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Prognostic Value of Urine Albumen/Creatinin Ratio in Sepsis in Critical Care Patients

Yousry El Saied Rizk[1], Ahmed Hamdy Abd El Rahman[1], Abdel Moneim Ahmed Abdel Moneim[1] and Waleed Ahmed Ali Amer[1*]

[1]Department of Critical Care Medicine, Faculty of Medicine, Benha University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Several scoring systems were developed for prognosis and outcome prediction in sepsis. This study aims to evaluate the urinary albumin/creatinine ratio (ACR) as a prognostic predictor in sepsis. The study included 50 adult septic patients in a prospective observational study. Study excluded patients with preexisting chronic kidney disease or diabetes mellitus. After clinical evaluation, urine spot samples were collected on admission and 24 h later for ACR1 and ACR2. Admission APACHE IV score and the highest recorded SOFA score of their daily estimation were considered. This study also evaluated the need for mechanical ventilation, inotropic or vasoactive support, renal replacement therapy (RRT), and in-hospital mortality. In a population with Mean±SD 51.4±16.3 (19-82) year old with 34 (68%) males, we found that the ACR2 is correlated with both APACHE IV and SOFA scores (P <0.001). ACR2 was higher in patients who needed mechanical ventilation and inotropic or vasoactive support [121(21-235) and 166.5(89-235) mg/g respectively] compared to [49(22-120) and 56.5(21-211) mg/g], P <0.001 in both. ΔACR, ACR2, increasing ACR and APACHE IV were predictors of mortality. The AUC for mortality prediction was largest for ΔACR (1), increasing ACR (0.985), ACR2 (0.963) then APACHE IV (0.90). ΔACR and ACR2 of 91.5 mg/g and -22 was 88.2% & 100% sensitive and 90.9% & 100% specific respectively to predict mortality. We concluded that the urinary ACR might be used as a simple test for prognosis and mortality prediction in sepsis.

**Corresponding author: E-mail: waleedamer344@gmail.com;*

Keywords: Microalbuminuria; urinary albumin/creatinine ratio; sepsis; mortality.

1. INTRODUCTION

A retrospective analysis of an international database reported a global incidence of 437 per 100,000 person-years for sepsis between the years 1995 and 2015, from low and middle--income countries [1].

Mortality rates for sepsis in recent years have ranged from18 to 40% [2]. Numerous immunopathologic alterations account for the morbidity and mortality of sepsis [3].

Sepsis and disease severity depend on various factors, ranging from the properties of the invading pathogen to the current immune status of the host. Severe sepsis can develop following local infection and can stem from a number of sites including the abdomen, skin, soft tissue, urinary tract, lungs and is usually due to a primary bloodstream infection [4]. Sepsis can also be triggered by viral, fungal, and parasitic components [5].

During sepsis, dysfunction of the epithelial barrier especially of the digestive epithelium causes bacterial translocations which probably contribute to organ failures [6]. The endothelial dysfunction is a milestone in sepsis pathogenesis. An early feature of sepsis is the loss of endothelial barrier integrity leading to systemic capillary leak [7]. Under pathologic conditions, inflammatory insult will lead to an increase in glomerular permeability to albumin and a reduction in tubular reabsorption, which consequently contributes to microalbumenuria (MA) development [8].

Microalbuminuria has been accordingly seen by several studies to occur early after severe inflammatory process and to persist in more severe cases [9]. Various intensive care units scoring systems like the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE IV, and Simplified Acute Physiology (SAPS II) scores to predict mortality are in current use and SOFA scores in some studies [10,11].

We intended in our study to evaluate the prognostic value of urinary albumin/creatinine ratio (ACR) in patients with sepsis and to compare this prognostic value with the APACHE IV and Sepsis-related Organ Failure Assessment Score (SOFA) scoring systems. These scoring systems require a large number of variables derived from the patient's history, examination, and initial laboratory data. Microalbuminuria was shown to be promising as a predictor of organ failure, vasopressor requirement and mortality prediction. It was shown to be even similar to APACHE IV.

2. PATIENTS AND METHODS

This is a prospective observational study that recruited all adult critically ill patients admitted to the ICU department, Benha Uneversity Hospital, Egypt from February 2017 to August 2017. The present study included in the study patients with diagnosis of sepsis syndrome with the presence of SIRS based on the diagnostic criteria of 1992 ACCP/SCCM [12] and its update in 2001 International Sepsis Definition Conference [13], exhibiting two or more of the following signs: (1) temperature of >38 C or <36 C, (2) pulse rate of >90 beats/min, (3) respiratory rate of >20 breaths/min or hyperventilation with a PaCO2 of <32 mmHg, or (4) white blood cell (WBC) count of >12,000 IL1 or <4000 IL1, or >10% immature cells. The presence of infection was defined according to the clinical and microbiological criteria of the Centers for Disease Control and Prevention (CDC) definitions [14].

Study excluded the patients less than 18 year old, patients with anuria or hematuria, patients with preexisting chronic kidney disease, diabetes mellitus, proteinuria due to renal or post renal causes, patients with urinary tract infection, and patients with ICU length of stay less than 24 h.

The study protocol was approved by the institutional review board at Benha University.

All patients (included) were subjected for clinical evaluation such as history, physical examination, routine laboratory investigations (capillary blood glucose, coagulation profile, arterial blood gases, liver and kidney function tests, random blood sugar, and serum electrolytes), and cultures from suspected sources of infection including sputum and urine.

APACHE IV score was calculated in an integer score form that is web based computed by applying worst values of the measurements observed during 24 h following ICU admission, with a maximum score of 286 [15]. The score was previously validated in sepsis patients [16]. The SOFA score is a scoring system to

determine the extent of organ dysfunction [17]. SOFA score was evaluated daily until ICU discharge or demise or up to a total of 28 days. The highest recorded SOFA score was considered for statistical analysis.

Other parameters of disease severity that were studied included need for mechanical ventilation, need for inotropic and/or vasoactive support and need for renal replacement therapy (RRT). Outcome was evaluated by ICU length of stay (ICU-LOS) and the in-hospital mortality [18,19].

Urinary albumin creatinine ratio ACR: Urine spot samples were collected at the time of ICU admission for Albumin Creatinine Ratio 1 (ACR1) and 24 h following ICU admission for Albumin Creatinine Ratio 2 (ACR2). Urinary microalbumin was measured by the immunoturbidimetric method and urinary creatinine by modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., U.S.A).

Trends of microalbuminuria was assessed as the change from ACR1 to ACR2. The difference between those values represents the delta albumin/creatinine ratio (D ACR) and is calculated as Δ ACR = ACR 1 – ACR 2. When D ACR is negative, it is defined as increasing ACR and when it is positive, it is defined as decreasing ACR.

