



Original Article



Serum Endocan as a Diagnostic Marker of Late Onset Sepsis in Preterm Neonates (Single center prospective study)

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DOI: 10.21608/ANJ.2020.36995.1013

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Abstract

Background: Despite the improvement in neonatal care, late onset sepsis (LOS) remains an important issue in neonates admitted to Neonatal Intensive Care Unit (NICU) and has been thought to be one of the main causes of morbidity and mortality especially in preterm ones. **Objective:** The aim of this work was to assess the clinical usefulness of serum endocan as an indicator of late onset sepsis (LOS) in preterm neonates. **Study Design:** We carried out this prospective cross sectional study on 111 preterm neonates; 61 treated for LOS and 50 preterm neonates without sepsis as controls. Sepsis group was further subdivided to proven and suspected sepsis groups according to positive blood culture. CBC, with differential count including immature by total ratio (I/T ratio), CRP, IL-6, and serum endocan were done to all preterm neonates within the first 2 hours of sepsis suspicion and at 3days and 7days later.

Results: Sepsis group showed significantly higher I/T ratio, CRP, IL-6, and serum endocan than control group ($p < 0.01$). Serum endocan was higher in preterm neonates with proven sepsis than suspected ones ($p = 0.04$); also increased at the 3rd day of onset of the sepsis then decreased at the 7th day of onset ($p < 0.01$ for both). There were significant positive correlations between serum endocan and both CRP and IL-6 ($p < 0.01$). ROC curve analysis showed that endocan at a cut-off point of > 5.5 ng/ml showed 88% sensitivity and 85 % specificity with 87% negative and positive predictive values.

Conclusions: Serum endocan was higher in septic than non-septic preterm neonates; which may indicate the usefulness of endocan as a marker of LOS not only in the early diagnosis but also as a follow up of treatment in those neonates

Key words: Endocan; late onset sepsis; LOS; preterm.

Background

Despite the improvement in neonatal care, late onset sepsis (LOS) remains an important issue in neonates admitted to Neonatal Intensive Care Unit (NICU) and have been thought to be one of the main causes of morbidity and mortality especially in preterm ones [1,2].

Neonatal late-onset sepsis (LOS) can be defined as infection which is clinically evident more than 72 hours after birth, and it is usually caused by nosocomial acquired organisms [3]. Early and conclusive diagnosis of LOS can be difficult because of general manifestations, which can be confused with other non-septic conditions, also the time required to get blood culture results may reach 72 hours and diagnosis couldn't be excluded by negative results [1,4-6]. Mortality rate of LOS may reach 50 % in untreated cases, so most neonatologists believed that the risk of LOS did not allow them to wait for the results of cultures. So In critically ill newborns, the decision of beginning

antimicrobial therapy is mainly based on clinical situations, regardless of the laboratory data [7].

Currently, there is no diagnostic biomarkers can prove LOS diagnosis. It may be impossible to easy differentiate between proved sepsis from those with suspected sepsis with query clinical manifestations [8]. Researchers continue to evaluate new markers for LOS in neonates other than C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin, or combinations of them which were believed as conventional markers of neonatal sepsis [9, 10].

Endothelial activation is an important factor of the host response to inflammation and can explain many aspects in the pathophysiology of sepsis. So markers related to it can be used to confirm sepsis and to follow-up those patients [11]. Endocan (also known as endothelial cell-specific molecule 1) is a 50-kD a proteoglycan which can be found in endothelial cells of different organs, and can be detected in human

blood [12,13]. It was found that serum endocan levels were significantly increased in sepsis adult patients compared to healthy controls; also its levels were correlated to disease severity and prognosis [14]. On the other hand, another study showed that serum endocan may be non-conclusive for systemic inflammatory response and its increase may be equivocal in these situations [15].

Aim of the work

We aimed in our study to assess the clinical usefulness of serum endocan as an indicator for LOS diagnosis in preterm neonates and compare it with traditional markers of LOS as I/T ratio, CRP, and IL-6.

