Value of soluble urokinase plasminogen activator receptor as biomarker of sepsis in critically ill children in intensive care unit

Abstract

Objective: the ability of SUPAR (soluble urokinase plasminogen activator receptor) to evaluate sepsis and predict mortality in critically ill children in pediatric intensive care unit (PICU). **Methods:** the study included 70 critically ill children admitted to PICU , divided into two groups group (A)(critically ill children with sepsis)& group (B) (critically ill children without sepsis(SIRS)) compared to matched age ,sex 30 healthy children as a control group. Clinical examination was performed ,including calculation of the pediatric Risk of mortality (PRISM) and (q sofa) in first 24 hr of admission. **Results:** suPAR level was significantly higher among the total patient study group compared to controls ($p<0.001$) . suPAR was higher in patients with sepsis Group (A)compared to group (B)(critically ill without sepsis) ($p<0.001$) ,SUPAR level has significant positive correlation with mortality risk scores (PRISM) score and(q SOFA) score with p-value(<0,001),Furthermore, suPAR level was significantly elevated in non-survivors compared to survivors (p 0.001). AUC was 0.99 for suPAR for diagnosis of sepsis while C-reactive protein (CRP) had an AUC of 0.90 and total leucocyte count (TLC)) had an AUC of 0.87. Our study show good sensitivity for marker (SUPAR) 90% with specificity 96.7% at cut off value >or=120,2 pg/ml with accuracy 92%. **Conclusions:** suPAR has both a diagnostic and a prognostic value for diagnosis sepsis between critically ill children. It also may be superior to the classic laboratory markers as CRP and TLC also can be considered predictor for mortality or organ damage in critically ill children.

Keywords Soluble urokinase plasminogen activator receptor; Sepsis; PICU(pediatric intensive care unit); SIRS(systemic inflammatory response syndrome)

Introduction:

Sepsis newly defined as infection lead to dysregulation of host response if un treated may lead to life threatening multisystem failure, considered burden of mortality and morbidity in children(1). Epidemiological data reported high incidence of pediatric sepsis reaching up to 8% of all children in intensive care unit, representing one of four deaths in PICU(2).

The definition of (SIRS) systemic inflammatory response syndrome describes acondition of pathological complex response to an insult as trauma, burn,infection or any other injury(3),while diagnosis of sepsis can be considered when there is evidence of (SIRS)plus presence of suspected or proven infection(4).

Sever sepsis defined in case of presence of organ dysfunction and septic shock in presence of cardiovascular dysfunction(5).

Early administration of antibiotic and hemodynamic stabilization by intravenous fluid or colloids or inotropes considered the main steps for initial management of sepsis, Recent studies recommended starting antibiotic within three hours of admission and only within one hour in case of septic shock(6).

Up till now ,Blood culture is considered as the gold standard in identification for fungal and bacterial organisms but may be time consuming and its results may be affected by prior antimicrobial intake, So extensive studies nowadays searching for early detectors of sepsis, considering novel biomarkers or combination of biomarkers with clinical scores may relieve significant value in early detection of pediatric sepsis(7)

SUPAR(soluble urokinase plasminogen activator receptor) is the soluble form of membrane bound receptor UPAR, introduced in blood stream during the pro-inflammation conditions during cleavage from the surface of immunological active cells. concentration of SUPAR thought to be reflection of aperson level of immunity activity as its expression and release upregulated by immune activation(8),So SUPAR can be considered amarker of disease severity associated with risk of morbidity and mortality in several both acute and chronic disease(9).

It is expressed on anumber of different cells especially on vascular endothelial cells ,neutrophils ,monocytes and activated T-cells, for that it is involved in several immune functions including migration ,adhesion, angiogenesis, fibrinolysis and cell proliferation, Supar level is elevated in several diseases including, cardiovascular disease,malignancy,infections,type2 DM ,renal disease, focal segmental glomerulosclerosis ,HIV, tuberculosis and autoimmune disease like rheumatoid arthritis and SLE and can predict mortality early(10,11)

SUPAR also present in plasma , blood ,urine ,serum and cerebrospinal fluid also pericardial, pleural and peritoneal fluid. In the present study, the authors hypothesized that suPAR measurement at admission into the PICU has a value in diagnosing sepsis among critically ill children as well as in predicting mortality and disease severity among them

Subject and method

This case control study, included 70 Egyptian children who had been admitted into a PICU in benha University Hospital and another matched age and sex 30 healthy child as control, Egypt from February 2021 to October.2021,this study was approved by the Research and Ethics Committee of the Faculty of Medicine,Benha University.

