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RESEARCH ARTICLE

PRESEPSIN AS AN EARLY RELIABLE DIAGNOSTIC AND PROGNOSTIC MARKER OF NEONATAL SEPSIS.

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Abstract

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Background: Sepsis is a common cause of morbidity and mortality among neonates, and current biomarkers for diagnosis are not adequate. The objective of the study was to assess the diagnostic and prognostic value of presepsin.

Methods: One hundred and twenty neonates were enrolled in the study; 80 cases and 40 controls. Presepsin and CRP levels were measured during 1st, 2nd & 6th days of admission for cases while were measured once for each control.

Results: Initial presepsin levels were significantly higher in group produced neonatal sepsis than in the non-septic group. At a cut off value $\geq 0.722 \mu\text{g/L}$, Presepsin sensitivity for prediction of neonatal sepsis was 100 %, specificity 97.5%, positive predictive value (PPV) 98.7%, negative predictive value (NPV) 100%, area under curve (AUC) 0.99 with high sensitive positive correlation with sepsis (P value < 0.001). At a cut off value < 2.3 $\mu\text{g/L}$, Its prognostic sensitivity was 75.9%, specificity 72.5%, PPV 61.1, NPV 84.1 and AUC 0.76.

Conclusion: Presepsin sensitivity for early diagnosis of neonatal sepsis was 100 % with specificity 97.5%. Presepsin is an accurate biomarker for early diagnosis of neonatal sepsis. It also provides a useful tool for prediction of improving.

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Introduction:-

Sepsis is defined as a systemic inflammatory response to infection. It is a common cause of morbidity and mortality, particularly in immune-compromised and critically ill patients.[1]

In Egypt, a study was conducted in NICUs in Mansoura Hospitals over a period of 18 months founded that the incidence of suspected neonatal sepsis was 45.9% (357/778) among the admitted neonates. [2]

It is well known that an early diagnosis and treatment of sepsis with appropriate drugs can improve the prognosis and increase the survival rate in patients with sepsis [1]

A blood culture is the gold standard for the diagnosis of neonatal sepsis. However, the long time for results and frequent false-negative culture results due to the small volume of blood samples limit its use for decision making

about antibiotic therapy. Therefore, many biochemical markers, hematological indices, and scoring systems are used to help in decision-making about antibiotic therapy in newborns with suspected sepsis. [3]

CRP was first described in the 1930's and since then multiple studies have shown elevation of the CRP in several infectious and non-infectious etiologies that share a common background of inflammation or tissue injury. [4]

Presepsin (sCD14 st) is a truncated portion of soluble CD14, released by shedding from the surface of many immune cells, such as macrophages, monocytes, and neutrophils, after being stimulated by pathogens. Presepsin has recently been described as a reliable diagnostic and prognostic marker of sepsis. [5]

The aim of this study is to compare presepsin level in neonatal sepsis with CRP level which is the most frequently used marker for neonatal sepsis in Egypt and with CBC results to evaluate presepsin as a potential early diagnostic and a reliable prognostic marker for neonatal sepsis.

Subjects:-

This case control study was carried out in the NICU of Banha university hospitals from November 2015 to April 2016 in which 120 newborns were enrolled to the study regardless their gestational age. From which, 80 newborn produced sepsis and considered as cases and 40 newborn didn't produced sepsis during they stay and were considered as controls. Inclusion criteria included maternal history of fever or resistant UTI, immune suppressant drugs intake, history of PROM or bad odor of amniotic fluid, regardless mode of delivery, number, or sex. Patients with major congenital malformations were excluded.

Sepsis was diagnosed according to **Griffin Neonatal Sepsis Score** in which Feeding intolerance, Severe apnea or Immature/total neutrophil (I:T) ratio greater than 0.2 gives score of 2 and Increase in ventilator support, Lethargy, hypotonia, Temperature instability, Hyperglycemia or Abnormal white blood cell count gives score of 1. A score ≥ 2 is highly suggestive for sepsis. [6]

Ethical consideration:-

The current study was approved by the Local Ethics Committee of Faculty of Medicine, Benha University and all study participants' parents gave a written informed consent prior to enrollment in the study.

Methods:-

For each case a Complete blood count (CBC) was done by sysmex XS-800 I at admission, C-reactive protein for each case was done 3 times; the first was during 1st day of admission, the second was taken during the 2nd day, and the 3rd was taken during the 6th day. It was done using Biosystem BTS 350 spectrophotometer by turbidimetric method. [7] Arterial blood gas was done at admission using easy state kits.