2.1 Statistical Method

The collected data were tabulated and analyzed using SPSS version 16 soft ware (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation, median and range. Chi square test (X^2), or Fisher's exact test (FET) were used to analyze categorical variables. Quantitative data were tested for normality using Shapiro-Wilks, assuming normality at P>0.05, Student "t" test was used to analyze normally distributed variables among 2 independent groups. While non parametric variables were analyzed using Man Whitney U (Z_{MWU}) test for 2 independent groups. Spearman's correlation coefficient (rho) was used to assess correlation between non parametric variables. ROC curve was used to determine cutoff value of ACR with optimum sensitivity and specificity in prediction of mortality in sepsis patients. The accepted level of significance in this work was stated at 0.05 (P ≤0.05 was considered significant).

P value >0.05 is non significant (NS)
P<0.05 is significant (S)
P≤0.001 is highly significant (HS) [20].

3. RESULTS

During the period between February 2017 to August 2017, 50 adult critically ill patients staying for more than 24 hours in the ICU were included in our study.

The 50 septic patients that included in the study had an age ranging from 19 to 82 years old, with a Mean±SD of (51.4±16.3), 34 (68%) males and 16 (32%) females were included in our study.

Table 1. Shows source of infection among the studied sample

Source of infection	No. (N=50)	% (100%)
Chest infection	28	56.0
Infected wound	4	8.0
Peritonitis	4	8.0
GIT infection	4	8.0
infected bed sores	7	14.0
Central Venous Catheter infection	1	2.0
Infective Endocarditis	1	2.0
Gluteal abscess	1	2.0

This table shows that the main source of infection in our patients was chest infection that was identified in 28 patients (56.0%). Followed by infected bed sores that were identified in 7 patients (14.0%).

The highest SOFA score median was 5 ranging from 1 to 25 and APACHE IV score recorded within first 24 h of ICU admission was 45 ranging from 13 to 100.

Of the 50 patients eligible in this study, 25 (50.0%) needed ventilator support, 8 (16%) need inotrope or vasopressor to maintain hemodynamic while, there were no patients need renal replacement therapy(RRT).

The Length of stay in our study shows the median of 7.5 ranging from 4 to 45 days with Mean±SD (9.9±7.4). The mortality rate in our study is 34% (17 patients had been died while 33 had been survived).

Albumin/creatinine ratio (ACR) measurements:

When Albumin/ Creatinine ratio (ACR) was measured on admission and after 24 hours, the

admission ACR (ACR 1) was median 67(mean 79.4 & standard deviation 39.9) ranging from 27 mg/g and 170 mg/g. The 24 hours ACR (ACR 2) was median 67(mean 84.7& standard deviation 58.6) ranging from 21 mg/g and 235 mg/g. The Δ ACR was calculated by the formula Δ ACR = ACR 1 – ACR 2.

ACR1 was not significantly correlated with APACHE IV score (P-value 0.11) but significantly correlated with SOFA score (P-value 0.008). ACR2 was highly significantly associated with both APACHE IV and SOFA scores, (P value <0.001) in both. Lastly ΔACR was significantly associated with both APACHE IV and SOFA scores, (P values 0.0015 and 0.003 respectively).

Table 2. ACR measurements

N=50	Urine ACR1 (mg/g)	Urine ACR2 (mg/g)	Δ ACR
Mean	79.4	84.7	-5.32
Median	67.0	67.0	8.0
Std. Deviation	39.9	58.6	39.3
Minimum	27.0	21.0	-97
Maximum	170.0	235.0	87

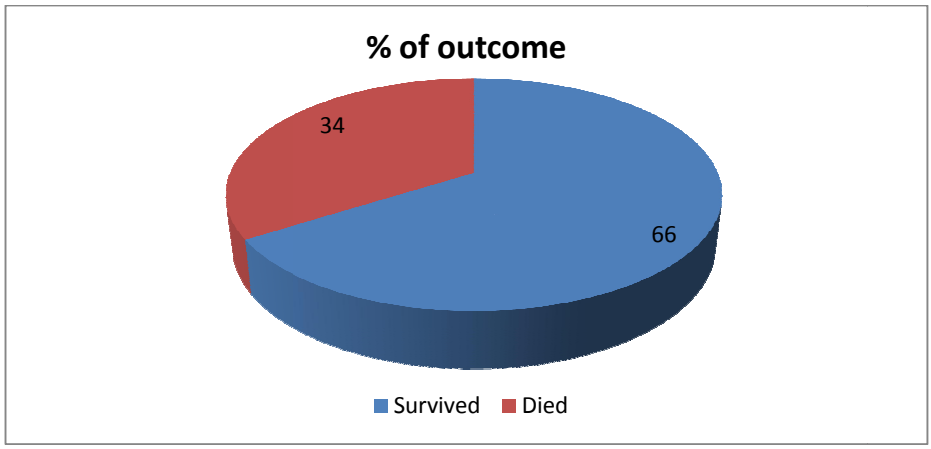

Fig. 1. Showing Mortality rate among the studied sample

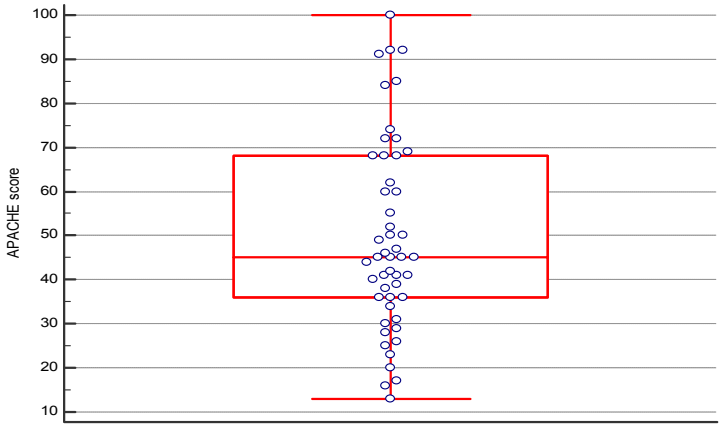

Fig. 2. Showing median and range of APATCHE IV score among the studied sample

Table 3. Correlation between ACR1, ACR2 & Δ ACR with SOFA & APACHE IV scores

	ACR1		ACR2		Δ ACR	
	rho	P	rho	P	rho	P
APACHE IV score	0.231	0.11	0.539	<0.001 (HS)	-0.436	0.0015 (S)
SOFA score	0.373	0.008 (S)	0.565	<0.001 (HS)	-0.410	0.003 (S)

ACR 1 was not statistically different in patients who needed mechanical ventilation [median 87.0 (27-160) mg/g compared to 66.0 (28-170) mg/g in patients needed no mechanical ventilation, P = 0.47]. While ACR 2 was significantly higher in patients required mechanical ventilation [121.0 (21-235) mg/g] compared to those who didn't need mechanical ventilation [49.0 (22-120) mg/g, P <0.001]. Δ ACR has a high significant correlation with needing to use MV as a disease severity parameter in our study (P <0.001).

