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Original article

Value of Soluble Urokinase Type Plasminogen Activator Receptor as Marker for Neonatal Sepsis or Infection

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Abstract:

Background: Neonatal sepsis is a common problem with global burden due to its related comorbidities and mortalities. Aim of the work: evaluating the clinical value of soluble urokinase type plasminogen activator receptor in the diagnosis and prognosis of neonatal sepsis. **Patients and methods:** The study was performed on 26 neonates with suspected or proven sepsis and 26 apparently healthy neonates with matched age and sex. All neonates were subjected to history taking, clinical examination and laboratory investigations including, complete blood count, C-reactive protein (CRP), blood culture, and suPAR. **Results:** The first suPAR levels of the sepsis group were significantly higher than those of the controls (p-value 0.001). The suPAR level sowed significant positive correlations with the respiratory rate (RR), hematological sepsis score and CRP and a significant negative correlation with the Apgar score. ROC curve analysis showed that a suPAR cutoff value of 7.1ng/ml can be a good diagnostic test for septic shock with 96.2% sensitivity and 96.2% specificity (AUC, 0.96 and 95% CI, 0.88-1.00). ROC curve analysis revealed that suPAR has 83.3% sensitivity, 85.7% specificity, 83.3% PPV, and 85.7% NPV for predicting prognosis of newborn sepsis at cut-off point > 16 ng/ml with AUC 0.86, 95% CI (0.69-1.00). **Conclusions**: The suPAR level is a good marker of inflammation in neonatal sepsis for it was significantly increased among neonatal sepsis patients compared to controls and is a prognostic marker among these patients. The suPAR level has significant positive correlations with the respiratory rate (RR), hematological sepsis score and CRP and a significant negative correlation with the Apgar score.

Keywords: Neonatal; sepsis; suPAR; hematological score.

Introduction:

Neonatal sepsis is the most important cause of neonatal deaths in hospital as well as community in developing countries (1). It is defined as any infection involving the newborn during the first 28 days of life, also known as "sepsis neonatorum". Many organisms are involved in neonatal sepsis like viruses (as herpes and rubella), bacteria (as group B streptococci) and more rarely fungi (as candida) (2). It does not yet have a consensus case definition, especially for low- and middle-income countries (LMICs) (3).

Neonates are immunologically immature. They have reduced skin barrier, reduced humoral response and diminished microbial diversity in gut microbiota. All contribute to a higher risk of life-threatening bacterial infection, often presenting as sepsis (4). Neonatal sepsis is widely classified into early onset sepsis (EOS) and late-onset sepsis (LOS). Early onset sepsis is defined as sepsis within 48-72 hours of birth;

late-onset sepsis usually appears three days after delivery (5).

Soluble urokinase plasminogen activator receptor (suPAR) is a protein present in the blood, and its concentration is thought to reflect a person's level of chronic inflammation and immune activation (6). The soluble urokinase plasminogen activator receptor (suPAR), a secreted circulating glycoprotein ranging from 20 to 50k Da, was recently described as a promising biomarker in various clinical conditions (7). It is a marker of immune activation, and its levels are elevated in various conditions such as increasing age, diabetes, atherosclerosis, heart failure, sepsis, HIV, autoimmune diseases, and smoking (8, 9, 10).

The actions of suPAR, highly expressed during immune system dysfunction, include activating plasminogen conversion to the proteolytically active plasmin through localization of urokinase, and as an orchestrator in dynamic substratum interactions such as cell adhesion, extracellular matrix degradation and in cytoskeletal reorganization (6).

Aim of Study

In this study, we evaluated the clinical use of soluble urokinase type plasminogen activator receptor in the diagnosis and prognosis of neonatal sepsis.

Patients and Methods

This is a comparative sectional study. The study was carried out in neonatal intensive care unit (NICU) of Benha University Hospital and El-Mahlla General Hospital during the period from October 2021 to September 2022.