Materials and Methods

Study design & subjects

This is a prospective cross-sectional study which was carried on 111 preterm neonates admitted to our tertiary NICU of Children Hospital of Minia University in Upper Egypt during the period of October 2018 to January 2020.

We obtained informed written consents from the parents of all neonates before they were included in this study. Our study was approved by the ethical committee of Faculty of Medicine, Minia University, Egypt.

Our preterm neonates were subjected to full history taking (pre-natal, natal and post-natal history, also serious clinical events after admission). Inclusion criteria were preterm neonates with clinical or laboratory manifestation of sepsis which occurred between 3 days old up to 1 month age. We excluded preterm neonates with early onset sepsis in the first 3 days of life, if their mothers had Chorioamnionitis or received antibiotic therapy, preterm neonates with hypoxic ischemic encephalopathy, multiple congenital anomalies, chromosomal abnormalities, or organ failure not associated with sepsis.

The sepsis group was subdivided into two groups according to the results of blood culture into group Ia preterm neonates with proven sepsis (30 preterm)

and group Ib preterm neonates with suspected sepsis (31 preterm). We start antibiotic therapy for all preterm neonates with suspected or proven sepsis according to our NICU protocol and the results of culture and sensitivity tests. Fifty apparently healthy preterm neonates with weight, postnatal ages and sex matched with the septic group. All neonates of this group were clinically free of signs of neonatal sepsis and normal laboratory parameters

Sepsis diagnosis: We suspected sepsis if three or more of the following clinical manifestations and risk factors for sepsis were found in addition to one of the following laboratory abnormalities as increased CRP levels (> 10 mg/L) or IL-6 (> 25 pg/mL), with exclusion of non-infectious syndromes that may show the same results [2,16-18]. These manifestations include (1) Respiratory abnormalities (e.g. tachypnea, apnea with increasing severity, or need for higher ventilator support); (2) Cardiac abnormalities (e.g. tachycardia

bradycardia, , mottling, or hypo-perfusion); (3) Metabolic changes (e.g. hypo or hyperthermia, metabolic acidosis, or hypoglycemia,); (4) Central nervous system abnormalities (e.g. irritability, disturbed conscious level, decreased activity, or convulsions); (5) Hematological findings (pallor, subcutaneous hemorrhage , splenomegaly, or bleeding); and (6) GIT abnormalities (feeding problems, abdominal distention, vomiting, or bleeding per rectum).

Sampling: Blood samples were withdrawn within 2 hours of neonatal involvement in our study and at the 3rd and 7th days after the first blood sample. CBC and CRP were routinely done according to our NICU protocol to all cases with suspected sepsis. Serum samples were stored at -60°C for later IL-6 and endocan measurements.

Laboratory methods: Complete blood count was done using automated cell counter sysmex KX-21N (TAO Medical Incorporation, Japan). CRP levels were

measured immunoturbidimetrically (detection limit: 6 mg/L); levels more than 10 mg/L were considered as abnormal. IL-6 assessment was done using commercially available enzyme-linked immunosorbent assays (ELISA, R&D Systems, Minneapolis, MN, USA). Endocan levels were measured by ELISA sandwich technique (Sunred Bio Company, Shanghai, China). Blood cultures were done using the BacT/ALERT® 3D Microbial Detection System (BioMerieux, France) and BacT/ALERT® PF plus culture bottles were employed for pediatric use. All samples were processed according to standard guidelines recommended by the manufacturer.

Statistical methods: we use SPSS program (Statistical Package for Social Sciences) software version 22 for analysis of data obtained from our study. Descriptive statistics were expressed for quantitative data using mean, standard deviation and range, while they were

presented for categorical data by number and percentage. Analyses were done for quantitative data among the three groups using One Way ANOVA test followed by Post-hoc Tukey correction between each two groups. Analysis for qualitative data was done using Chi-square test or Fisher Exact test. The degree of relationship between the variables was calculated using the Pearson correlation analysis. Correlation coefficient (r) ranges from (0-1):- weak (r = 0–0.24), fair (r = 0.25–0.49), moderate (r = 0.5–0.74), strong (r = 0.75–1). We use SPSS to perform Receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off values and diagnostic performance of the variables. The level of significance was taken at (P value < 0.05).