Inclusion criteria was

1) age beyond neonatal period to 16 years

2) Critical illness requiring ICU admission

3) study includes both sex

4) blood sample withdrawn with in first 24 hours of admission

5) Parental consent

Exclusion criteria included

1) Patient in the neonatal period or older than 16 years

2) With no parent consent

3) Critically ill patient with blood sample cannot be withdrawn in first day of admission

4) Critically ill patient with chronic inflammatory condition who are known to coexist with an elevated SUPAR level as ankylosing spondylitis or malignancy

5) Critically ill children with condition associated with low grade chronic inflammation& as morbid obesity or atherosclerosis already coexist with high SUPAR level.

In this study patient group was subdivided into two groups

A) Critically ill patient with sepsis or sever sepsis

B**) Critically ill patient without proven sepsis(SIRS criteria**):have two of 4 criteria , 1 of which must be abnormal temperature or abnormal leukocyte count: .

- core temperature >38 or< 36
- tachycardia or bradycardia after exclusion of other causes
- leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophil
- respiratory rate >2SD above normal for age

A single suPAR measurement was performed for all the patients within 24 h of admission in the PICU as well as for the control group

Sample size:

Using a confidence level of 95 %, a margin of error (confidence interval) of 5 %, and supposing a population size of 20,000, sample size found 377 was needed. , due to financial and other issues, a smaller sample was taken

All children will be subjected to the following

- 1) Full history taking and clinical examination ,including Temperature, heart rate , respiratory rate systolic and diastolic blood pressures, Glasgow coma scale, Clinical features of respiratory distress, Need for mechanical ventilation , or respiratory support Need for inotropic support, Need for blood product transfusion ,FFP or platelet , History of drug intake or preceeding infection History of previous admission or chemotherapy and length of PICU stay
  2) The work-up investigation included arterial blood gases, random blood glucose, complete blood count, C-reactive protein ,serum electrolytes ,liver function tests ,kidney function tests, prothrombin time, partial thromboplastin time, and blood culture chest radiograph, brain CT, and other laboratory or radiological investigations were performed when appropriate.

Serum urokinase plasminogen activator receptor with in 24 hr of admission

Blood samples will be collected within 24 h of admission into the PICU .serum will be isolated and put in serum separating tube P after centrifugation at 3000 g for 10 min, then immediately frozen at −80 °C. serum suPAR levels were determined using a commercial double monoclonal antibody sandwich enzyme immunoassay according to the manufacturer's instructions

3)clinical scoring system, All cases were subjected to mortality risk score ,namely pediatric risk of mortality(PRISM 3)& sepsis score (q SOFA)score calculated in 1st 24 hour of admission.

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 26 to obtain. Descriptive data: Descriptive statistics were calculated for the data in the form of Mean, Standard deviation (±SD) and 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; Student's *t*-test:- Used to compare between mean of two groups of numerical (parametric) data, ANOVA (analysis of variance):- Used to compare between more than two groups of numerical (parametric) data, and post hoc analysis was used to detect intergroup comparison; For continous non- parametric data, Mann-Whitney *U*- test was used for inter-group analysis, pearson and spearman rank correlation coefficient (r) test was used correlating different parameters; Inter-group comparison of categorical data was performed by using chi square test (X^2-value), 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. A *P* value <0.05 was considered statistically significant.

Results

Our study enrolled 70 critical ill child admitted in PICU undergo serum SUPAR level withdrawn compared level to another 30 healthy child as control group.

The main sub groups :goup (A)(critically ill children with sepsis),group (B) (critically ill children with out sepsis) and group (c) (control group).

Age, sex , anthropometric measures ,liver enzymes and renal function was found of no significant difference between study sub groups ,while CBC parameters ,INR ,albumin was found to be significant difference between groups.

Also ,our study relieved no significant correlation between age,sex and anthropometric measurements to SUPAR level .

A significant difference was found between the whole patient cohort and the healthy controls regarding suPAR level ($p<0.0001$) as in Figure (1)

In addition,The two patient subgroups were compared to each other regarding suPAR level revealed a significant difference ($p<0.001$) between “sepsis group" group (A) &(SIRS) group group (B), also serum SUPAR level was found to have significant positive correlation with bacterial growth with p-value(0.04).