It was conducted on 52 neonates; 26 neonates with suspected or proven neonatal sepsis and 26 apparently healthy neonates with matched age and sex who had no signs of clinical and laboratory infection. Ethical permission was obtained from the parents after approval from Research Ethical Committee of Benha Faculty of Medicine.

Statistical Analysis

The data were recorded on an "Investigation report form". These data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 16 to obtain

***Descriptive data*:**

Descriptive statistics were calculated for the data in the form of:

1. Mean.
2. Standard deviation (±SD).
3. Median and Range.
4. Number and percent.

***Analytical statistics*:**

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests: -

1- Student's t-test was used to compare between means of two groups of numerical (parametric) data, for continuous non-parametric data, Mann-Whitney U-test was used for inter-group analysis.
2- Pearson and spearman correlation coefficient (r) test was used correlating different parameters.
3- Inter-group comparison of categorical data was performed by using chi square test (X2-value).
4- Paired t test was used for two values within the same group (pre and post) for continuous non- parametric data, Wilcoxon test was used.
5- The sensitivity and specificity were examined at different cutoff points using ROC curve analysis to determine the best cutoff point as well as the diagnostic power of each test. P value <0.05 was considered statistically significant in all analyses.

Inclusion criteria

All neonates which fulfilled the following criteria:

1- Term and preterm neonates.
2- Age from day 1 to 28 day.
3- Early onset sepsis and late onset sepsis.
4- Bacterial infection.

Exclusion criteria

1-Administration of antibiotic treatment before the study entry
2-Congenital anomalies
3-Metabolic syndromes
4-Surgery

The studied neonates were divided into two groups:

Group I, patients' group:

It includes 26 neonates admitted to NICU with neonatal sepsis risk factors or with suspected or definite sepsis

Neonates with suspected sepsis who had sepsis risk factors such as foul-smelling amniotic fluid, maternal leukocytosis, maternal fever, or increased maternal C-reactive protein.

Neonates with definite sepsis were diagnosed based on history, clinical sepsis score, haematological sepsis score, and laboratory findings (positive blood culture and positive CRP).

3- Investigations:

Both the patient and control groups were subjected to**:**

a) Complete blood count including Hb**%,** platelet count and differential leucocytic count (**12**).

b) Measurement of C-reactive protein (CRP) was done at admission and after 72 hours for the patients' group and once only for the control group.

c) Blood culture (patients group only): if the result was no growth, the culture was repeated again.

For the blood culture:

Members of this group have a gestational age (GA) of 38.08 weeks and a birth weight (BW) of 2.78 kg; fourteen males (53.8%) and twelve females (46.2 %).

Group II, control group:

The 26 neonates in this group were matched for age, weight, and sex and appeared to be in good health with no signs of infection.

Neonates with physiological jaundice, with low birth weight, or coming for routine medical examination served as the control group.

The members of this group have the gestational age (GA) ±38,38weeks and a birth weight (BW) of 3.08 kg, thirteen males (50.0%), and thirteen females (50.0%).

Methods

On admission full history, clinical examination and investigation were done for all participating neonate in the study

1- Full medical history taking: -
   Including antenatal, natal, and postnatal history
2- Medical examination: -
   Physical exam included vital signs, estimation of gestational age and neurological exam (11).

CBC measurement was done on (5-part 2 Sysmex XN330 Hematology Analyzer, made in Japan)

Two milliliters of blood were obtained after thorough cleaning of the withdrawing site using alcohol followed by iodine solution and then allowed to dry. Blood was put into two culture bottles containing broth to let both aerobic and anaerobic microorganisms to grow (**13**).

d) Soluble Urokinase Plasminogen Activator Receptor:

Serum levels of human soluble uPAR were measured by enzyme linked immunosorbent assay (ELISA) using quantikine human uPAR immunoassay; supplied by Sunred, China, catalogue No.; 201-12-5720.
Sensitivity: 4.368pg/ml, detection rang: 5pg/ml→1000pg/ml.

