Association Between Urinary Albumin/Creatinine Ratio Alterations and Mortality in Patients with Sepsis: Clinical Implications for Critical Care Management

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Abstract
Introduction : Microalbuminuria has proven to be a predictor of organ function failure in septic patients. Microalbuminuria assessed by calculating ratio of urine albumin/ creatinine could be used as a simple, non-invasive to assess prognosis and predict mortality in early septic patients.
Method : Thirty one septic patients weretaking urine samples for examination of albumin levels in the urine using urine albumin/ creatinine ratio (ACR). Patients also were observed for a maximum of 28 days to assess mortality.
Result : Mortality of septic was found in 21 subjects (67.7%). Pneumonia was the most common source of infection (58.1%). Changes in ACR (p=0.02) and ACR II value (p=0.016) had a significant correlation with mortality in septic patients. In the contrary, no significant correlation was found between age, sex, vital signs, and source of infection with mortality of septic patients (p> 0.05). Hb values, platelets, ad random blood sugar, procalcitonin,urea and creatinine also did not have a significant correlation with mortality in septic patients (p> 0.05).
Conclusion : This study suggested association between changes in ACR and ACR II with mortality of septic patients. The higher the value of ACR II would resulted in higher the patient mortality.

Keywords: septic, microalbuminuria, albumin/ creatinine ratio, mortality.

Introduction
Septic is one of the serious health problems that occurred in the community. Septic is one of the ten biggest causes of death in the world. Early diagnosis of septic is often difficult to assess, because the appearing clinical septic is very diverse. If its not promptly treated it could lead to multiple organ failure lead to death.[1]One month observation in 2012 in the intensive care room of the Cipto Mangunkusumo Hospital (RSCM), Jakarta showed severe septic and septic shock was found in 23 of 84 cases of intensive care, with mortality rate reaching 47.8% and the mortality rate in the early stages reaching 34.7%.[2] According to some studies, microalbuminuria is the initial picture after a severe inflammatory process and persists in some of severe cases. Microalbuminuria has proven to be a predictor of organ failure, vasopressor needs and mortality assessment. Microalbuminuria shown to be better predictor than APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Septic-related Organ Failure Assessment) scores in several studies.[3] The PILOT study states that the occurrence of microalbuminuria assessed by urine albumin / creatinine ratio could be used to stratify the risk of emergency patients with septic or severe septic, meningitis, pneumonia, or febrile neutropenia where identification of septic patients without hemodynamic instability is a challenge nowadays.[4]

Method
This is a prospective cohort study to examine the correlation of changes in urine albumin/ creatinine ratio to mortality of septic patients in Haji Adam Malik General Hospital, Medan since October - December 2018. The minimum sample size in this study was 31 subjects.

Inclusion Criteria: Patients over 18 years old, Diagnosis of septic based on criteria from the *Surviving Septic Campaign: International Guidelines For Management Of Severe Septic And Septic Shock*, 2012 and informed consent were given to the patients or relatives who are willing to participate in this study.
Exclusion Criteria *:* Patients with a history of diabetes mellitus, hypertension, stroke, chronic kidney disease (CKD) with or without hemodialysis, chronic heart failure, anuria or hematuria, pregnancy, nephrotic syndrome and nephritic syndrome, massive proteinuria, taking drugs causing albuminuria such as avastin, Phenazopyridin etc and patients who die <48 hours prior to treatment.

Examination of albumin levels in the urine calculated with urine albumin/ creatinine ratio (ACR) method. Specimens needed approximately 30-60 ml. If possible, use fresh specimens; otherwise the specimens can be stored for up to 6 days at 4° C. If being stored, the urine should be thawed at room temperature. Urine specimen

is taken when the patient is diagnosed with septic in the ED (ACR I) and 48 hours later when hospitalized (ACR II).

Changes in urine albumin/ creatinine ratio (ACR) is assessed as changes from ACR I to ACR II. The difference between these values represents a change in urine albumin/ creatinine ratio (Δ ACR). Δ ACR= ACR II - ACR I. If Δ ACR is negative it is defined as a decrease in ACR and if positive it is defined as an increase in ACR.

Result

This study involved 31 subjects where 18 subjects (58.1%) were male with an average age 51.94 years. On clinical examination compos mentis state shown on 12 subjects (38.7%). On physical examination, the mean value of systolic blood pressure (SBP) was 112.26 mmHg, the average diastolic blood pressure (DBS) was 71.94 mmHg, the mean pulse frequency was 104.55 x /minute, the average respiratory rate was 29.39 times/minute and average temperature was 38.39° C. The most common source of infection was pneumonia as seen in 18 subjects (58.1%). The results of laboratory tests showed a mean hemoglobin (Hb) value of 10.16 g/dl, the mean leukocyte value was 20,362.26 /mm^3, the average platelet value was 251,580.65/mm3, the average ad random blood sugar level was 107.52 mg /dl, the mean value of procalcitonin was 16.48 ng/ml, the mean value of urea was 51.54 mg/dl, and the mean creatinine value was 0.77 mg/dl.