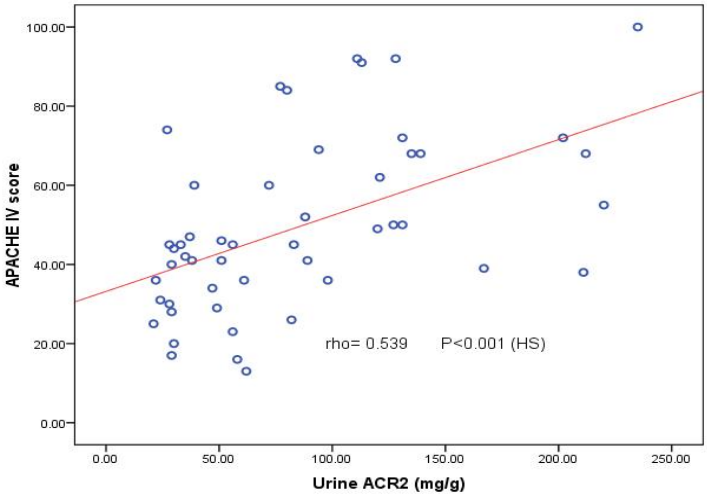

Fig. 3. Showing a significant positive correlation between urine ACR2 and APACHE IV score

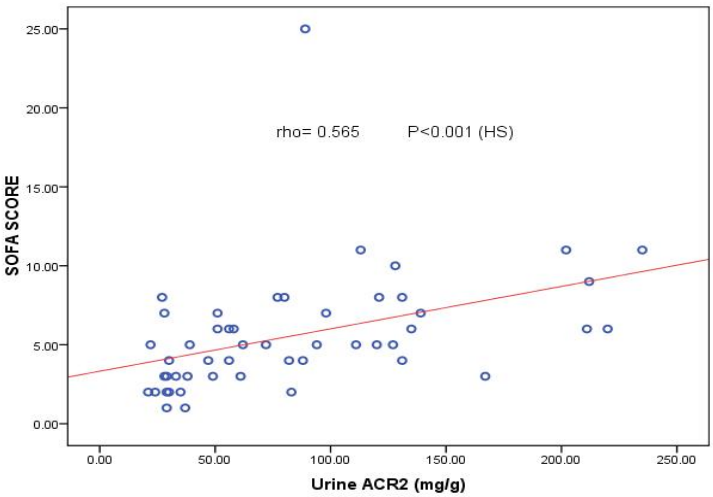

Fig. 4. Showing a significant positive correlation between urine ACR2 and SOFA score

Table 4. ACR1, ACR2 & ΔACR in different disease severity parameters (need of mechanical ventilation)

Variable	Need MV (n=25)		Not need MV (n=25)		ZMWU test	P
	Median	Range	Median	Range		
ACR1	87.0	27-160	66.0	28-170	**0.73**	**0.47 (NS)**
ACR2	121.0	21-235	49.0	22-120	**3.64**	**<0.001 (HS)**
Δ ACR	-40	-97- 4.0	18	24-87	**4.79**	**<0.001 (HS)**

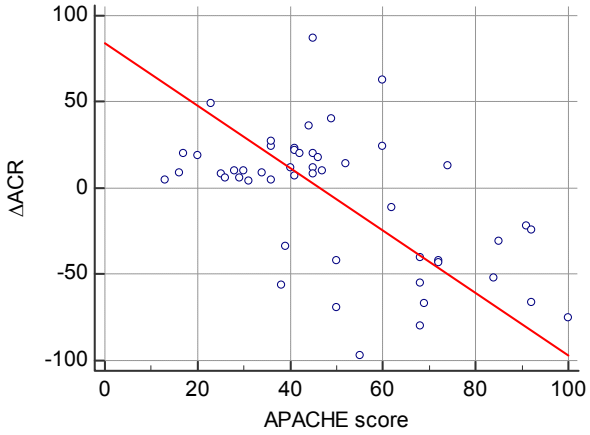

Fig. 5. showing a significant negative correlation between APACHE IV score and Delta ACR

A similar relation was found between ACR1 and ACR2 and the need of inotropic and/or vasoactive support. ACR 1 & 2 were significantly higher in patients needed inotropic support or vasopressors compared to those who didn't need support or vasopressors. ACR1 median 127.5 (87-160) mg/g and 62.5 (27-170) respectively, P = <0.001). ACR2 median 166.5 (89-235) mg/g and 56.5 (21-211) respectively, P = <0.001). ∆ ACR has a significant correlation with needing inotropes or vasopressors as a disease severity parameter in our study (P 0.018).

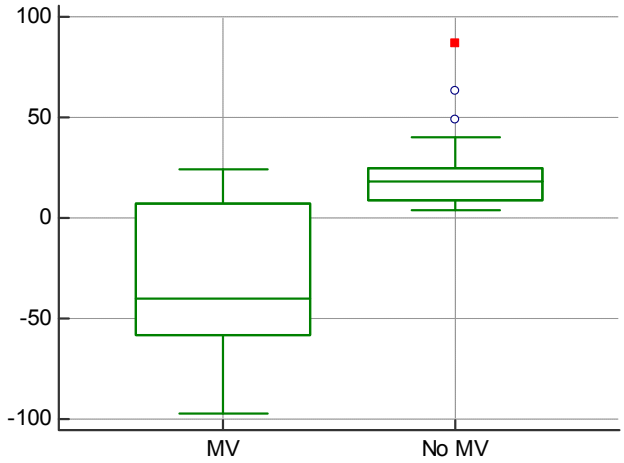

Fig. 6. Delta ACR according to the need of MV

Table 5. ACR1, ACR2 & ΔACR in different disease severity parameters (need of inotropes or vasopressors)

Variable	The need of inotropes or vasopressors (n=8)		Not need of inotropes or vasopressors (n=42)		ZMWU test	P
	Median	Range	Median	Range		
ACR1	127.5	87-160	62.5	27-170	**3.27**	**<0.001 (HS)**
ACR2	166.5	89-235	56.5	21-211	**3.56**	**<0.001 (HS)**
∆ ACR	-42.5	-97-40	9.5	-69-87	**2.36**	**0.018 (S)**

Albumin/creatinine ratio and outcome:

There was a significant correlation between ACR1and ICU length of stay per days (ICU-LOS) (P= 0.048). While ACR2 was a significant predictor of mortality with highly substantial association with ICU-LOS per days (P <0.001). ΔACR had a significant negative correlation with ICU-LOS (P= 0.009). This means that more increase in ACR2 (increasing ACR), the more negativity of ΔACR whis is calculated by the formula (ΔACR = ACR1- ACR2) and the more days expected for the patient to stay in ICU.