For each septic neonate, a sample was withdrawn early on admission and suPAR was measured on initial sepsis evaluation at day 1 and another sample was withdrawn at 72 hours after antibiotic therapy. For the control group, suPAR levels were examined once.

Results

Our study involved 52 neonates, 26 of whom had suspected or confirmed neonatal sepsis and 26 of whom seemed to be healthy. The results indicated that there were no statistically significant differences in terms of age, sex, gestational age, method of birth and consanguinity between the sepsis and control groups, but there was a statistically significant difference in terms of type of feeding (p-value = 0,001). In the infected group, the most common feeding pattern was intravenous feeding (IVF) (in 50% of the patients) followed by artificial feeding (23.1%), mixed feeding (19.2%) and breastfeeding (7.7%). In the control group, the most common feeding pattern was breast milk (46.2%), followed by artificial (26.9%), mixed feeding (26.9%), and no IVF.

We found no statistically significant differences in body temperature, pulse rate, systolic blood pressure or diastolic blood pressure between the sepsis and control groups. The neonatal sepsis group showed a statistically significant increase in RR and Apgar score at 1 and 5 minutes compared to the control group with a P-value of 0.001, as well as an increase in the first CRP level and first haematological sepsis score. Moreover, an increase of the first suPAR level of the sepsis group compared to control groups with p-value < 0.001.

As for the patients' group, we found no statistically significant differences between the first and second sepsis haematological scores, first and second CRP levels, first and second suPAR levels and first and second clinical scores with p-value (0.37, 0.25, 0.9, and 0.6 respectively). With 96.2% sensitivity and 96.2% specificity (AUC, 0.96 and 95% CI, 0.88-1.00), ROC curve analysis showed that a suPAR cut-off value of 7.1 ng/mL might be a very good diagnostic test for septic shock (Fig. 1). According to Receiver Operating Characteristic (ROC) curve study, suPAR at cut-off point >16ng/ml with AUC 0.86, 95% CI (0.69-1.00), had 83.3% sensitivity, 85.7% specificity, 83.3% PPV, and 85.7% NPV for predicting the prognosis of newborn sepsis (Fig. 2). The results showed a positive and statistically significant relationship between the baseline suPAR levels, RR, total haematological score, and CRP level. Baseline suPAR levels had no statistically significant relationship to gestational age, body mass index, height, weight, head circumference, abdomen circumference, pulse rate, or systolic or diastolic blood pressure. However, there was a statistically significant negative correlation between baseline suPAR levels and APGAR scores at 1 and 5 minutes.

In early and late sepsis, group B Streptococci, Staphylococcus aureus, and coagulase-negative Staphylococcus aureus were the most frequently found pathogens. However, in follow-up cultures, these pathogens had decreased frequency with an increase in Klebsiella pneumonia frequency. Regarding the first SUPAR level and second SUPAR level, Table (1) demonstrates that statistically significant decrease of the first SUPAR level

and second SUPAR level of the improved group compared to the deteriorated groups with p-value < 0.001. According to table (2), suPAR had an AUC of 0.96 with a 95% CI, 0.884-1.00 and 96.2% sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of newborn sepsis. Based on this table, CRP had an AUC of 0.942 with a 95% CI (0.877-1.00 range) and 92.3% sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the diagnosis of newborn sepsis. This table, also, shows that for the diagnosis of newborn sepsis, the hemological score at cutoff point > 3.5 had an AUC of 0.950 with 95% CI (0.876-1.00), 88.5% sensitivity, 92.3% specificity, 92% PPV, and 88.9% NPV and that the clinical score at cutoff point >2 had an AUC of 0.951 with 95% CI (0.893-1.00) sensitivity and 84.6% specificity.