Presepsin measurement: Presepsin (sCD14 st) level was measured using human sCD 14 st ELISA kit, produced by R&D Systems, inc. 614 McKinley Place NE, Minneapolis, MN 55413, USA.

Two mls of blood were obtained from each newborn by using available commercial sets under complete aseptic technique; blood was left for 20 minutes to coagulate then centrifuged for 20 minutes at 3000 rpm. The sera were separated and stored at -20°C , avoiding multiple freeze-thaw cycles until the assay.

This ELISA kit is based on the principle of double antibody sandwich technique to detect human soluble cluster of differentiation 14 (sCD14) which is also named presepsin [8]. Test was done using Dynx Best 2000 ELISA apparatus. For each control CRP level and presepsin level was measured once.

Statistical analysis:-

The collected data were tabulated and analyzed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean \pm standard deviation, median inter quartile range (IQR) and range. Chi square test (χ^2) was used to analyze

categorical variables. Quantitative data were tested for normality using KolomogrovSmirnov test, using Student "t", if normally distributed, or Wilcoxon test, Man Whitney U test, and Spearman's correlation coefficient (rho) if not normally distributed. ROC curve was used to determine cutoff values of CRP and presepsin with optimum sensitivity and specificity in early diagnosis of neonatal sepsis. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

Results:-

Regarding socio-demographic characters of the studied sample, there was no significant difference as regarding gender between the cases' group and controls' group. Mode of delivery has a significant difference between cases' and controls' groups (P value = 0.003). Gestational age has a high significant difference between cases' and controls' groups (P value <0.001). Birth weight has no significant difference between cases' group and controls' group. (Table 1)

Table 1:- Socio-demographic characters of the studied sample.

Variable		Patients (N=80)		Controls (N=40)		Total (N=120)		X ² test	P
		No.	%	No.	%	No.	%		
Sex	Male	36	45.0	15	37.5	51	42.5	0.61	0.43 (NS)
	Female	44	55.0	25	62.5	69	57.5		
Mode of delivery	NVD	36	45.0	7	17.5	43	35.8	8.77	0.003 (S)
	C.S	44	55.0	33	82.5	77	64.2		
GA (w)	Mean ±SD	36.1±2.36		38.02±1.31				St."t" =4.79	<0.001 (HS)
	Range	28-39		34-40					
Weight (kg)	Mean ±SD	2.59±0.62		2.84±0.83				St."t" =1.84	0.069 (NS)
	Range	1.15-3.9		1.16-4.2					

96.2% of cases were admitted for respiratory distress syndrome (RDS), 2.5% for hypoxic ischemic encephalopathy & 1.2 % for hydrocephalus (Fig 1), while in control group, 52.5% were admitted for transient tachypnea of newborn (TTN), 27.5% for neonatal jaundice (N.J.), 17.2% for low birth weight as a grower and 2.5 % for neonatal bleeding.

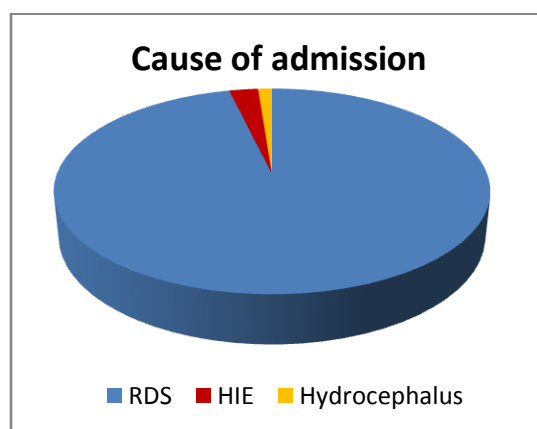


Fig1:-Cause of admission among the cases group

81.2 % of cases were exposed to an invasive procedure while all members of control group were not exposed to any invasive procedures. 50 % of cases were on mechanical ventilation, and 31.2 % were on CPAP. (Fig 2)

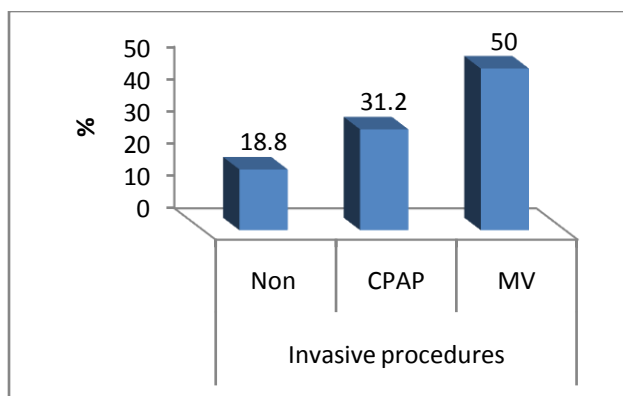


Fig2:-Forms of invasive procedures among cases.