Results:

We included 111 neonates in our study, 61(55%) were males, while 50(45%) were females. Mean gestational age was 31.6 weeks; mean birth weight was 1.73 kg. Sixty one of the studied neonates had

LOS, 31 (51%) of them showed negative blood cultures (suspected sepsis group) and 30 (49%) showed positive blood culture (proven sepsis group). Fifty healthy preterm neonates were considered as control group. Our results showed no significant differences between the sepsis and control groups regarding maternal age, gender, gestational age, weight, Apgar score, and caesarian section delivery (Table 1). The results of blood cultures showed that 8 (27%) of positive cultures had *Escherichia coli* growth, 6 (20%) *Klebsiella* and *staphylococcus aureus*, 5 (17%) with *Streptococcus pneumonia*, 4 (13%) *Enterobacteria*, 1(3%) had *Pseudomonas aeruginosa* (Figure 1).

Table 2 showed that all of the studied sepsis biomarkers at 1-2 hours of study entry were significantly higher in the sepsis group than the control group [I/T ratio, CRP, IL-6, and endocan ($p<0.01$)]; except total leucocytic count TLC which showed insignificant difference between them ($p=0.09$).

Comparison between the suspected and proven sepsis subgroups as regard the studied sepsis biomarkers at enrollment or after 3 and 7 days of study entry showed no significant differences between all of them except serum endocan which was higher in proven than suspected sepsis group within 2 hours of sepsis suspicion ($p=0.04$) (Table 2). Serum endocan showed significant increase within 3 days from the onset of sepsis then significant decrease within 7 days ($p<0.01$ for both)

There were significant positive correlations between serum endocan and both CRP and IL-6; but there were insignificant correlations between it and gestational age, weight, TLC, and I/T ratio (Table 3, Figure 2,3,4). There were no correlations between serum endocan and the type of organism detected in blood culture results ($p=0.1$).

Roc curve analysis for the studied sepsis biomarkers (serum endocan, CRP, I/T ratio, and IL-6) showed good performance of all of them in

discriminating sepsis and healthy control preterm neonates. I/T ratio had 78% sensitivity and 75% specificity at a cut-off point 0.20, while CRP at a cut-off point of >19 mg/dl showed an 89% sensitivity and 90% specificity. (Table 4, Figure 5). The same table and figure showed that IL-6 had 91% sensitivity and 88% specificity at a cut-off point 29.2 pg/ml, while serum endocan at a cut-off point of >5.5 ng/ml showed an 88% sensitivity and 85 % specificity

Discussion:

Late onset sepsis remains one of the most important factors of morbidity and mortality in the neonatal period [19, 20]. Because of different causes, preterm neonates may show increased risk to develop late onset sepsis with incidence reaching 20% [21].

Blood culture is the gold standard in the diagnosis of LOS, but their results may need more than 48 hours, with the possibility of false negative results which ranged from 20-50 % of blood culture results [5,22]. As symptoms and signs of

LOS are non-specific, early and accurate diagnosis of LOS is difficult or may be delayed [3,5]; so other indicators are needed for rapid and accurate management. Traditional sepsis markers as CRP and IL-6 may be helpful in detecting LOS, but with different sensitivity and specificity, time and levels of elevation, and their affection by other systemic disorders [5,22,23]

The vascular endothelium is a component of the primary defense system involved in early recognition and protection against bacterial invasion. One of the most important functions of vascular endothelium is the control of vascular permeability by expression of surface proteins also the secretion of mediators, which can regulate coagulation, and coordinate migration of leucocytes towards the affected sites [12]. Endothelium activation due to microbial components release cytokines, chemokines and adhesion molecules which activate and attract leukocytes. Activated white blood cells and

endothelial cells secrete vasoactive substances. Excessive activation can generate vasodilation and systemic inflammatory response [24].