Table (1): 1st and 2nd SUPAR levels in the improved and worsened groups

SUPAR levels	Improved (n=12)		Worsened (n=14)		p-value
	Mean	SD	Mean	SD	
1st SUPAR level	12.53	2.62	17.91	4.51	<0.001*
2nd SUPAR level	9.03	1.62	26.95	11.31	<0.001*
p-value	<0.001*		<0.001*		

Table (2): ROC curve analysis of different parameters for diagnosing neonatal sepsis

Variable (baseline)	Cutoff value	AUC	95% CI	Sensitivity	Specificity	+PV	-PV
suPAR (ng/mL)	>7.1	0.96	0.884 - 1.00	96.2	96.2	96.2	96.2
1st CRP	>10.5	0.942	0.877 - 1.00	92.3	92.3	92.3	92.3
1st Haematological sepsis score	>3.5	0.950	0.876 - 1.00	88.5	92.3	92	88.9
1st Clinical Score	>2	0.951	0.893 - 1.00	100	84.6	86.7	100

suPAR: soluble urokinase plasminogen activator receptor. ROC: Receiver Operating Characteristic

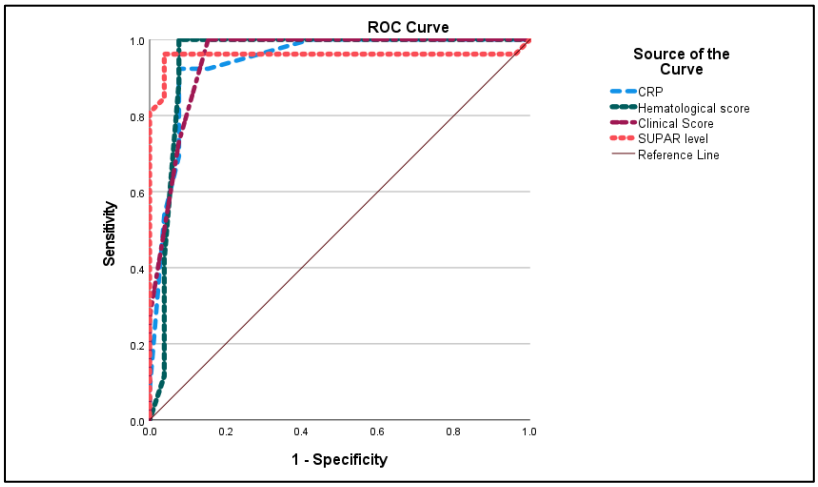

Fig. (1): Receiver Operating Characteristic (ROC) curve analysis of different parameters for the diagnosis of neonatal sepsis

Table 3 shows that suPAR had cut off point > 16, an AUC of 0.86 with a 95% confidence interval of 0.69-1.00, 83.3% sensitivity, 85.7% specificity, 83.3% PPV, and 85.7% NPV for predicting the prognosis of neonatal sepsis. CRP at cut-off point > 36 showed an AUC of 0.714 for neonatal sepsis prognosis, with 95% CI (0.5-0.93) sensitivity, 64.3% specificity, 75% PPV, and 64.3% NPV. According to this table, the homological score at the cut-off points of >4.5 had an AUC of 0.607 with a 95% (0.38-0.84), 58.3% sensitivity, 71.4% specificity, 63.6% PPV, and 66.7% NPV for prediction of new-born sepsis. This table demonstrated the clinical score at the cut-off point of >3.5 had an AUC of 0.613 with a 95% CI (0.39-0.84) with 91.7% sensitivity, 42.9% specificity, 57.9% PPV, and 85.7% NPV for new-born prognosis.

Table (3): ROC curve analysis of different parameters for prognosis of neonatal sepsis

Variable (baseline)	Cut-off value	AUC	95% CI	Sensitivity	Specificity	+PV	-PV
suPAR (ng/mL)	>16	0.86	0.69 - 1.00	83.3	85.7	83.3	85.7
2nd CRP	>36	0.714	0.5 – 0.93	75	64.3	75	64.3
2nd Haematological score	>4.5	0.607	0.38 - 0.84	58.3	71.4	63.6	66.7
2nd Clinical Score	>3.5	0.613	0.39 – 0.84	91.7	42.9	57.9	85.7

suPAR: soluble urokinase plasminogen activator receptor. ROC: Receiver Operating Characteristic