Regarding maternal risk factors among cases, 12.5 % of cases had a history of prolonged rupture of membranes (PROM), 6.2% with maternal hypertension, 2.5% with diabetes mellitus and 1.2 % with chronic renal failure. (Table 2)

Table 2:-Forms of maternal risk factors among cases.

Variable	No. (N=80)	% (100%)	
maternal risk factors	Non	61	76.2
	Chronic Renal failure	1	1.2
	DM	2	2.5
	HTN	5	6.2
	HTN, DM	1	1.2
	PROM	10	12.5

Regarding controls, 7.5 % of control had a history of maternal anemia, 5% with placenta previa, 2.5% with placental separation.

Levels of CRP and presepsin at admission:-

Comparing the studied groups, there is highly significant difference for both CRP and presepsin levels between cases and controls at admission (P value <0.001). (Tables 3&4) and (Fig 3&4)

Table 3:-Comparing the studied groups regarding CRP levels.

Variable	Cases (n=80)			Controls (n=40)			MWU test	P
	Mean	±SD	Median (IQR)	Mean	±SD	Median (IQR)		
CRP at admission	4.28	2.01	3.75 (2.9-5.57)	2.21	0.50	2.4 (1.8-2.6)	6.99	<0.001 (HS)
CRP at 2 nd day	4.82	1.81	4.8 (3.5-5.17)	2.21	0.50	2.4 (1.8-2.6)	7.97	<0.001 (HS)
CRP at 6 th day	5.32	2.21	5.2 (3.6-6.47)	2.21	0.50	2.4 (1.8-2.6)	7.78	<0.001 (HS)
Wilcoxon & P ₁	2.37 & 0.017 (S)			IQR→ Inter Quartile Range MWU test→ Mann Whitney U test P ₁ → between CRP at admission & 2 nd day P ₂ → between CRP at admission & 6 th day P ₃ → between CRP at 2 nd day & 6 th day				
Wilcoxon & P ₂	2.49 & 0.012 (S)							
Wilcoxon & P ₃	1.78 & 0.075 (NS)							

Table 4:-Comparing the studied groups regarding presepsin levels.

Variable	Cases (n=80)			Controls (n=40)			"Z" MWU test	P
	Mean	±SD	Median (IQR)	Mean	±SD	Median (IQR)		
Presepsin at admission a	2.57	1.26	2.72 (1.32-3.12)	0.56	0.09	0.57 (0.49-0.64)	8.9	<0.001 (HS)
Presepsin at 2 nd day	2.90	0.98	2.99 (2.31-3.25)	0.56	0.09	0.57 (0.49-0.64)	8.91	<0.001 (HS)
Presepsin at 6 th day	2.26	0.78	2.38 (1.88-2.79)	0.56	0.09	0.57 (0.49-0.64)	8.91	<0.001 (HS)
"Z" Wilcoxon & P ₁	4.45 & <0.001 (HS)			IQR→ Inter Quartile Range MWU test→ Mann Whitney U test P ₁ → between Presepsin at admission & 2 nd day P ₂ → between Presepsin at admission&6 th day P ₃ → between Presepsin at 2 nd day &6 th day				
"Z" Wilcoxon & P ₂	2.72 & 0.007 (S)							
"Z" Wilcoxon & P ₃	5.33 & <0.001 (HS)							

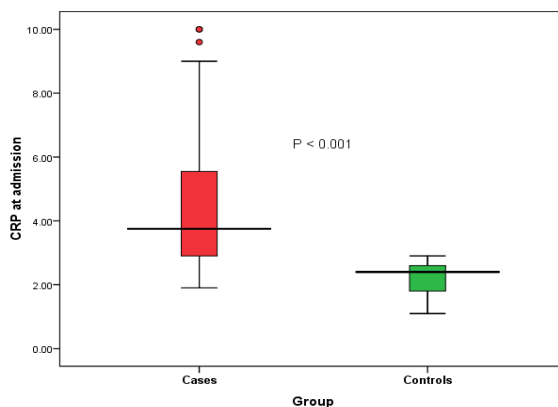


Fig 3:- Box plot for median and IQR of CRP among the studied groups at admission.