Endocan is a soluble proteoglycan which is secreted by the vascular endothelium [24].

The main objective of our study was to evaluate the potential role of serum endocan as a suitable indicator of LOS and to compare its levels with those of other traditional biomarkers of neonatal sepsis as CRP, I/T ratio, and IL-6.

In other studies [11, 14, 15, 25-27] in which the serum endocan was evaluated as a sepsis indicator, it was significantly increased in patients with sepsis. Similarly, the results of our study showed increased endocan in our neonate with LOS compared to the control group, which may indicate the significant value of endocan in diagnosing LOS in preterm neonate. Moreover, our results showed higher CRP, I/T ratio, and IL-6 levels in preterm neonates with LOS than the control group.

Serum endocan showed significantly increased levels in the preterm neonates with proven sepsis compared to the suspected sepsis group at study entry. On the other hand CRP, I/T ratio, and IL-6 demonstrated insignificant difference between the proven and suspected sepsis groups.

There is increasing evidence that endocan can be used in diagnosis of sepsis in adults. The first relevant study was conducted in 2006 by Scherpereel et al. [14], who stated that endocan level not only was higher in adult with sepsis but also, it was related to the severity of sepsis. Other studies [28, 29] showed the possible role of serum endocan as an indicator of sepsis in adults with a better discriminative power to differentiate septic patients from non-septic in comparison to CRP and procalcitonin.

During the neonatal period, there is few data evaluated the use of endocan in neonatal populations. To date, there are only two published studies on the usefulness of endocan in the neonatal

LOS diagnosis [11, 25]; both of them showed increased in endocan levels neonates with LOS.

The role of endocan in sepsis may be explained by binding of endocan to the Leukocyte Function-associated Antigen-1 (LFA-1) integrin on the surface of lymphocytes, monocytes and Jurkat cells and inhibits its interactions with endothelial Inter Cellular Adhesion Molecule-1 (ICAM-1). So, it regulates leukocyte migration to the site of inflammation. In this way, endocan acts as a protective molecule, decreasing tissue damage caused by excessive leukocyte diapedesis [25,29,30].

The significant decrease of serum endocan level on day 7 compared to the concentration measured on day 3 is compatible with the resolution of the systemic inflammatory response following specific treatment, as there are several data linking the synthesis and release of endocan to pro-inflammatory cytokines [8].

There were significant positive correlations between serum endocan and both CRP and IL-6; but there were insignificant correlations between it and gestational age, weight, TLC, and I/T ratio. This was against the results obtained by Seo et al, [31] who demonstrated insignificant correlations between serum endocan and both CRP and procalcitonin.

Serum endocan was higher in preterm neonate with positive blood culture early at the stage of sepsis suspicion but there were no correlations between serum endocan and the type of organism detected in blood culture results. This was in agreement with Seo et al., [31] who showed that positive blood cultures tended to be related to high endocan levels, but not significantly (odds ratio: 4.24, 95% CI: 0.99-10.34, P=0.05).

Sharma et al., [32] stated that sensitivity of minimum 80%, specificity more than 85%, PPV more than 85%, and NPV of approximately 100%, is needed to

consider any marker for the diagnosis of sepsis in neonates.

Our results demonstrated that endocan at a cut-off point of > 5.5 ng/ml showed 88% sensitivity and 85 % specificity with 87% negative and positive predictive values. This was in the same line with CRP, I/T ratio, and IL-6, indicating that all of them can be considered as good biomarkers of LOS in preterm neonates.

Our results were in agreement with Buyuktiryaki et al., [25] who showed that endocan may be used as a marker to differentiate LOS in preterm neonates with specificity, and sensitivity quite similar to CRP and IL-6 (using a cutoff value of 9.2 ng/ml); also, they showed that endocan was able to better differentiate between suspected and proven sepsis compared to CRP, IL-6 and WBC. Saldir et al.,[11] studied LOS in late preterm (GA > 34 weeks) and term neonates, and also demonstrated a predictive value of endocan like other new markers such as sTREM and IL-6 in

LOS, although with sensitivity and specificity around 70%.