SUPAR level was found of higher level in non survivors than survivors of significance difference p-value(<0.001) (Figure 2) having negative correlation with both systolic and diastolic blood pressure and no correlation with pulse and temperature.Table (1)

In correlation to clinical scoring system, significant positive correlation was found between SUPAR and risk scores as(PRISM)and (q SOFA) with significant p-value for both (<0.001) Table(2),and also found to be negatively correlated with (GCS).

Our study ,found that serum level of SUPAR was significant higher in critically ill children who need mv ,inotropic support Table(3). And who stay longer at PICU Table(2)

The performance of suPAR,as a diagnostic marker relative to other inflammation and sepsis biomarkers was tested through ROC curve analysis ,SUPAR show AUC 0.99 compared to CRP and TLC with (AUC) 0,90 &0.87 correctively Figure (3).

Also our studyshow good sensitivity for marker (SUPAR) 90% with specificity 96.7% at cut off value > or =120,2 pg/ml, also show positive predictive value (PPV) 98.4% and negative predictive value (NPV) 80.6% with accuracy (92%) Table (4)

The correlations of suPAR with other clinical and laboratory parameters were also tested, found to have significant positive correlation to s.creatinine with p-value(<0.001), (INR), base excess and CRP, while having significant negative correlation with HCT, hemoglobin, MCV , platelet count and albumin, no significant correlation was found between total leucocytic count, total bilirubin, blood urea and liver enzymes.(ALT&AST).Table (5)

Discussion

In this observational case control study it may include relative small number of cases have demonstrated that suPAR level at admission was significantly elevated in the whole cohort of critically ill children, compared to healthy controls as in Figure (1),there are studies support its role as early diagnostic and prognostic biomarker for sepsis between critically ill children, one study results demonstrate that suPAR is a powerful marker of inflammation in infants with sepsis, another one considered SUPAR has good prognostic and diagnostic value for critically ill children.(12,13).

Also was found of significant higher level in group (A) who have proven sepsis than group (B)(SIRS) group with p-value (<0.001),there are studies denoting SUPAR role in identifying blood stream infections in different stages of SIRS, sepsis and sever sepsis (14)

While other study demonstrated that no significant difference in SUPAR level between (SIRS) and non SIRS study group patients.(7)

Regarding to age,sex and anthropometric measures correlation to SUPAR level, no significant correlation was found , that may be against other two studies who concluded that age and (BMI) has significant positive correlation to SUPAR ,being of high level in female than male.(15,16,17)

This study as regarding vital sign of this critically ill children correlation with serum SUPAR level, pulse and temperature at admission was found of no correlation this biomarker ,while both systolic and diastolic blood pressure on admission found having significant negative correlation to serum level of SUPAR as in Table (1),.and also this BM found of higher level in critically ill children who need inotropic supports as in Table (3),it may agree with other studies who reported that SUPAR levels were significantly higher in patients with septic shock than other healthy control(18) and another study which reported that SUPAR concentrations predict the need of ICU admission and need for vasopressor use in patients admitted by SIRS(19)

In this study , groups of study under go clinical scoring systems as(PRISM),(q SOFA) and(GCS) ,SUPAR level found to have significant positive correlation with both (PRISM)and(q SOFA)score with significant p-value (<0,001) as in Table (2), while having negative correlation with (GCS). Up to positive correlation between (q SOFA) and SUPAR ,there are other studied reported high SUPAR levels were associated with high SOFA scores and also another study demonstrated that

combination of both may increase the predictive value of SOFA for out come of pediatric sepsis(20) ,while one study reported that SUPAR plasma level did correlate weakly with (q SOFA) score in patients with sever sepsis.(21)

Positive correlation between PRISM and SUPAR was not supported by one study who show Non significant weak positive correlation with PRISM score(13)

Also SUPAR was found to have significant higher level in non survivors than survivors as in Figure (2) ,several studies may support its role as indicator for risk of mortality.one of these studies show, higher levels of SUPAR were found amoung those who died compared to survivors(22) ,also another study explained its role that high SUPAR concentration primarily reflect endothelial dysfunction that is key driver in sepsis mortality and morbidty (23),another study (18)found no significant difference in level between survivors and non.

