Prognostic Value of Albumin/Creatinine Ratio in Urine in Septic Patients

Nagwa Mohammed Daha (MD) [1], Elham Mohammed El-Feky (MD) [1], Ayman Mohamed Azzam (MD)[1], Mahmoud Mohammed Abdul-Aleem El-Badawy (MBBCh)[2]

[1]Anesthesiology, Intensive Care and Pain Management Department, Faculty of Medicine, Menoufia University.
[2]Resident of critical care at Ministry of Health, Shebin El-Kom Fever H., Menoufia governorate, Egypt
drbadawy80@yahoo.com

Abstract: Objective: A review of Prognostic Value of Albumin/Creatinine Ratio in Urine in Septic Patients. **Data Sources:** Medical text books, medical journals, and medical websites that have updated researches with key words (Albumin/Creatinine Ratio in sepsis) in the title of the paper. **Study Selection:** Systematic reviews that addressed Albumin/Creatinine Ratio and studies that addressed Sepsis and septic shock. **Data Extraction:** A special search was conducted at midline with the key words (Albumin/Creatinine Ratio in sepsis) in the title of the paper; extraction was performed, including the assessment of the quality and the validity of the papers that met with the prior criteria that describe the review. **Data Synthesis:** The main result of the review. Each study was reviewed independently; the data obtained were rebuilt in a new language according to the need of the researcher and arranged into topics through the article. **Recent Findings**: Urinary albumin/creatinine ratio may be used as a simple, rapid, noninvasive, inexpensive, easy to perform and interpret test for early prognosis and prediction of mortality in septic patients, this early risk stratification is of particular significance in the intensive care environment where it allows clinicians to make more rational therapeutic decisions to ensure that the hospital resources are used efficiently and appropriately. Thus, together with conventional illness severity scores, the measurement of ACR on entry to the ICU, and 24 hours later, can provide additional information on patient outcome. **Conclusions**: Urinary albumin/creatinine ratio would be an interesting prognostic tool to study septic patients.

Key words: Urinary albumin/creatinine ratio, Sepsis, Septic shock

1. Introduction

Sepsis is defined as SIRS (systemic inflammatory response syndrome) that has a proven or suspected microbial etiology [1]

Another definition has been introduced for Sepsis as two or more SOFA score (Sequential Organ Failure Assessment Score or Sepsis-related Organ Failure Assessment Score) plus suspected infection.

Invasive bacterial infections are the prominent causes of death around the world, particularly among young children. Non-typhoidal salmonella species, Streptococcus pneumonia, Haemophilus influenza, and Escherichia coli were the most commonly isolated bacteria. [2]

Sepsis is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release a plethora of pro-inflammatory molecules into the circulation. The endothelium becomes dysfunctional due to the sustained onslaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak. Increased capillary permeability is an early feature of Systemic Inflammatory Response Syndrome (SIRS). The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine. In various studies microalbuminuria has been correlated with rapid changes in vascular integrity. [2]

Early prediction of mortality among critically ill sepsis patients and early institution of intensive therapy is of paramount importance which has significant implications on survival of the patient. [2]

Various ICU scoring systems to predict mortality are in current use like the APACHE II, APACHI IV and SAPS II score. These scoring systems are cumbersome and are done at24hours of admission during which precious time is lost in administering therapy and require input of a large number of variables derived from the patient's history, physical examination, and initial laboratory data.[3]

Microalbuminuria, defined as 30–300 mg/day of albumin excretion in the urine, occurs rapidly after an acute inflammatory insult such as sepsis and persists in patients with complications. It is a common finding in critically ill patients, where it has shown promise not only as a predictor of organ failure and vasopressor requirement but of mortality. [3]

This study is an attempt to understand the usefulness of Urine Micro albumin and creatinine ratio

in predicting the mortality of the patient and to compare it with validated ICU scoring systems such as APACHI IV. [4]

2. Materials and methods:

The guidance published by the Centre for Reviews and Dissemination was used to assess the methodology and outcomes of the studies. This review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. The institutional review board and ethics committee of Menofiya University approved this study.

Search strategy:

A systematic search of several bibliographical databases was performed to identify relevant reports in any language. These included MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, TRIP database, Clinical Trials Registry, ISI Web of Knowledge, and Web of Science. Articles electronically published ahead of print were included. The search was performed in the electronic databases from the start of the database up to 2016.