Table 6. Correlation between ACR1, ACR2, ΔACR with ICU-LOS

With	ICU-LOS	
	rho	P
ACR1	0.281	0.048 (S)
ACR2	0.466	<0.001 (HS)
Delta ACR	-0.364	0.009 (S)

Both ACR2 and ΔACR (increasing or decreasing ACR) were highly significant predictors of mortality in our study. ACR 2 was median 47.0 (21-121) mg/g for survivors and 131.0 (77-235) mg/g in non-survivors compared to ΔACR median 13.0 (-11 - 87) mg/g in non survivors and -52.0 (-97 - (-22)) mg/g for survivors (P <0.001) for both. ACR1 had no significant correlation with survival and not a good predictor of mortality. ACR1 median 63.0 (28-170) mg/g in survivors and 89.0 (27-160) in non survivors (P= 0.06).

The increase of ACR after 24 hours compared to admission ACR was associated with increased mortality. 18 patients had an increasing ACR (negative ΔACR), 17 (94.4%) of them, and only one (5.6%) was survived. 32 patients had a decreasing ACR (positive ΔACR), all of them were survived with no mortality (with high significant P value <0.001).

Receiver operator characteristic (ROC) curve was examined for the use of APACHE IV and ACR concentrations as a predictor of ICU mortality (Fig. 9).

The area under the ROC curve (AUC) for ACR2, ΔACR & increasing ACR to predict ICU mortality were 0.963, 1.0 & 0.985 (95% confidence interval (0.91-1.0), (1.0-1.0), (0.95-1.0) respectively (high significant P value <0.001). The optimal cutoff values of ACR2, ΔACR to predict ICU mortality were ≥91.5 & ≤ -22 respectively. These cutoff values gave a sensitivity of 88.2% & 100% and specificity of 90.9% & 100% respectively, for ICU mortality. Increasing ACR had a sensitivity of 100% and specificity of 97%, for ICU mortality.

The area under the ROC curve for APACHE IV score to predict ICU mortality was 0.90 (95% confidence interval 0.81-0.99 (high significant P-value <0.001). The optimal cutoff value for APACHE IV to predict ICU mortality was ≥49.5. This cutoff value gave a sensitivity of 88.2% and a specificity of 84.8% for ICU mortality.

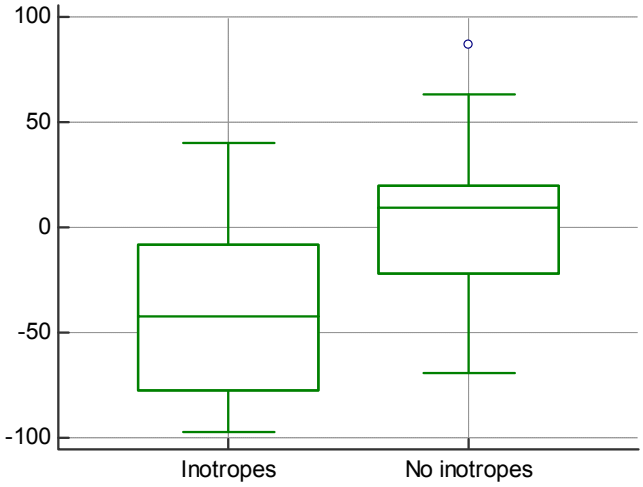

Fig. 7. Delta ACR according to a need of inotropes

Table 7. Mortality according to urine ACR

Variable	Survived (n=33)		Died (n=17)		Z_{MWU} test	P
	Median	Range	Median	Range		
ACR1	63.0	28-170	89.0	27-160	**1.86**	**0.06 (NS)**
ACR2	47.0	21-121	131.0	77-235	**5.3**	**<0.001 (HS)**
∆ ACR	13.0	-11- 87	-52.0	-97- (-22)	**5.75**	**<0.001 (HS)**

Table 8. Outcome according to ∆ACR (increasing & decreasing)

			In-hospital mortality		Total
			Survived	Died	
∆ACR:	Positive (decreasing)	-Count	32	0	32
		-% within DELTAs	100.0%	.0%	100.0%
	Negative (increasing)	Count	1	17	18
		% within DELTAs	5.6%	94.4%	100.0%
Total		-Count	33	17	50
		-% within DELTAs	66.0%	34.0%	100.0%

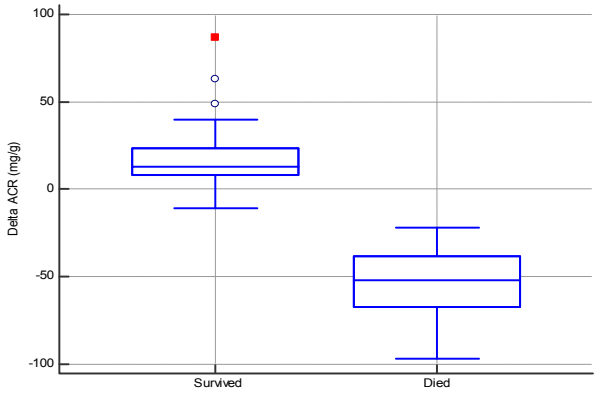

Fig. 8. Showing median and range of ∆ ACR according to the outcome

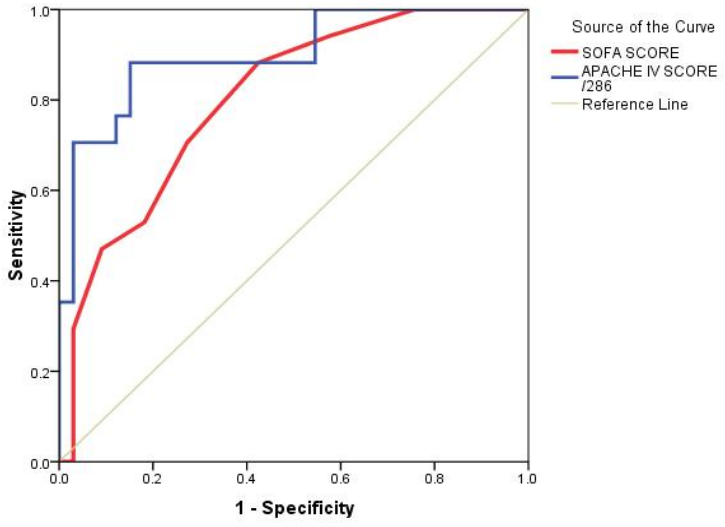

Fig. 9. ROC curve is showing the performance APACHE and SOFA scores in prediction of mortality