In the present study, significant positive correlation was fond between SUPAR and length of ICU stay as Table(2) , need for MV(mechanical ventilation).,need for inotrpes ,with agreement with other studies(24) that reported that SUPAR concentrations can predict the need for ICU admission ,mechanical ventilation and vasopressor use for patient who presented by SIRS at ER and also was reported significant higher SUPAR level in septic shock compared to control group by another study (18,19,24,31),in contrast to other studies that found no significant correlation between SUPAR level and ICU stay.(25)).

Correlation between suPAR and other laboratory markers of disease severity or organ damage investigated in the present study .results show significant positive correlation to INR ,PTT,base excess, serum creatinine as Table(5) and positive blood culture bactermic patient,on the other hand the authors failed to find significant correlation between SUPAR and liver enzymes (ALT&AST) , total bilirubin as Table(5) and TLC .in contrast, study that demonstrated no significant correlation between suPAR and other markers of organ function including creatinine, total bilirubin, and base excess(13)

Other studies support marked elevation of SUPAR in early stages of liver dysfunction suggesting its application as avaluable marker for risk stratification serum suPAR concentrations might serve as an interesting biomarker in ALF,another recent study demonstrated that SUPAR was directly associated with parameters indicating cholestasis(26)
In line with our study two studies found no significant correlation between SUPAR level and TLC (25), while others reported positive correlation between both (22)

Also in line with our study ,the are several studies confirmed the role of SUPAR as indicator biomarker for risk of deterioration in kidney function,also another study reported that SUPAR had better capacity than albuminuria and eGFR as biomarker for assessing severity of renal impairement, considering it anovel good biomarker for early stages of renal failure between children with sepsis at PICU.(27)

On the other hand ,our study found significant negative correlation between SUPAR and other CBC parameters (haemoglobin, haematocrit value ,MCV, platelet count) and serum albumin as Table(5) which was supported by another study also,in agree with another study which reported that low platelet count and haemoglobin level were independent predictors of high concentration of SUPAR(28),also in line with our

study another two studies confirmed the negative correlation between albumin and SUPAR level(29),(13)

Also results in this study ,show positive correlation between SUPAR and CRP with significant p-value (0,03) ,In line with other studies(22) which accept that ,Further more, another study concluded that combination of both considered very useful for patients with SIRS to detect community acquired bacterial infection and also in cancer diagnosis (30,18).,while others was adverse and found no correlation betweem SUPAR and CRP Lining with another study who found no correlation between both in pneumococcal bactermia.(25)

In the present study, suPAR was found to have a good diagnostic power, with an AUC of 0.99 ,higher than that of CRP (AUC=0.90) and TLC (AUC=0,87)as Figure(3),that show more diagnostic value fir SUPAR than TLC and CRP which was opposed another study which concluded the more diagnostic value for CRP Than SUPAR(13).

Our results show that The best suPAR cut-off for prediction of sepsis was equal or more 120,2pg/ml which had a sensitivity of 99 % and a specificity of 96.7 %. With estimated accuracy 92%,also show positive predictive value (PPV) and negative predictive value (NPV) 80,6%. as Table (4),while other studies reported different cut off levels.

Another study(18),. found that a suPAR cut-off of 11 ng/ml had a sensitivity of 83 % and a specificity of 76 % in predicting mortality in adults with bacteremia with an AUC of 0.84 Other investigators found that suPAR level higher than 6.15ng/mL had 66% sensitivity and 64 % specificity for prediction of ICU mortality, with an AUC of 0.72)

Certainly, larger pediatric studies are needed to confirm our results as this study has limitations. One limitation of this study is that the authors did not measure suPAR serially to monitor the change of the level in response to treatment ,also need larger number for better interpretation of data, .Also, suPAR concentrations are related to renal and hepatic dysfunction, which may themselves increase morbidity and mortality, but multivariate analysis did not identify these dysfunctions as independent predictors of outcome .Also it lack the ability to differentiate between different types of organisms viral, fungal or bacterial.

Conclusion

Our study identifies SUPAR as astable promising marker in critically ill children to asses disease severity and also can predict risk of organ damage and mortality ,also considered having agood diagnostic value as biomarker in early detecting blood stream infection superior to another classic inflammatory biomarker. Further studies should focus on understanding of the biochemical properties and regulatory mechanisms of suPAR in critically ill patients to be able to better evaluate changes in response to specific therapies and its ability to detect different organisms.