Study selection:

All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria.

Participants: Adults patients >18years fulfilling two or more Systemic Inflammatory Response Syndrome criteria plus suspicion or confirmed source of infection, with exclusion of patients with hematuria, anuria, chronic kidney disease, UTI, menstruation or pregnancy.

Interventions: On admission, the following data was collected for each patient: age; gender; date and time of admission; patient's clinical classification (medical or surgical), provisional diagnosis; co-morbid conditions. Clinical and laboratory data were collected; cultures sent and antibiotics administered within 24 hours of admission were noted. SOFA and APACHE II score was calculated from data collected during the first 24 hours following ICU admission.

Outcomes: Higher levels of ACR 2 (urinary Albumin/Creatinine ratio after 24 hrs) were associated with worsening prognosis and mortality in participants.

If the studies did not fulfill the above criteria, they were excluded. Articles in non-English languages were translated. The article title and abstracts were screened initially, and then, the selected articles were read in full and further assessed for eligibility. All references from eligible articles were reviewed to identify additional studies.

Data extraction:

Study quality assessment included whether ethical approval was gained, the prospective design, the specified eligibility criteria, whether appropriate controls were used, whether adequate follow-up was achieved, and defined outcome measures such as SOFA and APACHE II scores.

Quality assessment:

The quality of all the studies was assessed. Important factors included the prospective study design, attainment of ethical approval, evidence of a power calculation, the specified eligibility criteria, appropriate controls, specified outcome measures, and adequate follow-up. It was expected that confounding factors would be reported and controlled for and appropriate data analysis would be made in addition to an explanation of the missing data.

Data synthesis:

Because of the heterogeneity in septic patients and outcome measures reported, it was not possible to pool the data and perform a meta-analysis. Comparisons were made by a structured review.

Findings:

In this study we sought to obtain spot urine samples within 6 hours of admission and again at 24 hours, for quantification of ACR, which were referred to as ACR1 and ACR2 respectively, trend of microalbuminuria was assessed. The difference of ACR2 from ACR1 (Δ ACR = ACR1 - ACR2) was calculated.

Urine samples were received in the biochemistry lab and stored at -20o C till analysis. Urinary albumin/creatinine ratio was measured by the immunoturbidimetric method and urinary creatinine by modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., U.S.A). The methods covered an analytical range of 1.3–100 mg/L for microalbuminuria and 0-20 mg/dl for creatinine. Microalbuminuria was defined by ACR values between 30 and 299 mg/g. ACR of > 300 mg/g is considered as clinical proteinuria. ACR < 30 mg/g is normal for a healthy population.

3. Results and Discussion:
Sepsis Diagnosis:

Sepsis is defined as SIRS (systemic inflammatory response syndrome) two or more of the following:[5]

- Temperature less than or equal to 36o OR more than or equal to 38o.

- Heart rate more than or equal to 90bpm.

- Respiratory rate more than or equal to 20 breaths/min.

- White blood cell count more than or equal to 12,000 OR Less than or equal to 4,000 cells/mm3 OR > 10%band.

Plus a proven or suspected microbial etiology.

Another definition has been introduced for Sepsis as two or more SOFA score (Sequential Organ Failure Assessment Score or Sepsis-related Organ Failure Assessment Score) plus suspected infection. [6]

Pathophysiology of Sepsis:

The pathophysiology of sepsis & septic shock include **three stages:**

First: The host- pathogen interaction:

Two protein families involved in the detection of the pathogens have been discovered; they belong to the group of pattern recognition receptors (PRR): the Toll-like Receptors (TLR) and the nucleotide-binding oligomerisaton domain (NOD) molecules, Nod1 and Nod2. These molecules induce an inflammatory response through an enzymatic cascade leading to the activation of the nuclear transcription factor kappa B (NF-kB). Pro-inflammatory mediators, an increase of cytokines has been evidenced in the plasma of patients presenting with septic shock. High cytokines concentrations have been associated with poor prognosis. However, they are also essential in the host response to aggression by a pathogen as demonstrated by the failure of treatments targeted against these cytokines and the increased infection susceptibility in patient's deficient for these molecules.[7]

Second: The different mechanisms leading to organ dysfunction.