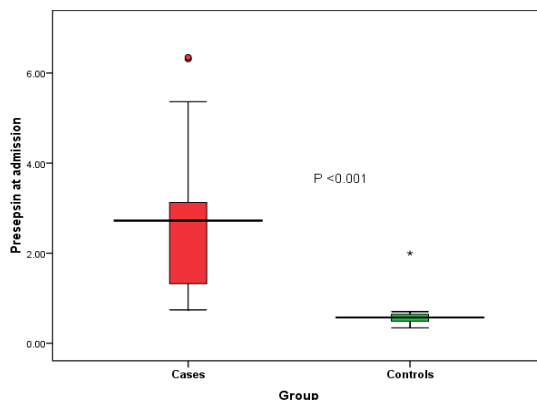


Fig4:-Box plot for median and IQR of presepsin among the studied groups at admission.

Regarding the correlation between initial levels of Presepsin and the studied variables among the studied cases, there was highly significant positive correlation between initial presepsin and CRP level (P value < 0.001) (Fig 5) and

positive significant correlation between it and platelet count (P value 0.022). There was a significant negative correlation between initial presepsin level and Hb level, blood PH and HCO₃ level (P values 0.005, 0.023 & 0.003 respectively).

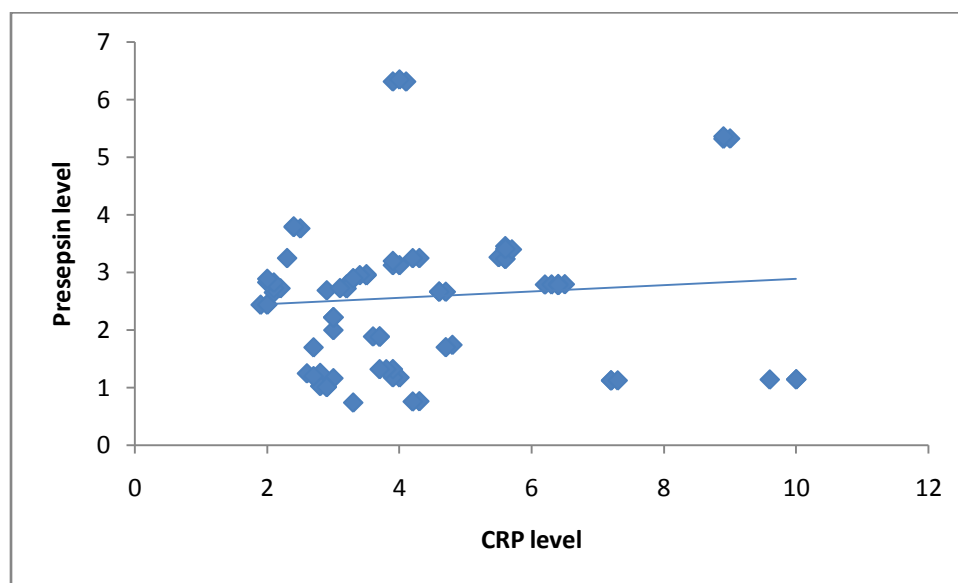


Fig 5:- correlation between presepsin level and CRP level.

On the other hand, there was a highly significant negative correlation between initial CRP level and blood PH (P value 0.001). There was also a significant negative correlation between initial CRP level and Hb level (P value 0.009).

Changes occurred in biomarkers levels during NICU stay:-

CRP shows significant differences between its level at admission and both 2nd day and 6th day levels, but there was no significant difference between CRP levels at 2nd and 6th days. (**Fig 6**)

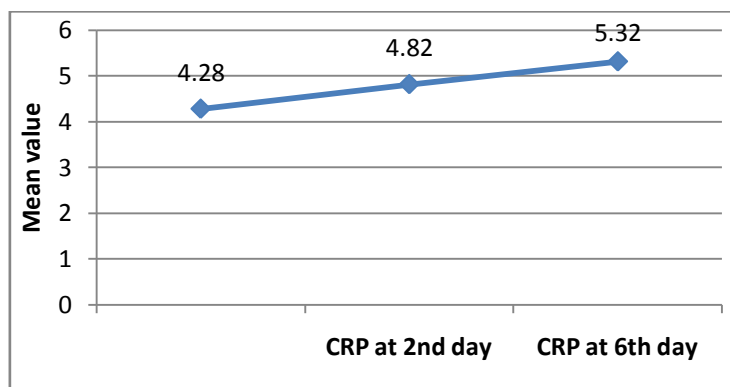


Fig 6:-Line graph for the mean values of CRP.