The mean value of urine albumin creatinine ratio I (ACR I) in the survival group was 159.84 mg/gr and in the non survival group was 172.19 mg/gr. The mean value of urine ACR II in the survival group was 173.90 mg/gr and in the non survival group was 236.76 mg/gr. Statistical analysis with Fisher's test shows significant correlation between changes in ACR and mortality of septic patients (p = 0.02). Statistical analysis using the Mann Whitney method shows there was a significant correlation between mortality and the value of ACR II (p = 0.016).

Table 1. Association between laboratory characteristics and mortality of septic patients

Variable	Survival (n = 10)	Non survival (n = 21)	p
Laboratory, mean (SD)			
Hb, g/dl	9,94 (3,53)	10,26 (3,59)	0,805 [b]
leukocyte , /mm^3	22.247,00 (5.835,75)	19.464,76 (17.340,65)	0,627 [b]
Platelet, /mm^3	266.500 (153.839,20)	244.476,19 (189.048,04)	0,751 [b]
Random blood sugar , mg/dl	117,8 (61,45)	102,62 (30,76)	0,475 [b]
Procalcitonin , ng/ml	13,11 (19,27)	13,81 (19,93)	0,916 [c]
Urea, mg/dl	51,40 (36,42)	51,60 (26,25)	0,986 [b]
Creatinine , mg/dl	1,41 (1,09)	0,83 (0,41)	0,574 [b]
ACR I, mg/gr	159,84 (72,97)	172,19 (59,36)	0,647 [c]
ACR II, mg/gr	173,90 (53,3)	236,76 (68,93)	**0,016** [c]
Change of ACR, n (%)			
Increase ACR	5 (50,0)	19 (90,5)	**0,02** [d]
Decrease ACR	5 (50,0)	2 (9,5)	

[a] *Chi Square,* [b] *T Independent*[c] *Mann Whitney* [d] *Fisher Test*

Discussion

Albumin is normally filtered at the glomerulus at a rate of 1-2 mg / minute, and reabsorbed (99%) in the proximal tubule, leaving <5ug / minute to be excreted. But on pathological conditions, the occurrence of inflammation causes an increase in glomerular permeability in albumin and a decrease in tubular reabsorption, which results in microalbuminuria.[6,7] Microalbuminuria is a condition that is common in critical patients including septic. Increasing the value of microalbuminuria at 48 hours of treatment can signify a significant prognostic among survivors and deaths in septic patients. Serial microalbuminuria measurements could help in the clinical assessment of critically ill patients who are at risk of experiencing a poor prognosis.[8]

The mortality in this study showed that 21 subjects died with a mortality rate of 67.7% while the living subjects were ten people (32.3%). This is higher than some previous studies where in the study by Sidharth et al (2016) the results of the percentage of deaths were 34.4%. The sample characteristics in the study by Sidharth et al (2016) assessed patients with SIRS (Systemic Inflammatory Response Syndrome) who were also used in this study to assess patients in septic. The difference in mortality in this study is likely due to limited ICU facilities and infrastructure at the Adam Malik General Hospital so that not all patients with a diagnosis of septic receive intensive care whereas in previous studies all septic patients received intensive care.[9]

The results of this study found that the source of the most infections was pneumonia as much as 58.1%. This is in line with a study conducted by Angus DC et al (2001) showing that 44% of causes of death had a source of infection originating from the respiratory tract, 17.3% had bacteremia from unknown sources and 8.6% had a source of infection that from stomach / digestion and 6.6% have local wounds as a source of infection.[10]

In this study there was a significant relationship between changes in ACR and mortality of patients assessed by statistical analysis with the Fisher test to assess the relationship between changes in ACR and mortality of septic patients (p = 0.02). This is in accordance with previous research by Surupa Basu et al (2010) which states that there is a relationship between increasing levels of microalbuminuria obtained from urine albumin / creatinine ratio values with mortality of septic patients. In this study the value of microalbuminuria was found to be significantly increased in patients with septic at 24 hours of treatment. The ACR value was significantly increased, especially in the group that did not survive / died (P = 0.004).[11]

This study also assessed the relationship between the value of ACR II and mortality of septic patients (p = 0.016). In the group of septic patients who live found the average value of ACR II amounted to 173.90 mg / gr and in the group of septic patients who died found a mean value of ACR II of 236.76 mg / gr with a value of p = 0.016 which was significant. This concludes that the value of ACR II is different for the group living with the deceased group where the value of ACR II is higher in the group who died.The study by Sidharth et al (2016) found that ACR II urine values ranged from 16.4-230.4 µg / mg with an average of 75.8. ACR II urine was significantly different between groups living with the group who died where the median ACR II among the living groups was 34.6 µg / mg and among those who died was 151.4µg / mg. The p value is statistically significant with p 0,0001.[9]

This study has several limitations, among others, the use of urine albumin / creatinine ratio can only be used in certain patients who do not have comorbidities that have the potential to cause research bias. Most septic patients are always accompanied by comorbid conditions such as the presence of diabetes mellitus, hypertension, chronic kidney disease where urine albumin / creatinine values cannot be used in this situation so that this study cannot describe the condition of septic in general.

Conclusion

Increased urine albumin / creatinine ratio can be used as a predictor of mortality in septic patients. The proportion of living septic patients is 32.3% and the proportion of septic patients who die is 67.7%. There is a relationship between the value of ACR II and the mortality of septic patients where the higher the value of ACR II, the higher the patient mortality.

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