Apoptosis: During sepsis, apoptosis occurs in several types of cells and associated with poor prognosis. Hotchkiss showed that this apoptosis mainly concerns B and CD4+ T lymphocytes. It is responsible for a change of circulating cytokine profile which favors anti-inflammatory cytokines produced by TH2 (T-helper) cells. Consequently, apoptosis, contrary to necrosis, is responsible of an immune anergy which facilitates the development of secondary infections. Apoptosis affects T and B lymphocytes as well as NK (Natural Killer) cells leading to a state of immunoparalysis observed in sepsis.[8]

Cellular dysoxia: During sepsis, major alterations of microcirculation occur; their persistence is associated with organ dysfunction and mortality. Sepsis is characterized by a prothrombotic state responsible of micro thrombi which decrease the quantity of oxygen available for tissues resulting into hyper-lactatemia which is not equivalent to tissue hypoxia. Hyper-lactatemia results both, from a rise of its production and a drop in its clearance, especially hepatic. The increased production observed during sepsis is not the consequence of anaerobic metabolism but of an acceleration of muscle aerobic glycolysis. [9]

Third and Last: The involvement of numerous systems of the body [MODS][10].

Management Of Sepsis

The treatment of patients with septic shock has the following major goals:[11]

• Start adequate antibiotic therapy (proper dosage and spectrum) as early as possible.

• Resuscitate the patient, using supportive measures to correct hypoxia, hypotension, and impaired tissue oxygenation (hypoperfusion).

• Identify the source of infection, and treat with antimicrobial therapy, surgery, or both (source control).

• Maintain adequate organ system function, guided by cardiovascular monitoring, and interrupt the progression to multiple organ dysfunction syndrome (MODS).

The Surviving Sepsis Campaign guidelines were last updated in 2012, and the current versions reflect the opinion of a reasonable approach to the treatment of septic shock, specific recommendations degraded.[11]

The first 6 hours of resuscitation of a critically ill patient with sepsis or septic shock are critical.

The following should be completed within 3 hours:[12]

• Obtain the lactate level.

• Obtain blood cultures before administering antibiotics.

• Administer broad-spectrum antibiotics.

• Administer 30 mL/kg of crystalloid solution for hypotension or for lactate levels of 4 mmol/L or higher (Again, although most patients presenting with severe sepsis are in a functional hypovolemic state, requiring fluid resuscitation, careful monitoring of right ventricular volume overload is essential if large quantiles of fluid are to be given quickly, to avoid inducing acute corpulmonale.) The following should be completed within 6 hours: [12]

• Administer vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher (Recent studies showed the validity of the 70-75 mm Hg lower mean arterial pressure target or 80-85 mm Hg in those patients with preexisting hypertension.).

• If hypotension persists despite volume resuscitation or the initial lactate level is 4 mmol/L or higher, then measure central venous pressure (CVP) (aiming for ≥8 mm Hg), measure central venous oxygen saturation (ScvO 2) (aiming for ≥70%), and normalize lactate levels (These recommendations will probably be modified in lieu of the findings that CVP does not represent an effective target. See below about the venoarterial PCO 2 gradient analysis as being a more specific measure of tissue hypoperfusion.) [12]

Scoring systems in ICU:

A) Outcome prediction scores (Mortality / Survival Prediction Systems): Scores that assess disease severity on admission and use it to predict outcome [13] (for example):

- Acute Physiology and Chronic Health Evaluation (APACHE).
- Simplified Acute Physiology Score (SAPS).
- Mortality Probability Model (MPM).

B) Organ dysfunction scores (Morbidity Prediction Systems): scores that assess the presence and severity of organ dysfunction [14] (for example):
- Logistic Organ Dysfunction Score (LODS).
- Multiple Organ Dysfunction Score (MODS),
- Sequential Organ Failure Assessment (SOFA).