There is a high significant difference between presepsin level at admission & 2nd day and between 2nd and 6th day (P value <0.001) and a significant difference between presepsin level at admission and 6th day (P value 0.007). (**Fig 7**)

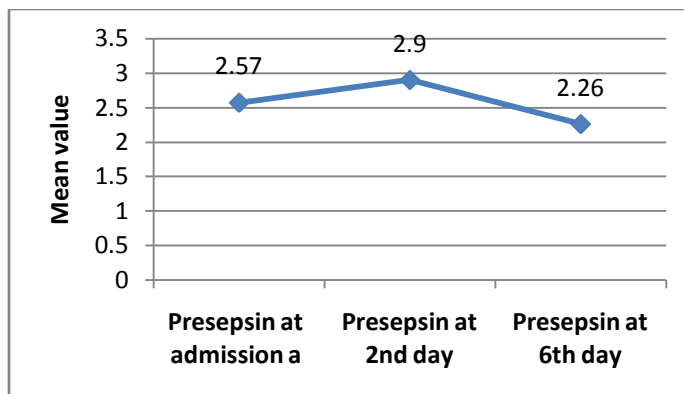


Fig 7:-Line graph for the mean values of presepsin.

Diagnostic accuracy for CRP and presepsin for sepsis:-

At a cut off value $\geq 0.722 \mu\text{g/L}$, Presepsin sensitivity for early diagnosis of neonatal sepsis was 100 % with specificity 97.5%, positive predictive value (PPV) 98.7%, negative predictive value (NPV) 100%, AUC: 0.99 and highly sensitive positive correlation with sepsis (P value < 0.001).

On the other hand, at a cut off value $\geq 2.65 \text{ mg/L}$, CRP sensitivity for early diagnosis for neonatal sepsis was 82.5% with specificity 77.5%, PPV of 88%, NPV of 68.9, AUC: 0.89 and high positive significant correlation with sepsis (P value < 0.001).(Table 5) & (Fig 8)

Table 5:-performance of CRP and presepsin in early diagnosis of neonatal sepsis.

Variable	Sens%	Spec%	PPV%	NPV%	AUC	95%CI	P
Presepsin $\geq 0.722 \mu\text{g/L}$	100%	97.5%	98.7%	100%	0.99	0.97-1.0	< 0.001 (HS)
CRP $\geq 2.65 \text{ mg/L}$	82.5%	77.5%	88%	68.9%	0.89	0.83-0.95	< 0.001 (HS)

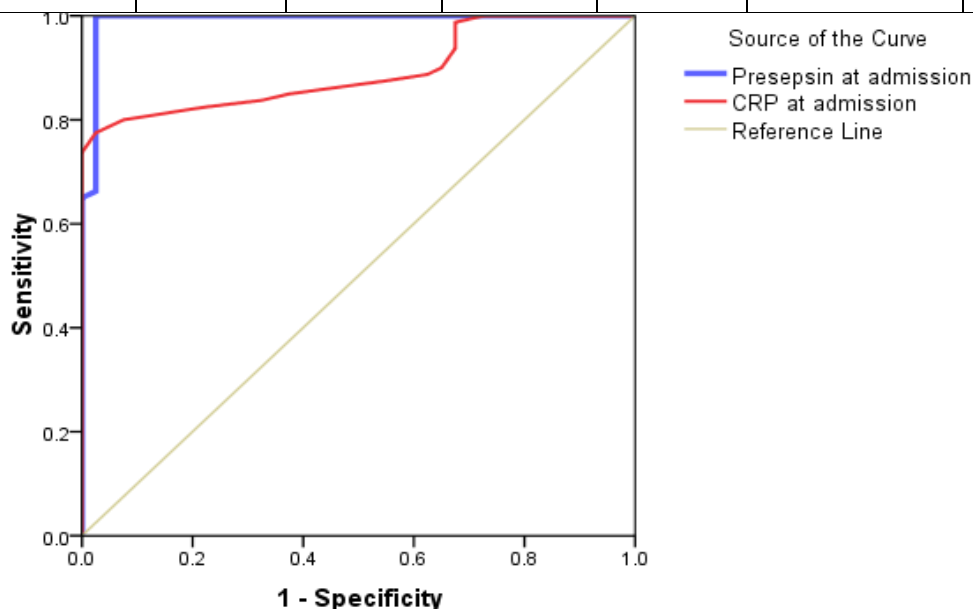


Fig8:-Performance of CRP and presepsin in Prediction for early diagnosis of sepsis.