Limitations for this work: A significant limitation of our study is the small number of the studied neonates. We recommend studies with larger sample size. Another limitation is the relation between serum endocan and outcome. Further studies are needed to evaluate the relation between serum endocan and mortality in those neonates.

Conclusion

In conclusion, we showed that serum endocan levels were significantly higher in preterm neonates with LOS than control preterm neonates especially early in the development of sepsis; its level increased in the first 72 hs from the onset of LOS and then decrease with treatment. This may indicate the usefulness of endocan as a marker of LOS not only in early diagnosis but also as a follow up of treatment in those neonates.

Acknowledgements

We would like to thank all staff members of our neonatology unit for their cooperation in this work

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Funding

Personally funded by the authors.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interests

No conflict of interest

Author's contributions

Mahgoub M: designing the work, Data acquisition, and interpretation of results and writing the manuscript. Mousa M: was responsible for doing the laboratory investigations and data interpretation, statistical analysis of the collected data and revision of the work. All authors have read and approved the submitted manuscript

Date received 26th July 2020, accepted 6th September 2020

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Table (1): Baseline demographic and clinical characteristics of the studied neonates.

Variable	Total (n=111)	Patients group (n=61)	Control group (n=50)	P. value (Sig.)
Maternal age (years)	29±7.5	28±6.4	29±5.4	0.29 ^{NS}
Sex (M/F)	61/50	33/28	28/22	0.38 ^{NS}
Gestational age (weeks)	31.6 ± 2.1	31.1 ± 1.8	31.8 ± 2.2	0.22 ^{NS}
Birth weight (kg)	1.73 ± 0.33	1.75 ± 0.29	1.57 ± 0.31	0.12 ^{NS}
Caesarean delivery (%)	85(77%)	44(40%)	41(37%)	0.24 ^{NS}
APGAR score at 5 min	7(6-8)	8(7-8)	7(6-8)	0.14 ^{NS}
Age at study entry (days)	7(6-14)	8(6-13)	7(6-14)	0.28 ^{NS}
Positive blood culture	30(27%)	30(27%)	0(0%)	0.000*

NS: Not significant.

*: Significant (p<0.01).

Table (2): The studied sepsis biomarkers among the studied groups

	Patients group (n=61)		p- value ^a	Control group (n=50)	p- value ^b
	Suspected sepsis (n=31)	Proven sepsis (n=30)			
At study entry					
TLC	16,214±3,415	17,524±5,274	0.14 ^{NS}	15,541±4,414	0.09 ^{NS}
I/T ratio	0.25±0.1	0.27±0.2	0.09 ^{NS}	0.12±0.05	<0.01*
CRP(mg/dl)	66.2±35.2	75.2±31.7	0.41 ^{NS}	2.5±2	<0.01*
IL-6 (pg/ml)	119.5±7.2	128.7±8.2	0.25 ^{NS}	11.8±0.5	<0.01*
Endocan (ng/ml)	35.9±12.4	37.4±7.8	0.004*	2.05±0.52	<0.01*
After 3 days					
WBC	12,321±3,114	11,981±5,254	0.25 ^{NS}		
I/T ratio	0.21±0.1	0.23±0.2	0.12 ^{NS}		
CRP (mg/dl)	33.4±15.1	35.4±12.4	0.22 ^{NS}		
IL-6 (pg/ml)	90.4±2.1	89.5±3.2	0.13 ^{NS}		
Endocan (ng/ml)	45.2±17.2	46.1±6.7	0.27 ^{NS}		
After 7 days					
WBC	13,142±4,214	11,117±3,654	0.11 ^{NS}		
I/T ratio	0.12±0.1	0.15±0.2	0.08 ^{NS}		
CRP(mg/dl)	4.3±1	3.9±1.2	0.74 ^{NS}		
IL-6 (pg/ml)	24.2±1.1	25.1±1.2	0.25 ^{NS}		
Endocan(ng/ml)	4.5±1.7	4.8±1.7	0.29 ^{NS}		

NS: Not significant.