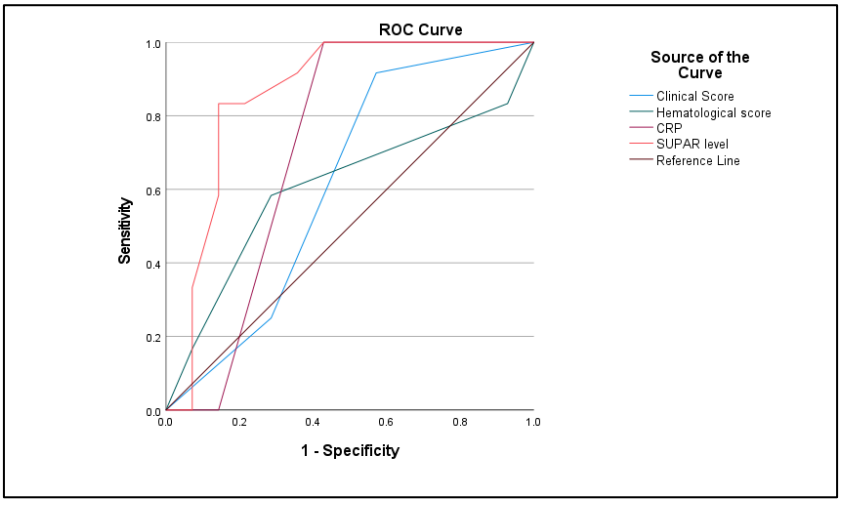

Fig. (2): Receiver Operating Characteristic (ROC) curve analysis of different parameters for the prognosis of neonatal sepsis

Discussion:

Neonatal sepsis is defined as a clinical syndrome characterized by systemic signs and symptoms of an inflammatory response in the presence of or as a result of suspected or proven infection during the first month of life (14). Several hematological tests such as total leukocyte count, total neutrophil count, immature neutrophil count, immature/total neutrophil ratio, morphological and degenerative changes in neutrophils have been used for early and reliable diagnosis of neonatal sepsis. The non-specific nature of these tests has directed clinicians to search for more specific laboratory tests (15).

The urokinase plasminogen activator receptor (UPAR) is expressed on most leucocytes including neutrophils, lymphocytes, monocytes, and macrophages which are crucially important in the pathogenesis of sepsis. The interaction of UPAR with its ligand the urokinase plasminogen activator results in numerous immunologic events including cell migration, adhesion, proliferation and fibrinolysis. After cleavage from the cell surface, the soluble form uPAR can be found in the blood and other organic fluids (16).

This study was performed on 26 neonates with suspected or proven neonatal sepsis and 26 age and sex matched apparently healthy neonates with no clinical and laboratory manifestations of infection. All the included neonates were subjected to full medical history taking, clinical examination and laboratory investigations including, complete blood count, C-reactive protein, blood culture, and serum level of suPAR.

In the current study, we found statistically significant increment of the RR of neonatal sepsis group compared to control group with p-value <0.001. This goes with the study which also found that the RR significantly increased in the neonatal sepsis group compared to the control group with p-value <0.001 (17). Similarly, an Egyptian study done on 30 neonatal sepsis patients and 30 controls to evaluate the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and procalcitonin as markers of sepsis and found significantly increased RR in neonatal sepsis group compared to control group with p-value <0.001 (18). Similarly, it was found that neonatal sepsis patients had significantly higher RR compared to control group (19)

In the current study, there were significantly lower APGAR scores at 1 and 5 minutes among the sepsis group compared to the controls with p-value <0.001. A previous study was done on 103 neonatal sepsis cases in addition to 797 control neonates to evaluate the predisposing factors of neonatal sepsis (20). They found a significant association between decreased APGAR score at 1st and 5th minutes and development of neonatal sepsis with p-value <0.001. A study was conducted on 423 patients with neonatal sepsis to determine the proportion and risk factors of neonatal sepsis and reported that low APGAR score was significantly associated with development of neonatal sepsis with p-value <0.05 (14).