List of abbreviations

SUPAR=soluble urokinase plasminogen activator receptor

SIRS=systemic inflammatory response syndrome

PRISM=pediatric risk of mortality score

(q SOFA)=quick sequential organ failure assessment

PICU=pediatric intensive care unit

SLE=systemic lupus erythromatosis

FFP=fresh frozen plasma

GCS=glascow coma scale

AST=Aspartate aminotransferase

ALT=Alanine aminotransferase

INR=International Normalized Ratio

PTT=partial thromboplastin time

PT=prothrombin time

MCV= mean corpuscular volume

BMI=Body Mass index

BM=Bio marker

eGFR=estimated glomerular filteration rate

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Author contribution

Authors contributed equally in the study**.**

Conflicts of interest

No conflicts of interest

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Table (1): Correlation between SUPAR level and vital sign

	r	**p-value**
Pulse	-0.04	0.73
Diastolic blood pressure	-0.38	0.001*

Systolic blood pressure	-0.34	0.004*
Temperature	0.16	0.19

Table (2): Correlation between SUPAR level & PRISM ,sepsis score and length of hospital stay.

	r	**p-value**
PRISM score	0.92	<0.001*
Sepsis score	0.67	<0.001*
Length of hospital stay	0.79	<0.001*

Table (3): SUPAR level regarding Need for inotropes or vassopressor

	N	**Mean**	**S.D**	**Mann-Whitney U**	**p-value**
No	49	240.15	124.96	4.3	<0.001*
Yes	21	483.28	227.34		

Table (4) Cut-off value for SUPAR LEVELS

Cut-off value	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
≥ 120.2	90%	96.7%	98.4%	80.6%	92%

Table (5): Correlation between SUPAR level and other laboratory investigation.

	r	**p-value**
Total bilirubin	0.01	0.92
Direct bilirubin	0.24	0.08
Albumin	-0.35	0.03*
AST	0.09	0.54
ALT	0.13	0.38
INR	0.31	0.01*
PTT	0.26	0.03*
PT	0.32	0.01*
Creatinine	0.33	<0.001*
Urea	0.19	0.12
CRP	0.38	0.03*
PLT	-0.24	0.05*
MCV	-0.29	0.01*
HCT	-0.36	0.00*
HG	-0.32	0.01*
TLC	0.13	0.30

