseila et al found that total leucocytic count (TLC) was not much informative for the diagnosis of neonatal sepsis, this may be because septic infants, in contrast to adults in whom hematopoiesis is developmentally mature, may deplete their neutrophil reserve and develop neutropenia during overwhelming infection. **Thurlbeck and Meintoch,** also stated that the TLC is often unhelpful in the diagnosis of sepsis because the normal range is wide and varies with gestational age and postnatal age [7].

In the present study, the ratio of immature to total neutrophil (I/T) ratio was much informative for diagnosis of neonatal sepsis. The I/T ratio was significantly higher in patients than in controls (p=<0.001)

This comes in agreement with **Narasimha and Harendra Kumeur,** and **Boseila et al,** who stated that I/T ratio provide a diagnostic information about sepsis [10].

Gonzalez et al, found that there was no statistical difference between patients with confirmed sepsis versus patients with no infection as regards T.L.C, I/T ratio and platelet count [11].

In the current study we found that thrombocytopenia was significantly higher in the confirmed sepsis group than control group.

This comes in agreement with **Alshorman et al, Boseila et al**; **Mike Smertka et al,** who stated that low platelet count is associated with sepsis. This could be due to direct toxic injury of platelets, megakaryocytic suppression, increased peripheral consumption as in DIC or presence of immune component due to increased level of platelet associated immunoglobulins [12].

In the current study we found that therethere was metabolic, respiratory or mixed acidosis among sepsis. This agrees with **Borna H and Borna S,** who found that metabolic acidosis was the commonest finding in the septic groups [13].

In the current study we found that CRP levels were significantly higher in the confirmed sepsis group than control group. This was in agreement with **Boseila et al**, **Mike Smertka et al [7].**

In our study we found that the percentage of negative culture was (26.67%) in sepsis group and (73.33%) were culture positive.

This comes in agreement with the study of **Chacko and Sohi,** found that culture proven sepsis occurred in 41.6% of cases with sepsis [14].

In the study of **Procianoy and Silveira,** it was found that blood cultures were positive in only eighteen of total eighty five cases (21%) [15].

Gandhi et al, found that out of 238 samples of patients with neonatal sepsis, blood culture was positive in 76 cases (32%) [16].

On the other hand **Vinay et al**, found a high blood culture positive rate of 80%, probably because of low antenatal antibiotics and Bac Tec culture methods used [17].

In our study, among culture positive group, klebsiella was the most prevalent organism representing 65.38% followed by Staphylococcus Haemolyticus, Pseudomonous, Enterococci and streptococci. In EOS group klebsiella was the most prevelant organism.

In the study of **Dzwonek et al.**, nearly half of the positive blood cultures grew Klebsiellapneumoniae. While in the study of **De Benedetti et al.**, the isolated pathogens included Klebsiellapneumoniae (47.5%), Pseudomonas aeruginosa (20%), Escherichia coli (10%), Candida albicans (10%), Staphylococcus aureus (7.5%) and Enterococcus (5%) [18].

This variation may be due to differences in the environment, the microbial etiology of sepsis and supportive care practice between centers[221]**.** The predominant bacterial causes of sepsis have changed over time and may vary from hospital to hospital.

In the current study, serum P-SPN level was significantly higher in patient group than control, with mean levelin EOS (1.832±1.791) in LOS (2.287±1.789) in patient and (0.062±0.030) in control group.

The results of this study came in accordance with **Chiara Poggi., et al.** who studied newborns ≤ 32 weeks' gestational age with LOS (n = 19) and non infected controls (n = 21) at 4 to 60 days' postnatal age. At enrolment, and 1, 3, and 5 days later, they ascertained the C-reactive protein, procalcitonin, and P-SEP in the LOS group, whereas P-SEP alone was ascertained in the control group. They found that P-SEP at enrolment was higher in the LOS than the control group and remained higher throughout the study period. Which means that P-SEP is an accurate biomarker for the diagnosis of possible LOS and may also provide useful information for monitoring the response to therapeutic interventions[19].

The results of this study came in accordance with **Lorenza Pugn., et al.** whostudid684 neonates enrolled in the study, 484 were born at term and 200 were preterm (24–36 weeks' gestation). For the first time, this study provides reference ranges of presepsin in term and preterm neonates. Having reliable reference values is crucial for obtaining an adequate diagnostic accuracy. Based on their results, most variables commonly affecting CRP and procalcitonin values do not affect presepsin levels, which suggests that presepsin could be an effective sepsis marker [20].

Also, the results of this study came in accordance with **Sevilay Topcuogl., et al.** Forty-two premature newborns ≤32 weeks gestational age with a diagnosis of LOS were prospectively involved in the study.

Levels of presepsin, C-reactive protein, and procalciton in were measured at enrolment and on the third and seventh days of sepsis. They found that Presepsin can be used as a reliable biomarker for LOS and treatment response in preterm infants [21].

In this current study, At cut of value of >799 pg/d L serum P-SPN yielded a sensitivity of 93.33 %, specificity 90.0 %, positive predictive value 94.9 % and negative predictive value 87.1 %.

The results of this study came in accordance with **Ioannis Bellos., et al.** who found that a presepsin range was (650:850 pg/mL) [22].

Also, The results of this study came in accordance with **Chiara Poggi., et al.** who found that the best calculated cutoff value was 885 ng/L, with 94% sensitivity and 100% specificity [19].

In this current study as regard CRP, At cut off value of >6 mg/l level yielded a sensitivity of 92.0% and specificity of 86.1%, PPV 93.4% and NPV 86.1.

The result of this study came in accordance with **P. Povao., et al.** who found that CRP, At cut off value of >8.7 mg/l level yielded a sensitivity of 93.4% and specificity of 86.1%, PPV 91.4% and NPV 86.0[23].

Limitation of the study

The study had some potential limitations such as; Surgical cases, asphyxia, fetal congenital malformations or chromosomal abnormalities, received antibiotics before hospitalization, fetal hydrops, confirmed intrauterine infection (toxoplasmosis, rubella, cytomegalovirus, syphilis and herpes), lack of parental consent and septic shock.

Conclusion

In this study, we can highlighted that:

Serum P-Sep level was significantly elevated in preterm with neonatal sepsis either early or late onset sepsis, were positively correlated with CRP, TLC, ANC and I/T ratio.

At cut off value of >6 mg/L serum CRP yielded a sensitivity of 92.0 %, specificity 86.1 %, positive predictive value 93.4 % and negative predictive value 86.1 %.

At cut of value of >799 pg/dL serum P-Sep yielded a sensitivity of 93.33 %, specificity 90.0 %, positive predictive value 94.9 % and negative predictive value 87.1 %.

Serum P-Sep was superior than CRP as an early diagnostic marker of neonatal sepsis with more sensitivity and specificity.

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