*: Significant (p<0.01).

Abbreviations: CRP, C-reactive protein levels; IL-6, interleukin 6; I/T ratio, immature by total ratio; TLC, total leukocyte count

P-value^a: Comparison between suspected and proven sepsis groups.

P-value^b: Comparison between the control group with both suspected and proven sepsis groups.

Table (3): Serum Endocan correlations with the studied parameters

	Serum endocan	
	r	p
Gestational age (weeks)	0.22	0.9 ^{NS}
Weight (kg)	-0.16	0.19 ^{NS}
TLC	0.40	0.14 ^{NS}
I/T ratio	0.23	0.09 ^{NS}
CRP (mg/dl)	0.63	<0.01*
IL-6 (pg/ml)	0.79	<0.01*

NS: Not significant. *: Significant (p<0.01).

Abbreviations: CRP, C-reactive protein levels; IL-6, interleukin 6; I/T ratio, immature by total ratio; TLC, total leukocyte count

Table (4): ROC curve analysis of I/T ratio, CRP, IL-6 and serum endocan for prediction of neonatal sepsis

Item	Cutoff point	Sensitivity %	Specificity %	PPV%	NPV%
I/T ratio	0.20	78	75	79	76
CRP (mg/dl)	18	89	90	91	90
IL-6 (pg/ml)	29.2	91	88	92	89
Endocan (ng/ml)	5.5	88	85	87	87

AUC, area under the curve; CRP, C-reactive protein levels; IL-6, interleukin 6; I/T ratio, immature by total ratio; NPV, Negative predictive value; PPV, positive predictive value; ROC, Receiver operating characteristic curve.

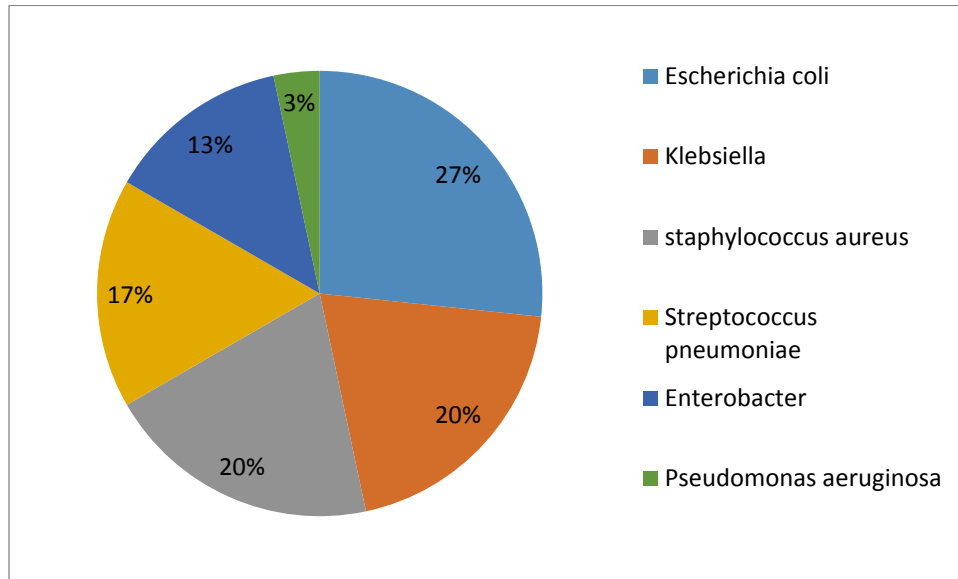


Figure (1): Distribution of pathogens in blood culture of proven sepsis preterm neonates.