Ninety-one patients with neonatal sepsis were examined, in addition to 193 controls to determine risk factors and etiology of neonatal (20). The results revealed that statistically significant decrease of APGAR score <7 at five minutes was significantly associated with risk of neonatal sepsis (p-value <0.05). This was explained by that the risk of development of perinatal asphyxia in low APGAR score neonates in turn leads to development of immunological insult (22). A study was performed on 351 neonates to find the prevalence of neonatal sepsis and found a statistically significant association between APGAR <6 score and the risk of neonatal sepsis with p-value <0.05 (23). Their explanation was that neonates who had a

decreased APGAR score might have been exposed to infective microbes at birth or might have a compromised respiratory and other body functions at birth which pose a risk to infection later in life compared to those neonates functioning well at birth**.**

Blood culture remains the gold standard for diagnosis of sepsis, here, in the current study, group B *Streptococci, Staphylococcus aureus* and coagulase negative *Staphylococcus aureus* (CONS) were the commonly detected organisms in early and late sepsis, while in follow up the cultures, and these organisms were less frequent with increased prevalence of Klebsiella pneumonia (7.7%). An Egyptian study was conducted on 40 neonates with sepsis and 25 controls to determine the significance of the hematological sepsis score (HSS) in early detection of neonatal sepsis (31). They found that the most commonly detected organisms were Klebsiella in 30% of the patients, *E. coli* in 20% and CONS in 10% **.** In the study of Jacob et. al. (24), it was found that the commonly detected organisms were *Staphylococcus aureus* in 22.5% of the patients, Klebsiella in 18.6% and Acinetobacter (12.8%)**.** From the variable results obtained from different studies, it is evident that the causative organisms of neonatal septicemia vary from nursery to nursery, between different geographical areas and in the same catchment area. This variation may be due to differences in the environment, microbial etiology of sepsis, supportive care practice and hygiene measures (25).

CRP is an acute phase reactant which belongs to the pentraxin family and is produced in the liver. The current study found significantly higher CRP levels among neonates with sepsis compared to control with p-value <0.001. This finding goes in concordance with the results of another prospective study which found CRP to be a valuable laboratory test in assessment of febrile infants aged <3months (26). Similarly, Li and co-workers **(17)** reported significantly higher CRP in neonatal sepsis patients compared to controls with p-value <0.001**.** Similarly, a study was conducted on 111 neonates with sepsis to determine its related clinical characteristics and found significantly higher CRP (<0.001) (29)**.** However, another study revealed that CRP level was not elevated at the onset of clinical sepsis in about one-fourth of the neonates with spontaneous bacterial infection and concluded that CRP level was an inadequate predictor of bacterial infection in neonates (27). The low sensitivity of CRP may be due to its delayed elevation; an estimated 6-12 hours is needed for significant increase (28). This gives attention to the development of other inflammatory markers rather than CRP.

In the current study, there was a significantly higher hematological sepsis score among neonatal sepsis patients compared to controls with p-value <0.001. This agrees with the recent study which was conducted on 51 neonates with sepsis and 30 controls to evaluate the performance of hematological sepsis score and revealed a significantly higher HSS among neonatal sepsis patients compared to a control group with p-value <0.001 (30)**.** Similarly, another recent study revealed statistically significant increase of hematological sepsis score among neonatal sepsis patients compared to the control group with p-value <0.001 (31)**.**

In the current study, there was a significantly increased soluble urokinase plasminogen activator receptor among neonatal sepsis patients compared to controls with p-value <0.001. This goes with the study which was conducted on 40 patients of neonatal sepsis and 26 controls in Ankara University Faculty of Medicine to investigate the level of suPAR in neonates with sepsis and revealed significantly higher suPAR levels among patients of neonatal sepsis (14.7±6.7 ng/ml) compared to the control group (6.3±1.8 ng/ml) with p-value =0.000 **(32).**