Table 9. Cut off values, predictive values and area under ROC curve of ACR, APACHI IV and SOFA

Variable	Cut off value	Sens%	Spec%	PPV%	NPV%	AUC	95% CI	P value
ACR1	≥78	70.6%	72.7%	57.1%	82.7%	0.662	0.49-0.83	0.06 (NS)
ACR2	≥91.5	88.2%	90.9%	83.3%	93.8%	0.963	0.91-1.0	<0.001 (HS)
∆ACR	≤ -22	100%	100%	100%	100%	1.0	1.0-1.0	<0.001 (HS)
Increasing ACR		100%	97%	94.4%	100%	0.985	0.95-1.0	<0.001 (HS)
APACHE IV score	≥49.5	88.2%	84.8%	75%	93.3%	0.90	0.81-0.99	<0.001 (HS)
SOFA score	≥5.5	70.6%	72.7%	57.1%	82.8%	0.802	0.68-0.93	0.001 (HS)

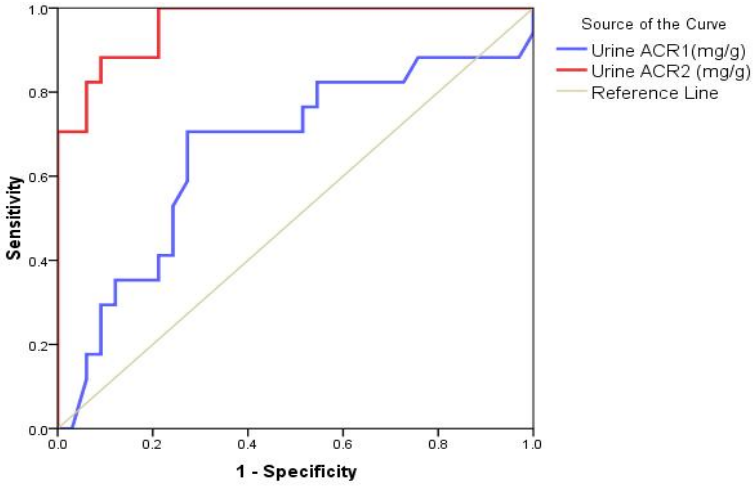

Fig. 10. ROC curve was showing the performance of urine ACR in the prediction of mortality

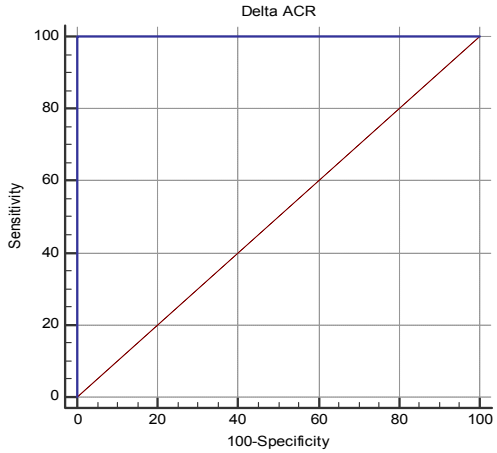

Fig. 11. ROC curve was showing the performance of ∆ ACR in the prediction of mortality

4. DISCUSSION

One national database analysis of discharge records from hospitals in the US estimated an annual rate of more than 1,665,000 cases of sepsis between 1979 and 2000 [21].

Another retrospective population-based analysis reported increased rates of sepsis and septic shock from 13 to78 cases per 100,000 between 1998 and 2009 [22].

In general, the earlier an accurate diagnosis is made, and appropriate treatment started, the higher the chance of survival, reduced complications, better quality of life, and reduced health care costs [23].

Currently, available tools for prediction of prognosis in ICU are the APACHE IV (Acute Physiology and Chronic Health Evaluation) score [15], which predicts mortality, and the SOFA (Sequential Organ Failure Assessment) score [17], which predicts morbidity. These scoring systems are based on several physiological indices and chemical analyses. Over the years, several problems, pitfalls, and limitations of these scoring systems have been identified.

To our knowledge, there is no laboratory examination has been definitively demonstrated to correlate with severity of illness and mortality in ICU patients. Several clinical studies showed that microalbuminuria, a urinary albumin excretion between 30 and 300 mg/day, may be a marker of severity of illness and mortality prediction in ICU patients with severe endothelial and renal involvement [24,25].

Microalbuminuria may indirectly quantify changes in systemic vascular permeability [26].

Several studies in various groups of critically ill patients have unequivocally established microalbuminuria as a significant prognostic marker of morbidity and mortality in the ICU [11]. Microalbuminuria was found to be prevalent in a broad spectrum of critically ill patients studied [27].

The level of microalbuminuria starts to increase within hours of an inflammatory insult as against delayed increases in levels of many other mediators [28].

The occurrence of microalbuminuria was demonstrated to be related to endothelial activation in uncomplicated essential hypertension that may occur very early, preceding the development of atherosclerosis [29].

It was concluded that the microalbuminuria might act as an inflammatory mediator. It is also well established that microalbuminuria is a significant predictor for the subsequent development of overt diabetic nephropathy, characterised by proteinuria, high blood pressure, and a fall in glomerular filtration rate [30].

Studies have shown that many acute inflammatory conditions are associated with microalbuminuria. The rapid increase in renal permeability to plasma proteins after trauma [31], surgery or ischemia which is proportional to the severity of the insult, led to the suggestion that increased renal and vascular permeability co-occur, and may share common pathways during the early stages of the acute disease process. Assay of the amount of albumin excreted in a random urine sample expressed as Albumin/creatinine ratio is a simple, validated and reliable test for evaluation of microalbuminuria [24].

We intended in our study to detect microalbuminuria in sepsis in intensive care patients. Moreover, the prognostic value of urinary albumin/creatinine ratio (ACR) in sepsis in the intensive care setting to predict mortality in sepsis.

This is a prospective study involving 50 critically ill patients with sepsis syndrome admitted to ICU. All included patients were subjected to the measurements of urinary albumin/creatinine ratio on admission (ACR1) and 24 hours later (ACR2). The recording of APACHE IV score (in the first 24 hours of ICU admission) and the highest SOFA score of their daily measurements was considered.

In this study, 28 patients (56%) had Chest infection as the primary source of disease, and 7 patients (14%) had infected bed sores, also the infected wound, peritonitis and GIT infection cases were (4 patients and 8% each = 24%) and the residual 3 patients (2% each with total 6%) had other different infections. A study was done by Angus DC et al. [32] showed that COPD was the most common underlying co-morbidity which was present in 12.3% of the patients. This indicates that lung is the most common source of infection leading to sepsis. A study was done by Angus DC, et al. [32] showed that 44% of the cause of mortality had a respiratory source of infection, 17.3% had bacteremia from an unidentified source and 8.6% had an inside source, and 6.6% had local wound as a source of infection. A similar study was done by Mandell G et al. [33] showed that most common primary sources of disease resulting in sepsis are the lungs, the abdomen, and the urinary tract.