Accuracy for CRP and presepsin for prediction of improvement:-

By the 6th day, 63.7 % of cases were improved while 36.3% were not improved. There is a high significant difference in presepsin levels between improved cases and non-improved cases (P value < 0.001) but there is a no significant difference in CRP levels between them. (Table 6) & (Fig 9)

Table 6:-Level of presepsin and CRP according to outcome at 6th day.

Variable	Not improved (n=51)			Improved (n=29)			"Z" MWU test	P
	Mean	±SD	Median (IQR)	Mean	±SD	Median (IQR)		
Presepsin at 6th day	2.53	0.65	2.61 (2.18-2.84)	1.79	0.78	1.98 (1.02-2.35)	3.88	<0.001 (HS)
CRP at 6th day	5.55	2.37	5.8 (4.0-6.9)	5.14	1.88	4.9 (3.6-6.45)	0.64	0.52 (NS)

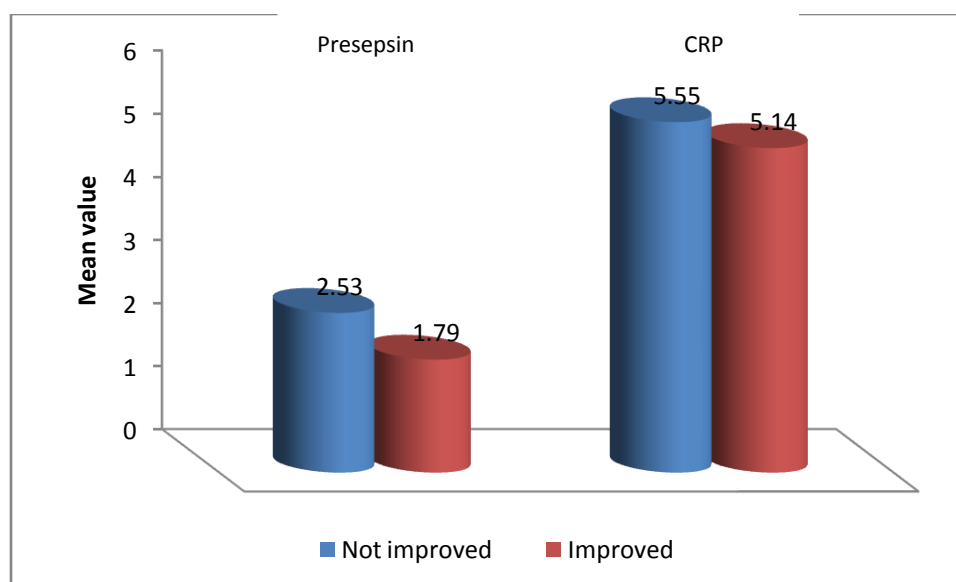


Fig9:- Level of presepsin and CRP according to outcome at 6th day.

Receiver operating characteristic curve analysis was performed for assessing the accuracy of both parameters in prediction of improvement.

At a cut off value < 2.3 µg/L, Prognostic sensitivity of presepsin was 75.9% with 72.5% specificity with PPV 61.1, NPV 84.1 and AUC:0.76.

On the other hand, at a cut off value <5.15 mg/L, prognostic sensitivity of CRP was 55.2%, with specificity of 56.9%, PPV of 42.1%, NPV of 69% and AUC: 0.54. (Table 7) & (Fig 10)

Table 7:-Performance of CRP and presepsin in Prediction of improved septic neonates.

Variable	Sens%	Spec%	PPV%	NPV%	AUC	95%CI	P
Presepsin < 2.3µg/L	75.9%	72.5%	61.1%	84.1%	0.76	0.65-0.88	<0.001 (HS)
CRP < 5.15mg/L	55.2%	56.9%	42.1%	69%	0.54	0.42-0.67	0.52 (NS)