Biomarkers of Sepsis:

Microalbuminuria and (albumin / creatinine ratio): is defined as a urinary albumin concentration of 30–300 mg/day. It is generally expressed as the urinary albumin to creatinine ratio (ACR) to correct for variations in urinary flow rate. Calculation of albumin excretion rate requires a timed urinary collection, whereas ACR is calculated from a spot urine test. However, this is based on the assumption that the urinary creatinine excretion rate remains constant. Microalbuminuria was initially used to predict the onset of chronic renal failure in diabetic patients. Also, it has shown promise as an early predictor of disease severity in many acute inflammatory conditions. More importantly, it has been found to be predictive of mortality in a heterogeneous group of critically ill patients.[15] Patients requiring intensive care frequently have some degree of systemic inflammatory response syndrome (SIRS), which, when severe, places them at risk of multiple organ failure. SIRS is characterized by a loss of homeostasis of the inflammatory response to injury or infection, which damages organs remote from the site of initial injury or infection. Although inflammation is recognized as the common mechanism leading to multiple organ failure and death, attempts to attenuate inflammation have not been successful. One reason proposed for this lack of success is that any intervention must be started early in the evolution of SIRS, and there is no rapid means of early identification of suitable patients for immunomodulating therapy. An early feature of the acute inflammatory process is capillary endothelial cell activation accompanied by a rapid increase in capillary permeability to plasma proteins such as albumin. The transcapillary escape rate of radiolabeled albumin from the circulation increases dramatically within 3 hrs in patients with infection and malignancies. [15]

C-reactive protein: is a long-established marker of sepsis. In 1930, Tillet and Francis identified, in the sera of patients with pneumonia, the capacity to precipitate polysaccharide fractions, designated as fraction C, from Streptococcus Pneumonia [132]. This property quickly disappeared as patients recovered and was not identified in healthy volunteers. When the cause of this reaction was identified as a protein, it was named CRP. The "acute phase" designation was introduced to classify acutely ill patients with infection whose sera was CRP positive. Since then, several other acute phase proteins have been described. The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples. Levels above these values are abnormal and indicate the presence of a disease process. he CRP response is very non-specific and can never be used as a single diagnostic tool, however it is very helpful in several disease states. Its application in infectious diseases is unquestionable. Its application in coronary artery disease is growing. It is also currently used in rheumatology and transplantation.[16]

Procalcitonin: has been recently studied as a possible marker of sepsis with a superior sensitivity and specificity comparing with other markers. PCT is a propeptide of calcitonin and is normally produced in the C cells of the thyroid gland and the normal PCT levels are very low (<0.2 ng/ml). During sepsis, PCT is produced by extra thyroid tissues (monocytes, liver) resulting in high levels. Comparing with other markers of infection and sepsis, PCT has several advantages: * PCT rises up to 20 h earlier than CRP in plasma and the dynamic concentration is useful for monitoring the evolution of the disease; when the severity of sepsis increases, the PCT levels rises and the effectiveness of anti-infective therapies are reflected by a decrease in PCT values.* High levels of PCT (>2.0 ng/ml) indicate severe infection, severe sepsis or MODS; PCT levels exceeding 10 ng/ml occurs almost exclusively in patients with severe sepsis or septic shock [62]. Various other stimuli, including major surgical procedures, severe trauma or burns, prolonged circulatory failure may induce plasma elevations of PCT but not as high as in patients with severe sepsis (generally between 0.5-2.0 ng/ml) [62].* The half life of PCT makes it a suitable parameter for daily measurements and the stability of the protein allows easy determination in clinical practice. PCT may help to differentiate between viral and bacterial Infections. Elevation of PCT levels may be an important predictor of septic complications in trauma, pancreatitis or major surgery.[17]

Inflammatory cytokines: IL-6 and IL-8 are most closely related to the severity of sepsis, particularly high levels of IL-6 were found in non-surviving septic patients. Like other cytokines, those cytokines are induced by various non-infectious causes that limit their diagnostic usefulness.[18]

Other markers of sepsis: Phospholipase A2 (PLA2), Neutrophil elastase, Neutrophil CD64, Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM), Cardiac troponin.[19]

Biomarkers in Sepsis-induced AKI:

Neutrophil gelatinase-associated lipocalin (NGAL): is a24kDa protein normally expressed in low concentrations in different human tissues (kidneys, lungs, stomach and colon), and is found in the secondary granules of neutrophils. NGAL is released when these cells are activated, particularly in response to bacterial infections. NGAL transcription and release is intensely induced in the presence of epithelial damage. In ARF, NGAL is promptly released from the proximal renal tubules following ischemic or toxic damage, and its levels can be measured in plasma and urine. A recent review involving over 4000 patients at risk of ARF due to sepsis, heart surgery, exposure to contrast media or transplantation, found NGAL to be significantly elevated in those individuals who develop ARF and that this elevation significantly precedes the clinical diagnosis of ARF.[20]