There was no correlation between ACR1 or ACR2 and age, and neither ACR 1 nor ACR 2 was different in both gender groups. This was also concluded in many other studies [34]. The commonly known factors that may cause increase in ACR and that might be confounding are the diabetes mellitus and chronic kidney

disease; accordingly, we excluded those patients from our study.

Urine ACR1 ranged from 27 mg/g to 170 mg/g with a mean of 79.4 (SD 39.9). Urine ACR1 differed non significantly among survivors and non-survivors. Patients who survived had median ACR1 of 63.0 mg/g and patients who died had median ACR1 of 89.0 mg/g (P value=0.06) (Z_{MWU} test applied). A study done by Basu S, et al. [34] and Gosling P, et al. [10] showed that Urine ACR at 6 hours was 70.4 mg/g and108 mg/g among survivors, 168.6 mg/g and 156.6 mg/g among non- survivors respectively.

Urine ACR2 ranged from 21 mg/g to 235 mg/g with a mean of 84.7(SD 58.6). Urine ACR2 differed significantly among survivors and non-survivors. Median ACR2 among survivors was 47mg/g and among non-survivors were 131 mg/g. P value was statistically highly significant with ($p < 0.001$). Gosling P, et al. [10] did a study, showed that Urine ACR at 24 hours was 36.96 mg/g among survivors and 156.64 mg/g among non-survivors with significant (p-value of 0.0002). Basu S, et al. [34] did a study, showed that Urine ACR at 24 hours was 50.8 mg/g among survivors and 154.0 mg/g among non-survivors with significant (p-value of 0.0004).

Microalbuminuria defined as ACR 30- 300 mg/g was present in all of our patients' population. This is explained by including only patients with sepsis syndrome and not non-infectious SIRS. Many other studies showed that ACR was significantly higher in sepsis compared to non-infectious SIRS [35].

The reason for increased incidence of microalbuminuria in sepsis is probably the result of widespread endothelial dysfunction arising from the effects of cytokines, and other inflammatory mediators, released during the intense inflammatory responses that are associated with sepsis leading to the systemic increase in capillary permeability. The results of disruption of the integrity of the endothelial barrier are manifested as altered glomerular endothelial permeability in the kidneys, allowing increased amounts of albumin to escape into the glomerular ultrafiltrate. The tubular reabsorptive mechanism for albumin from the ultrafiltrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine. Many authors found that ACR after 6 hours and 24 hours from onset of sepsis as well as the increase of ACR over time is higher in patients with sepsis than in those without sepsis [34,35].

In our study, there was a significant correlation between ACR1 obtained on admission and SOFA score but not with APACHE IV score. While ACR 2 obtained 24 hours after admission significantly correlated with SOFA and APACHE IV scores. Delta ACR (increasing or decreasing ACR) is significantly associated with both APACHE IV and SOFA scores. In a medical/surgical critically ill patients, Basu et al. [34] found that ACR 6 and 24 hours after admission were correlated with APACHE II score.

In a study on medical cases only, increasing microalbuminuria had good sensitivity and specificity to predict the development of multi-organ failure. Also, a high APACHE II score was significantly associated with increasing microalbuminuria levels [24]. They also found that APACHE II and SOFA scores were higher in patients with growing trend of ACR over their ICU stay compared to patients with stationary or declining ACR level [24]. De Gaudio et al. [25], reported that in 55 post operative patients with sepsis, an increasing ACR correlated with a rising SOFA score. In a study of 40 trauma patients, the same authors De Gaudio AR, et al. [36] reported that the degree of increase in microalbuminuria over the first 24 hours following trauma was related to the severity of the injury.

In our study, out of 50 patients, all patients (100%) didn't need dialysis therapy. We couldn't elucidate any relation between ACR either on admission or 24 hours later and the need for dialysis. In the study of *Zhang and colleagues* on patients with sepsis and normal initial kidney function, ACR on the second day of admission was higher in patients who developed acute kidney injury [37]. They found that ACR on the second day of admission of 143 mg/g was 91.7% sensitive and 79.2% specific for predicting acute kidney injury in patients with sepsis [37]. Gosling et al. [38] also found that ACR on admission correlated with serum creatinin but they didn't comment on the need for dialysis. The lack of relation between the ACR and need for dialysis in our study was due to the small sample size compared to other reviews.

We found that the ACR 2 (after 24 hours) and the Δ ACR and not the ACR 1 (on admission) are associated with higher incidence of the need of mechanical ventilation. While they all are

associated with higher prevalence of lack for inotropic or vasopressor support. Other authors also found that ACR is inversely associated with the Pao2/Fio2 ratio in post-trauma patients [38] and was associated with significantly more duration of mechanical ventilation in patients with initially normal lung function [39]. *Pallister and colleagues* demonstrated that ACR 8 hours after admission was predictive of the development of ARDS.

Other authors concluded that ACR on admission and 6 hours later are higher in patients with vasoactive and inotropic support and are positively correlated with ventilator days [40]. It was supposed that the underlying mechanism was proposed to be the increase in systemic capillary leakage [41]. However, another study conducted on 25 septic patients showed that ACR did not correlate to extra vascular lung water and PaO2/FiO2 ratio, concluding that microalbuminuria does not reflect increased systemic capillary permeability in septic shock [26]. This was explained by the fact that in this study, the population had very low serum albumin that may influence urinary albumin excretion. Pulmonary vascular permeability does not solely determine the extra vascular lung water; other factors, including volume status, cardiac function and severity of lung injury, all contribute to extra vascular lung water [42].

Studying the trend of ACR over time, the group of patients with increasing ACR had a higher incidence of acute respiratory failure and MODS compared with those with decreasing or stationary ACR. Increasing microalbuminuria had NPV of 100% for detecting the acute respiratory failure and of 96% for MODS and PPV of 57 and 50% for both respectively [24].

Basu et al. [34] also found an inverse relationship between the degree of change in microalbuminuria and the lowest Pao2/Fio2 ratio.

The Length of stay in our study was median7.5 (4-45) days with Mean±SD (9.9±7.4). 17 of our patients died with a mortality rate of (34%) while 33 patients (66%) were discharged from the ICU. This is consistent with various studies including a study done by Rangel-Frausto MS et al. [43] which showed mortality ranging from 20-35%.