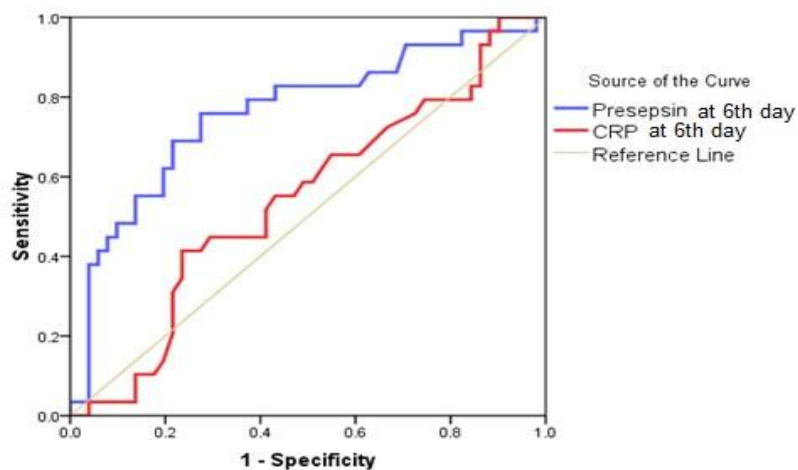


Fig10:-Performance of CRP and presepsin in Prediction of improvement.

Discussion:-

Late-onset neonatal sepsis (LOS) is a life-threatening condition, particularly for preterm newborns. It occurs in approximately 8–30% of very-low-birth-weight (VLBW) infants and in 40% of extremely low- birth-weight (ELBW) infants. [3]

Blood culture is considered as the criterion standard for establishing the diagnosis of bacterial sepsis, but several drawbacks such as high contamination rate, long turnaround time, and low sensitivity have led to the development of several biomarkers for establishing the diagnosis of sepsis. [1]

CD14, a cluster differentiation (CD) marker protein, is a multifunctional cell surface glycoprotein, which exists as a membrane-anchored form or in a circulating soluble form. [9]

The circulating soluble form of CD14 subtype (sCD14-ST), presepsin, is mainly used in acute care settings, such as emergency department and critical care, to distinguish between sepsis and systemic inflammatory response syndrome (SIRS) and for early detection of a possible bacterial cause. [10]

Recently it has also been proposed as a marker of the appropriateness of antibiotic therapy in patients with severe sepsis or septic shock. [11]

The aim of this study was to evaluate presepsin as an early diagnostic and better prognostic marker for neonatal sepsis and to compare it with CRP.

This case control study was conducted on 120 neonates; 80 cases who developed sepsis and 40 control patients who didn't produce sepsis during their stay period in the NICU in Benha university hospitals from November 2015 to April 2016 regardless their gestational age.

In the present work, results revealed that presepsin is present in the serum of healthy controls in low level normally. This agree with **Giavarina D and Carta M.** [11] study whom founded that Presepsin is normally present in very low concentrations in the serum of healthy individuals and it has been shown to increase in response to bacterial infections, according to the severity of the disease.

According to the results of the current study, gestational age and birth weight were risk factors for neonatal sepsis. They were inversely related to production of neonatal sepsis. This goes in hand with **Wu JH** et al. [12] who found that the relative risk for neonatal sepsis was higher in the lower birth weight groups and that the premature and VLBW babies were at increased risk of nosocomial infection because of more aggressive and invasive therapies, such as indwelling central lines, mechanical ventilation, parenteral hyperalimentation and longer hospital stay

Bizzarro [13] explained the effect of prematurity on neonatal sepsis that premature neonates in particular lack an effective skin barrier, have an immature and often ineffective immune system, and often necessitate prolonged support and hospitalization.

Also, preterm infants are more likely to require invasive procedures, such as umbilical catheterization and intubation. [14]

Results of the current study proved that using an invasive procedure such as Endo-tracheal intubation for mechanical ventilation and umbilical catheters increase the risk for neonatal sepsis. This is agreeing with a Swedish retrospective case-control study demonstrated that the risk of neonatal sepsis was directly related to duration of central and umbilical catheters and ventilator treatment. [15]

Wu JH et al. [12] also reported that Endotracheal tube placement with a mechanical ventilator was recorded in 19% of infants with late-onset sepsis during their study.

This was explained by **Bakr AF** [16] who stated that the routes of infection are multiple but the personal factor stays important. The hypothesis of his study was that intravenous lines may be important routes of infection and that contamination of cannula hub may precedes sepsis episodes.

This goes in hand with **Ponnusamy V** et al. [17] who reported that percutaneous central venous lines are independently responsible for most nosocomial bloodstream infections in the neonatal nursery and the density of skin flora at the insertion site is a major risk factor for catheter related sepsis.

In the present study, presence of maternal risk factors such as PROM, hypertension with pregnancy and diabetes mellitus didn't increase the risk for producing neonatal sepsis. This agrees with **Samuelsson A** et al. [15] who founded that premature rupture of membranes and fever during delivery did not seem to predispose to neonatal sepsis.