*Interleukin-18: Is a proinflammatory cytokine transcribed and released in the proximal renal tubules, and which can easily be detected in urine following ischemic damage. It does not appear to increase under conditions of infection, prerenal ARF or chronic renal failure.[21]

*KIM-1 (kidney injury molecule-1): is a transmembrane glycoprotein that shows a marked increase in expression on the part of the cell of the proximal renal tubules in response to ischemic or toxic stimuli. Its concentrations can be detected in urine and are seen to increase in patients with ARF. [21]

In the utility of these and other novel biomarkers including cystatin C, liver fatty acid-binding protein (L-FABA), and netrin-1 for early detection of sepsis-induced AKI is very encouraging and may have prognostic as well as pathogenetic implications. [21]

Conclusion:

The present study assessed the significance of raised levels of urinary Albumin/Creatinine ratio (ACR) in patients with sepsis on admission and 24 h later to the intensive care unit (ICU) in terms of its ability to predict disease severity, need for organ supportive measures or mortality. Our study have shown that the urinary Albumin/Creatinin ratio (ACR) concentrations were elevated early in patients who were admitted to the ICU with sepsis criteria, the urinary Albumin/Creatinin ratio (ACR) concentrations were also significantly higher in patients who needed the organ supportive measures (such as inotropic support) during their ICU stay.

The urinary Albumin/Creatinin ratio (ACR) concentrations were also significantly higher in ICU non-survivors than those who survived and when used as a predictor of ICU mortality.

In addition, the urinary Albumin/Creatinine ratio (ACR) concentration in our study was shown to be significantly correlated with SOFA score and APACHI II score (scoring systems already used to predict mortality in septic patients).

We can conclude that the urinary albumin/creatinin ratio may be used as a simple, rapid, noninvasive, inexpensive, easy to perform and interpret test for early prognosis and prediction of mortality in septic patients together with conventional illness severity scores.
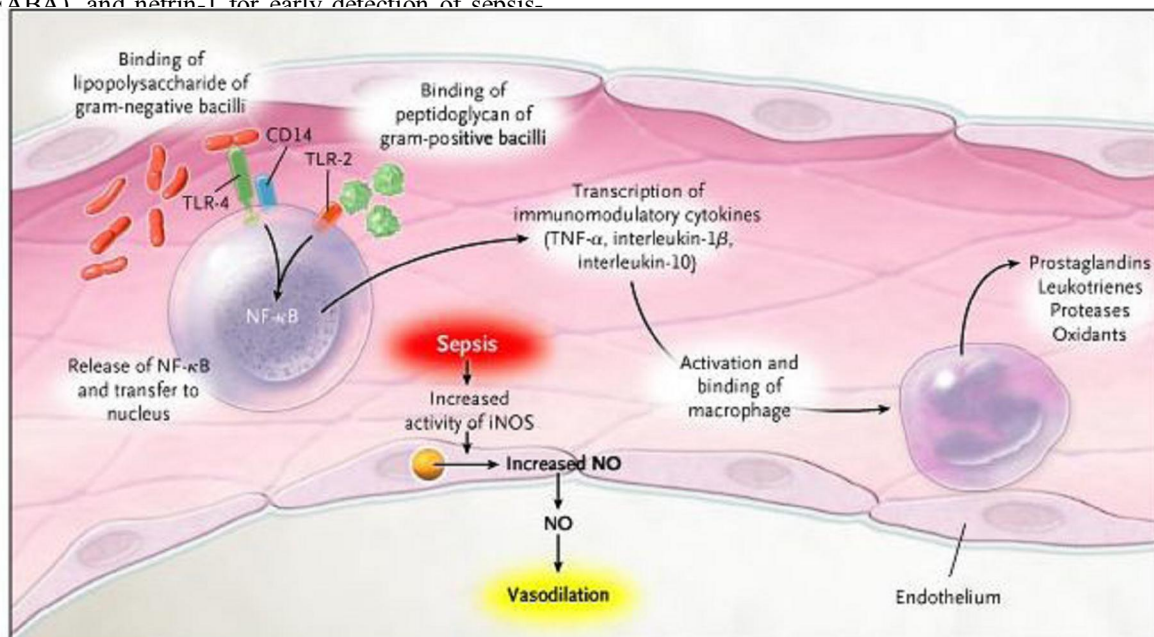