Statistically significant SD* = standard deviation

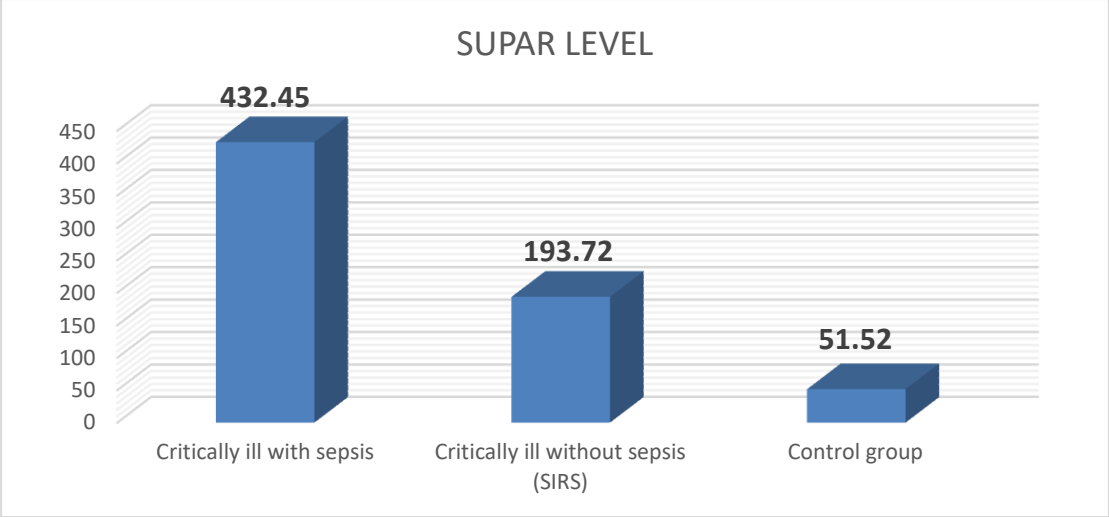


Figure (1) Bar chart compare SUPAR level in study groups

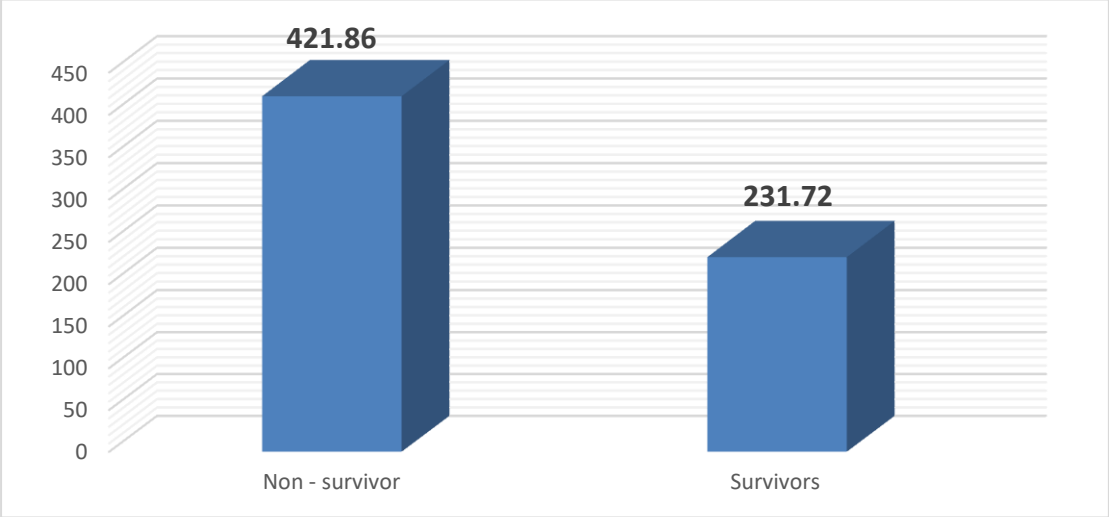
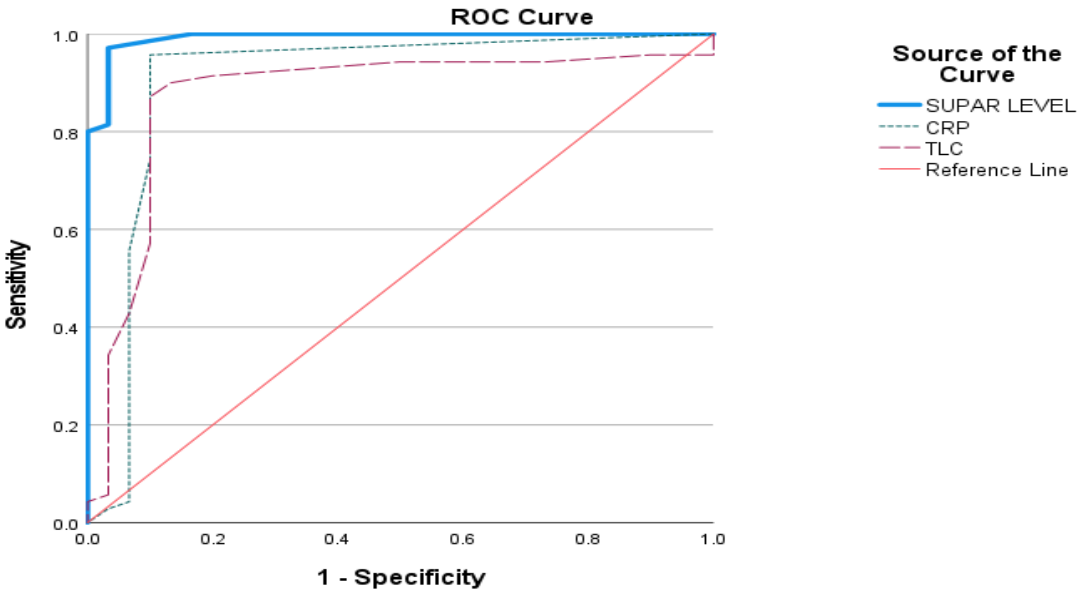


Figure (2) Bar chart compare SUPAR level in survivors and non survivors group.



The more the area under the curve the better the test

Figure(3) Receiver operating characteristic curve (ROC curve) of suPAR, C-reactive protein (CRP) and total leucocyte count (TLC) for diagnosis of sepsis