We detected that admission ACR and ACR 24 hours later and also ΔACR are predictors of ICU stay for more than seven days. All of them were found to have a significant positive correlation between them and ICU stay. The AUC for ROC analysis was high for ACR 2 (0.963) and then ACR 1 (0.662), but it was highest in ΔACR (1.0). We found that ACR1 of 78 mg/g (the cut off value) to have 70.6% sensitivity and 72.7% specificity, also ACR2 of 91.5 mg/g to have 88.2% sensitivity and 90.9% specificity and ΔACR of -22 mg/g to have 100% sensitivity and 100% specificity to predict mortality. We also found that the trend of ACR over time is a predictor of mortality with higher mortality in those with the increase in ACR 2 compared to ACR 1(increasing ACR). The rise in ACR was associated with 100% sensitivity and 97% specificity for detection of mortality in sepsis patients.

Also, we found that there is APACHE IV, SOFA scores of 49.5 and 5.5 respectively, to have 88.2% sensitivity & 84.8% specificity for APACHE IV score and 70.6% sensitivity & 72.7% specificity for SOFA score.

Gosling P, et al. [10] and Zhang Z, et al. [37] found that ACR values positively correlate with ICU-LOS. In *Gosling's* study, the ACR was measured on admission and 6 hours later. *Thorevska et al.* found that among survivors of critically ill patients, those with ACR more than or equal to 100 mg/g stayed five days longer in the ICU [27].

In a systemic review, Gobal et al. [11], concluded that ACR might hold promises as a predictor of mortality. Bhadade et al. [35], has demonstrated that the area under the ROC curves for prediction of death was highest for ACR2 (0.943) and change of ACR over time (0.943) followed by APACHE II (0.835), SOFA and ACR1 (0.725). Basu et al. [34] concluded ACR2 is as good as APACHE II for mortality prediction. They found ACR 24 hours after admission of 99.6 mg/g to have the sensitivity of 85 % and specificity 68 % and that APACHE II had a larger area under ROC curve than ACR. They concluded that absence of microalbuminuria at 24 hours is a predictor of survival. Gosling P, et al. [38], found results similar to Basu S, et al. [34] in surgical patients but not in medical patients.

In another study also in surgical patients, ACR measured upon arrival to the ICU was able to significantly differentiate survivors from non-survivors [44]. In the subset of surgical and trauma patients, *Gosling and colleagues* found that ACR more than 5.9 mg/mmol (52.2 mg/g) predict mortality with 100% sensitivity and 59%

specificity, however, in medical patients they didn't find any difference in ACR between survivors and non-survivors [38].

Gosling et al. in another study concluded that in both medical and surgical patients who died on the ICU, median ACR failed to decrease significantly 6 hours following admission [10].

In 104 mixed ICU patients, Thorevska et al. [27] found that patients with ACR more than or equal to 100 mg/g on admission were 2.7 times as likely to die compared to ACR less than 100. They concluded that ACR had similar predictive characteristics of APACHE II and SOFA scores as an independent predictor of mortality.

In our study ∆ACR and ACR2 has performed similar or slightly better than APACHE IV score and more better than SOFA score as the area under the curve was higher for ∆ACR and ACR2.

The finding of ACR2 as a predictor of mortality (median = 47 and 131 in survivors and non-survivors respectively with the highly significant p-value <0.001 in our study) could be explained on the presence of ongoing inflammatory processes among those who expired and hence the higher levels of ACR2 among them. On the other hand, a lower level of ACR2 might indicate a decrease in the inflammatory activity and explain the improved survival. This also demonstrates the ability of ∆ ACR in prediction of mortality (with highly significant p-value <0.001 in our study), where an increasing trend, (18 patients with 36% in our study) predicts a poorer outcome (17 died & one was survived), whereas a decreasing trend, (32 patients with 64% in our study) predicts a better outcome (all were survived). The decrease in levels after 24 hours of ICU admission could be the result of the reduction in the inflammatory processes occurring as a result of treatment.

The initiation of early treatment might help to protect the glycocalyx layer and prevent a further rise in capillary permeability. From these observations, it could be said that microalbuminuria has a role in checking the effect of treatment [35]. Also, some patients may have persistent microalbuminuria due to diabetic or hypertensive nephropathy, even if not previously diagnosed, so that it is essential to evaluate the trend rather than assess a single value. Many other studies had also found higher mortality among patients with increasing ACR levels than those with stationary or declining values [24,27,37].

5. CONCLUSIONS

Based in the study findings, it is conclude that the urinary albumin/creatinine ratio might be used as an unaffected, rapid, noninvasive, inexpensive, easy to perform and interpret test for early prognosis and prediction of mortality in septic patients. Late ACR after 24 h from ICU admission and ACR trend over time might be more important than the earlier entry ACR. Thus, together with current illness severity scores, the measurement of ACR on admission to the ICU, and 24 h later, can provide additional information on patient outcome.

6. RECOMMENDATIONS

We recommend using the albumin/creatinine ratio (ACR) as a scoring tool on admission and after 24 hrs to all patients admitted with sepsis.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital treated sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193:259.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165-228.
3. Russell JA. Management of sepsis. N Engl J Med. 2006;355:1699–1713.
4. Kumar V, Abbas A, Fausto N, Aster J. Robbins and Cotran pathologic basis of disease. (8th Edn), Elsevier Inc, Philadelphia, USA; 2010.
5. Fritz JH, Girardin SE, Fitting C, et al. Synergistic stimulation of human monocytes and dendritic cells by toll like-receptor 4 and NOD1-NOD2 activating

agonists. Eur J Immunol. 2005;35(8):2459-70.