Figure 1. Inflammatory mediators in sepsis

Table 2. APACHE II score

The APACHE II Severity of Disease Classification System

Physiologic Variable		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)		≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)		≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. FiO₂ > 0,5 use A-aDO₂	a	≥500	350-499	200-349		<200				
b. FiO₂ < 0,5 use PaO₂	b					> 70	61-70		55-60	<55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)		≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)		Score = 15 minus actual GCS								
Serum HCO₃ (venous, mmol/l, use if no ABGs)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points								

B = Age Points

≤44 years	0 points
45-54 years	2 points
55-64 years	3 points
65-74 years	5 points
≥75 years	6 points

C = Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative patients – 5 points
b. For elective postoperative patients – 2 points

APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)

Table 2. SOFA score:

| Organ system	Score				
	0	1	2	3	4
Respiratory PaO2/FiO2	>400	≤400	≤300	≤200	≤100
Renal Creatinine (µmol/l)	≤110	111-170	171-299	300-440 urine output ≤500ml/d	>440 urine output <200ml/d
Hepatic Bilirubin (µmol/l)	≤20	20-32	33-101	102-240	>240
Cardiovascular Hypotension	No hypotension	MAP<70mmHg	Dopamine≤5a or Dobutamine (any dose)	Dopamine >5a or epinephrine ≤0.1a or norepinephrine ≤0.1a	Dopamine>15a or epinephrine >0.1a or norepinephrine >0.1a
Hemotologic Platelet count (/mm³)	>150	≤150	≤100	≤50	≤20
Neurologic Glasgow Coma Score	15	13 14	10-12	6-9	<6
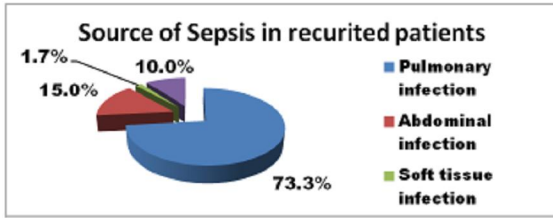
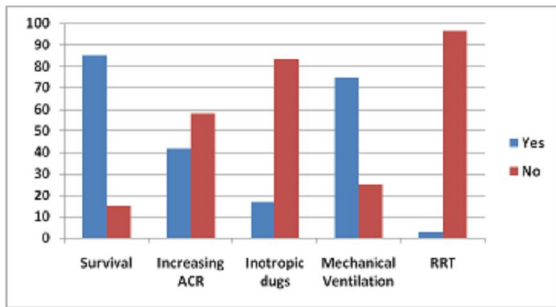**Figure 2.** Source of sepsis in recruited patients

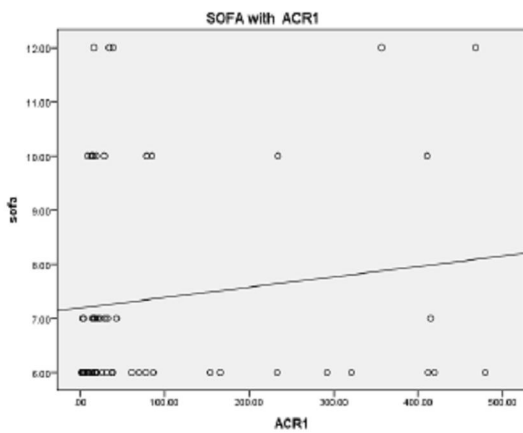**Figure 3.** Distribution of patients

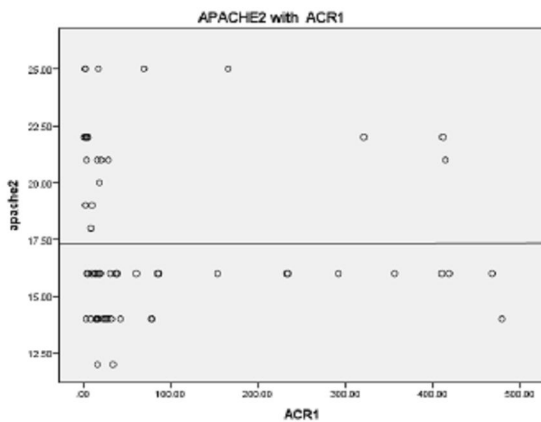**Figure 4:** Correlation of ACR1(albumin/creatinine ratio on admission) with SOFA