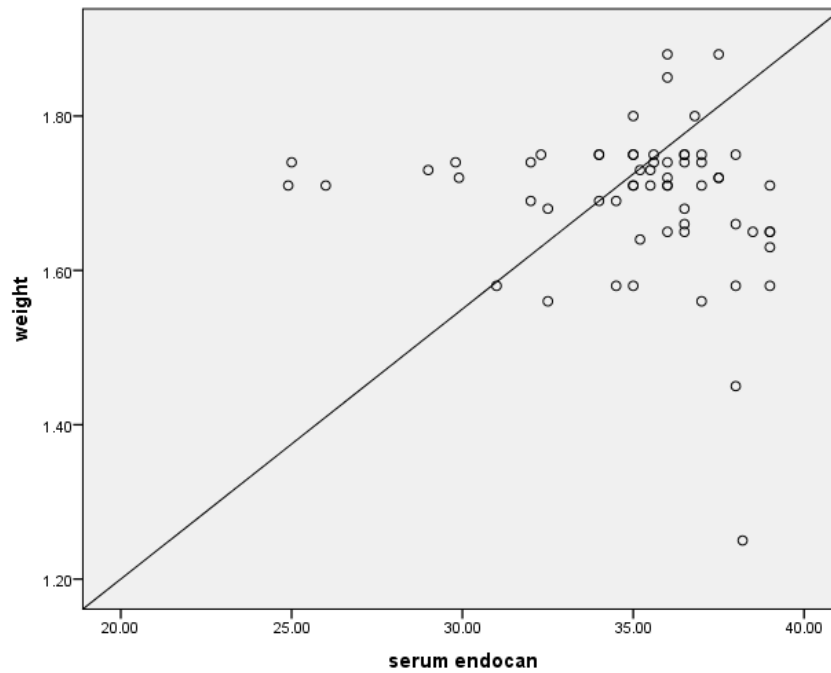


Figure (2): Correlation between serum endocan and weight

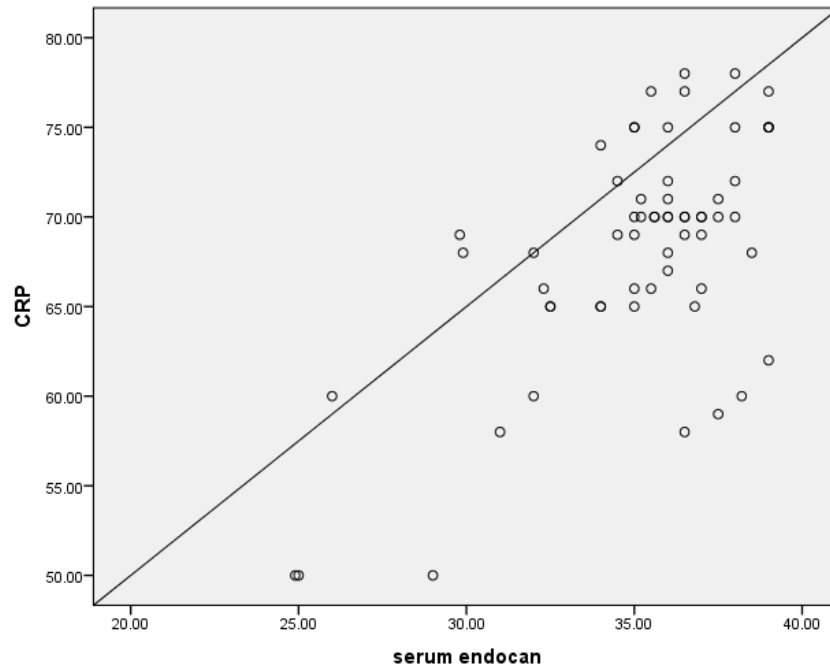


Figure (3): Correlation between serum endocan and CRP

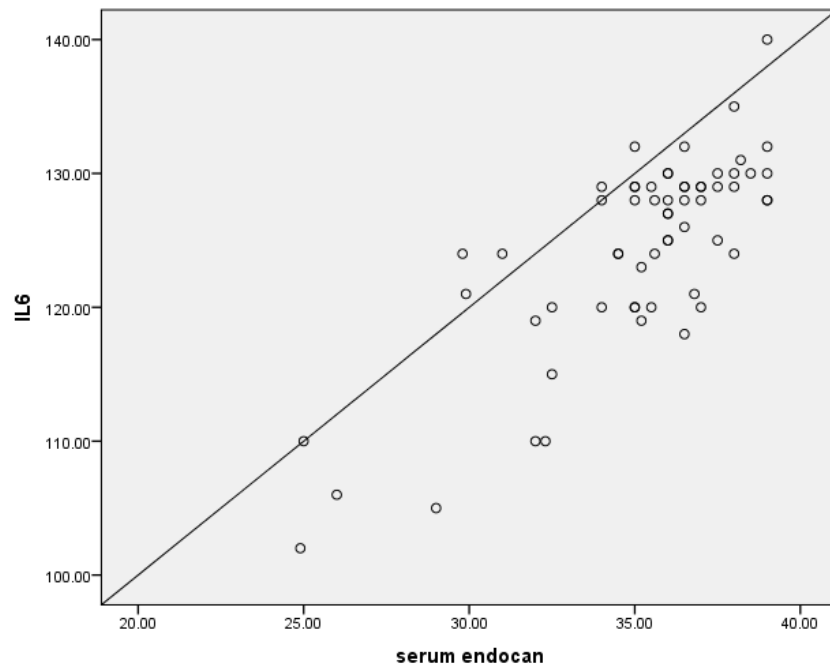


Figure (4): Correlation between serum endocan and weight

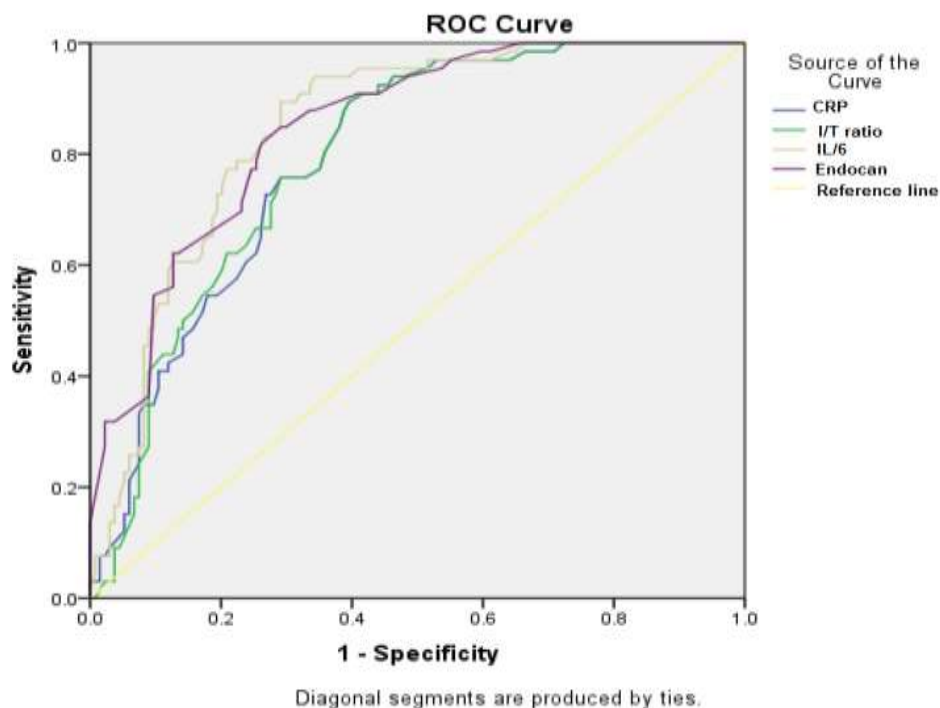


Figure (5): ROC curve analysis of I/T ratio, CRP, IL-6 and serum endocan for prediction of neonatal sepsis

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Citation: Mahgoob, M., Moussa, M. Serum Endocan as a Diagnostic Marker of Late Onset Sepsis in Preterm Neonates (single center prospective study). *Annals of Neonatology Journal*, 2021; 3(1): doi: 10.21608/anj.2020.36995.1013

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