6. Coopersmith CM, Chang KC, Swanson PE, et al: Over expression of Bcl-2 in the intestinal epithelium improves survival in septic mice. Crit Care Med. 2002;30(1): 195-201.
7. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood. 2003; 101(10):3765–77.
   Available:http://dx.doi.org/10.1182/blood-2002-06-1887
8. Haraldsson B, Nyström J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol Rev. 2008;88(2):451-487.
9. Terao Y, Takada M, Tanabe T, Ando Y, Fukusaki M, Sumikawa K. Micro-albuminuria is a prognostic predictor in aneurismal subarachnoid hemorrhage. Intensive Care Med. 2007;33(6):1000–6.
   Available:http://dx.doi.org/10.1007/s00134-007-0617-z.
10. Gosling P, Czyz J, Nightingale P, Manji M. Microalbuminuria in the intensive care unit: Clinical correlates and association with outcomes in 431 patients. Crit Care Med. 2006;34(8):2158–66.
    Available:http://dx.doi.org/10.1097/01.CCM.0000228914.73550.BD
11. Gopal S, Carr B, Nelson P. Does microalbuminuria predict illness severity in critically ill patients on the intensive care unit? Asystematic review. Crit Care Med. 2006;34(6):1805–10.
    Available:http://dx.doi.org/10.1097/01.CCM.0000217922.75068.EA
12. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55.
    Available:http://dx.doi.org/10.1378/chest.101.6.1644
13. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250–6.
    Available:http://dx.doi.org/10.1097/01.CCM.0000050454.01978.3B
14. Olmsted RN. Association for professionals in infection control and epidemiology. APIC Infection Control and Applied Epidemiology: Principles and Practice. St. Louis, London: Mosby; 1996.
15. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34(5):1297–310.
    Available:http://dx.doi.org/10.1097/01.CCM.0000215112.84523.F0
16. Dahhan T, Jamil M, Al-Tarifi A, Abouchala N, Kherallah M. Validation of the APACHE IV scoring system in patients with severe sepsis and comparison with the APACHE II system. Crit Care. 2009;13(Suppl 1): P511.
17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On Behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
18. Osama Tayeh, Khaled M. Taema, Mohamed I. Eldesouky, Adel A. Omara. Urinary albumin/creatinine ratio as an early predictor of outcome in critically-ill septic patients. The Egyptian Journal of Critical Care Medicine. 2016;4(2):47-55.
19. Saeed MA, Mahdy RE, Mohammed SA. Urine albumin/creatinine ratio as an early predictor of outcome in critically ill patients with sepsis. Research and Opinion in Anesthesia and Intensive Care. 2018;5(4): 267.
20. Khothari CR. Research methodology: Methods and techniques. New Age International, New Delhi; 2004.
21. Elixhauser A, Friedman B, Stranges E. Septicemia in U.S. Hospitals, Agency for Healthcare Research and Quality, Rockville, MD; 2009.
    Available:http://www.hcupus.ahrq.gov/reports/statbriefs/sb122.pdf
    (Accessed on February 15, 2013)
22. Walkey AJ, Wiener RS, Lindenauer PK. Utilization patterns and outcomes associated with central venous catheter in septic shock: A population based study. Crit Care Med. 2013;41:1450.

23. Surupa Basu, Mahuya Bhattacharya, Tapan K. Chatterjee, Subimal Chaudhuri, Subhash K. Todi, Arghya Majumdar. Microalbuminuria: A novel biomarker of sepsis. 2010;14(1):22–28.
24. Abid O, Sun Q, Sugimoto K, Mercan D, Vincent JL. Predictive value of micro-albuminuria in medical ICU patients: Results of a pilot study. Chest. 2001;120:1984-8.
25. De Gaudio AR, Adembri C, Grechi S, et al. Microalbuminuria as an early index of impairment of glomerular permeability in postoperative septic patients. Intensive Care Med. 2000;26:1364–1368.
26. Molnar Z, Szakmany T, Heigl P. Microalbuminuria does not reflect increased systemic capillary permeability in septic shock. Intensive Care Med. 2003;29(3):391–5.
Available:http://dx.doi.org/10.1007/s00134-003-1651-0
27. Thorevska N, Sabahi R, Upadya A, Manthous C, Amoateng Adjepong Y. Microalbuminuria in critically ill medical patients: Prevalence, predictors, and prognostic significance. Crit Care Med. 2003;31(4):1075–81.
Available:http://dx.doi.org/10.1097/01.CCM.0000059316.90804.0B
28. Molnár Z, Szakmány T, Köszegi T, Tekeres M. Microalbuminuria and serum procalcitonin levels following oesophagectomy. Eur J Anaesthesiol. 2000;17:464-5.
29. Cottone S, Mulè G, Nardi E, Lorito MC, Guareneri M, Arsena R, Briolotta C, Vadalá A, Cerasola G. Microalbuminuria and early endothelial activation in essential hypertension. Journal of Human Hypertension. 2007;21:167-172.
30. Jarrett RJ, Viberti GC, Argyropoulos A, et al. Microalbuminuria predicts mortality in non-insulin dependent diabetics. Diabet Med. 1984;1:17–19.
31. Moreno R, Vincent JL, Matos A, de MendonÃ§a A, Cantraine F, Thijs J, Takala J, Sprung C, Antonelli M, Bruining H, Willatts S. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Intensive Care Med. 1999;25:686-696.
32. Angus DC, Linde-Zwirble WT, Lidicker J. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
33. Mandell G, Bennet J, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 7th Ed. Philidelphia, PA: Churchill livingstone. 2009;Chapter 70:1660-64.
34. Basu S, Bhattacharya M, Chatterjee T, Chaudhuri S, Todi S, Majumdar A. Microalbuminuria: A novel biomarker of sepsis. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine. 2010;14(1):22.
35. Bhadade RR, deSouza R, Harde MJ, Sridhar B. Microalbuminuria: A biomarker of sepsis and efficacy of treatment in patients admitted to a medical intensive care unit of a tertiary referral center. J Postgrad Med 2014;60(2):145–50.
Available:http://dx.doi.org/10.4103/0022-3859.132320
36. De Gaudio AR, Spina R, Di Filippo A, et al. Glomerular permeability and trauma: A correlation between microalbuminuria and injury severity score. Crit Care Med. 1999;27:2105–2108.
37. Zhang Z, Lu B, Ni H, Sheng X, Jin N. Microalbuminuria can predict the development of acute kidney injury in critically ill septic patients. J Nephrol. 2013;26(4):724–30.
Available:http://dx.doi.org/10.5301/jn.5000231
38. Gosling P, Brudney S, McGrath L, Riseboro S, Manji M. Mortality prediction at admission to intensive care: A comparison of microalbuminuria with acute physiology scores after 24 hours. Crit Care Med. 2003;31:98-103.
39. Patila T, Kukkonen S, Vento A, et al. Relation of the sequential organ failure assessment score to morbidity and mortality after cardiac surgery. Ann Thorac Surg. 2006;82:2072-2078.
40. Gosling P, Sanghera K, Dickson G. Generalized vascular permeability and pulmonary function in patients following serious trauma. J Trauma. 1994;36:477–481.
41. Pallister I, Dent C, Wise CC, Alpar EK, Gosling P. Early post traumatic acute respiratory distress syndrome and albumin excretion rate: A prospective evaluation of a ‘point-of care’ predictive test. Injury. 2001;32(3):177-181.

42. Soumya Knati Dutta, Sulagna Sahu, Thatoi PK, Abhay Nath Chaturvedi, Sanjay Sarkar, Tushar Kanti Saha. Evaluation of microalbuminuria and serum Tnf A in patients with sepsis and their correlation with disease severity; 2014.
43. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA. 1995;273(2): 117-23.
44. Szakmany T, Molnar Z. Increased glomerular permeability and pulmonary dysfunction following major surgery: Correlation of microalbuminuria and PaO/FiO ratio. Acta Anaesthesiol Scand. 2004;48(6):704–10.
Available:http://dx.doi.org/10.1111/j.1399-6576.2004.00388.x

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