In the current study, soluble urokinase plasminogen activator receptor at cut off point > 7.1 ng/ml had AUC 0.96 with 95% CI (0.88-1.00), 96.2% sensitivity and 96.2% specificity for prediction of neonatal sepsis and at cut off point > 16 ng/ml had AUC 0.86 with 95% CI (0.69-1.00), 83.3% sensitivity and 85.7% specificity for prediction of neonatal sepsis. Another study revealed that at a cutoff point of 2.8 ng/ml suPAR had a sensitivity of 92% and specificity of 85% for diagnosis of neonatal sepsis (16). It was concluded that at cutoff point 11.3 ng/ml suPAR had sensitivity 82.5% and specificity 100% for diagnosis of neonatal sepsis (32)**.**

The current study revealed a statistically significant decrease in suPAR among improved patients with p-value <0.001, while there was significant increase in suPAR among worsen cases with p-value <0.001. Similarly, it was proved that in the study which was conducted on 47 neonatal sepsis cases and 18 healthy neonates to evaluate the clinical value of suPAR in detection of neonatal sepsis revealed a statistically significant decrease in suPAR among neonatal sepsis patients throughout their course of the disease which makes the importance of suPAR not only in diagnosis of neonatal sepsis but also in its follow up (33)**.**

A study conducted on 43 cases with neonatal infection and 10 controls to determine the levels of serum suPAR risk of infection among neonatal sepsis, found that the level of suPAR continues to decrease among improving sepsis group significantly with p-value <0.05 (34)**.** This can be because suPAR released in the circulation process is not only due to inflammation but more because of the inability of the host defense. This can explain why suPAR levels have quite high prognostic value compared to other biomarkers **(35).**

In the current study, there was a statistically significant positive correlation between the levels of soluble urokinase plasminogen activator receptor and CRP with p-value <0.001. This agrees with the previous Egyptian study of Abdel Rahman and colleague (36) in Benha University which was conducted on 70 critically ill children with sepsis and revealed a statistically significant positive correlation between suPAR and CRP with p-value =0.03**.** Similarly, the study done previously (**33)** revealed a statistically significant positive correlation between suPAR and CRP among neonatal sepsis cases with p-value =0.001**.** The positive correlation between suPAR and CRP is in accordance with the fact that circulating suPAR levels reflect the degree of immune activation and systemic inflammation (37).

The current study revealed that the hematological sepsis score was significantly higher among sepsis group compared to controls with p-value <0.001. Also, this hematological score at cutoff point >3.5 had AUC0.950 with 95%CI (0.876-1.00) had 88.5% sensitivity, 92.3% specificity, 92% PPV and 88.9% NPV for prediction of neonatal sepsis. This agrees with the study which was conducted on 40 neonates with sepsis to measure the hematological scoring and revealed that HSS score ≥4 had sensitivity 80%, specificity 90%, PPV 73%, and NPP 93% with AUC 0.902 (95% CI 0.803-1.0) **(38).** Another study was performed on 21 neonates with culture proven sepsis to evaluate the neonatal hematological score and revealed that HSS > 5 had 69% sensitivity, 76% specificity, 54% NPV, 85% PPV for prediction of neonatal sepsis (39)**.** The study of a group of researchers was conducted on 150 neonates with clinical suspicion of sepsis and revealed that HSS ≥ 5 had highest sensitivity 93.7% in prediction of neonatal sepsis (40)**.**

Conclusion

Based on our research, SuPAR can be considered as a powerful marker of inflammation in neonatal sepsis with statistically significant increment in newborn

sepsis patients compared to controls. SuPAR showed strong correlations with other inflammatory indicators such as CRP and the haematological sepsis score. The best cutoff point for determining the presence of neonatal sepsis was > 7.1 ng/ml with 96.2% sensitivity and 96.2% specificity and the cutoff point for determining the prognosis of neonatal sepsis was > 16 ng/ml, with 83.3% sensitivity and 85.7% specificity.

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