By studying the factors that may affect presepsin level and according to results of this study, at admission Hemoglobin level, serum HCO₃ level and blood PH were negatively correlated with presepsin levels, while platelets count was positively correlated with it.

This meets the findings of **Nagata T** et al. [18] whom founded a negative correlation between presepsin level and hemoglobin level & a positive but non-significant correlation between platelet count and presepsin.

CRP level was higher in septic group than in controls, also initial presepsin level was a highly sensitive marker for early diagnosis of sepsis being higher in cases than controls.

Rock curve analysis show that at a cut off value ≥ 0.722 $\mu\text{g/L}$, Presepsin sensitivity for early diagnosis of neonatal sepsis was 100 % with specificity 97.5%, positive predictive value (PPV) 98.7%, negative predictive value (NPV) 100%, AUC 0.99 and highly sensitive positive correlation with sepsis (P value < 0.001).

These results were close to **Poggi C** et al.[5] results who found that The area under the ROC curve for Presepsin was 0.972 (95% confidence interval [CI] 0.92–1.00) and that presepsin achieved the best accuracy for prediction of probable sepsis at the cutoff of 885 ng/L with 94% sensitivity (95% CI 74–100) and 100% specificity (95% CI 84–100). The positive and negative predictive values were 100% (95% CI, 83–100) and 95% (95% CI, 80–100).

Topcuoglu S et al. [3] founded that a presepsin value 800.5 pg/mL was established as a cut-off value with 67% (95% CI, 51–80.4) sensitivity and 100% (95% CI, 91–100) specificity. The positive and negative predictive values were 100% (95% CI, 88–100) and 74% (95% CI, 60–85), respectively.

On the other hand, in the current study and at a cut off value ≥ 2.65 mg/L, CRP sensitivity for early diagnosis for neonatal sepsis was 82.5% with specificity 77.5%, PPV of 88%, NPV of 68.9, AUC 0.89 and high positive significant correlation with sepsis (P value <0.001).

These results meet the findings of **Garnacho-Montero J** et al. [19]. They found that CRP sensitivity for early diagnosis of sepsis is 90.6%, specificity is 40.48%, PPV is 80.92% and NPV is 60.71%.

Khassawneh M et al. [20] reported that a CRP level >4 mg/L gave the best derived cutoff value with 95.7% sensitivity, 88.9% specificity, 78.6% PPV, and 98% NPV.

By the sixth day, presepsin levels had shown a high significant difference between improved and non-improved cases but this was not true regarding the CRP levels.

The prognostic value for presepsin was better than CRP as there was high significant difference between initial presepsin level and presepsin level at 6th day in improved group.

In the present study, at a cut off value < 2.3 $\mu\text{g/L}$, Prognostic sensitivity of presepsin was 75.9% with 72.5% specificity with PPV 61.1, NPV 84.1 and AUC 0.76. Presepsin has positive high significant difference with P value <0.001 which gives it a better prognostic value with better prediction of the outcome of septic cases.

These data agree with **Godnic M** et al. [21] results whose findings indicated that sCD14-ST may be a promising early diagnostic and prognostic marker in septic patients. In addition, because the sCD14-ST values were especially high in severe sepsis, and there was also positive correlation between the APACHE II scores ($p = 0.016$) and the presepsin values reflect the immune response to bacteria in sepsis.

On the other hand, in current work, at a cut off value <5.15 mg/L, prognostic sensitivity of CRP was 55.2%, with specificity of 56.9%, PPV of 42.1%, NPV of 69% and AUC of 0.54.

These results agree with **Poggi C** et al.[5] who found that CRP utility is questionable because its peak values are reached only after a 2- to 3-day delay after the infective stimulus, and its value can increase after non-infective inflammatory events.

Kordek A et al. [22] also founded that C-reactive protein concentrations began to decline after two days of antibiotic therapy but were still higher than in the control group after 5-7 days of treatment.

In the current study, CRP level was a good marker for diagnosis of sepsis but not in prognosis and expecting the outcome.

Conclusion:-

Our study showed that presepsin levels were significantly elevated in neonates that produce sepsis compared to those didn't produce neonatal sepsis. Presepsin sensitivity for early diagnosis of neonatal sepsis was 100 % with specificity 97.5%. Prognostic sensitivity of presepsin was 75.9% with 72.5% specificity. Presepsin can be used as a reliable biomarker for early diagnosis of neonatal sepsis, and also it is a promising marker for detection of improvement.

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