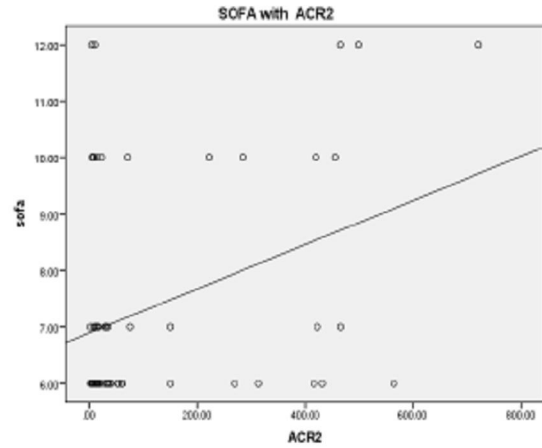**Figure 5:** Correlation of ACR1 with APACHE II
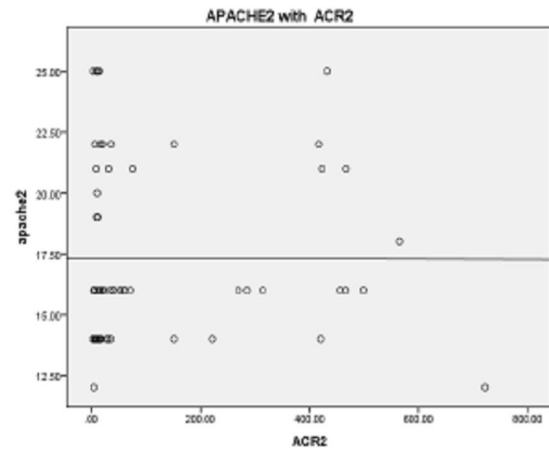

Figure 6: Correlation of ACR2 with SOFA

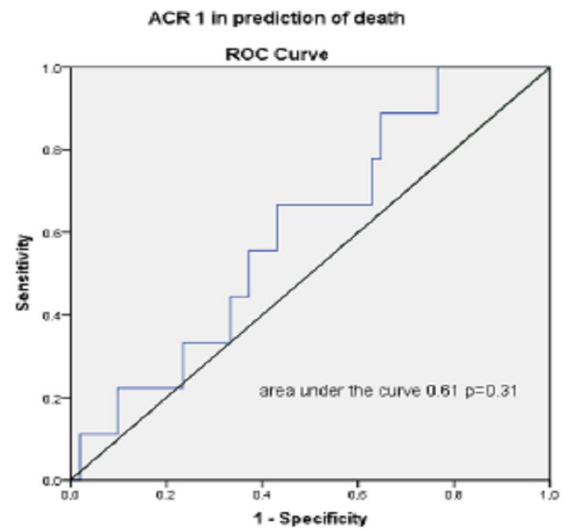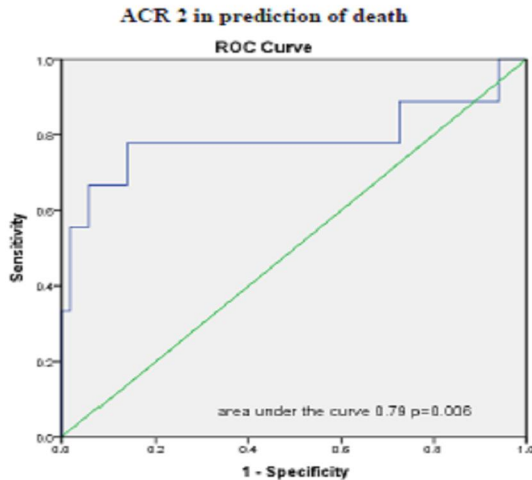**Figure 7:** Correlation of ACR2 with APACHE II

Figure 8: Receiver operating characteristic curves of ACR1 in prediction of death

Figure 9: Receiver operating characteristic curves of ACR2 in prediction of death

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Corresponding author:
Name: Mahmoud Mohammed Abdul-Aleem El-Badawy
Address: Apartment 7, 2nd floor, El-Rabie Borg, Quiesna Street, Shebin El-Kom, Menoufia Governorate
Email: drbadawy80@yahoo.com
Post code: 13511

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