ORIGINAL ARTICLE

Alpha1-microglobulin as an early biomarker of sepsis-associated acute kidney injury: a prospective cohort study

Terzi I[1], Papaioannou V[2], Papanas N[1], Dragoumanis C[2], Petala A[2], Theodorou V[2], Gioka T[3], Vargemezis V[4], Maltezos E[1], Pneumatikos I[2]

[1]Second Department of Internal Medicine
[2]Intensive Care Unit
[3]Department of Biopathology
[4]Department of Nephrology
General University Hospital of Alexandroupolis, Greece

Abstract

Background: Sepsis emerges as the leading risk factor for acute kidney injury (AKI) development in critically ill patients. Much effort has been invested so far on early diagnosis of AKI using promising biomarkers. This study aimed to determine whether urine alpha1-microglobulin (α1m), a lipocaline member previously used as an indicator of proximal tubular dysfunction, can early predict the development of sepsis-associated AKI (SAAKI) in critically ill patients.

Methods: A prospective, observational study was conducted in a single center Intensive Care Unit (ICU). Patients with normal renal function admitted to the ICU followed for sepsis and AKI development. Urine α1m levels were analyzed in pooled samples from 24-hour urine collections on sepsis onset and at various time points thereafter. The diagnostic performance of urine α1m was assessed using the nonparametric calculation of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

Results: Among 286 critically ill patients admitted to our ICU in a year, 45 patients with sepsis met the inclusion criteria. SAAKI developed in 16 septic patients (35.6%). Urine α1m levels were significantly elevated in all septic patients (average value of all samples on the day of sepsis: 46.02 ± 7.17 mg/l) and showed a trend to increase in patients who finally developed SAAKI. The AUC for SAAKI prediction according to α1m urine levels 24-hours before SAAKI onset was 0.739 (sensitivity 87.5%, specificity 62.07%, cutoff level 47.9 mg/l). Urine α1m 24-hours before SAAKI, serum creatinine on sepsis onset and Acute Physiology and Chronic Health Evaluation II (APACHE II) score on sepsis onset emerged as the most powerful independent predictors of SAAKI. The combination of these three parameters improved the AUC for SAAKI prediction to 0.944.

Conclusion: Urine α1m levels might help in the early prediction of SAAKI development and may prove useful biomarker. The pathogenetic implications of α1m in sepsis and SAAKI need further investigation. Hippokratia 2014; 18 (3): 262-268.

Keywords: Acute kidney injury, Sepsis, Critically ill patients, Urinary biomarkers, alpha1-microglobulin

Corresponding Author: Terzi Irene, Intensivist - Consultant in Internal Medicine, 2nd Department of Internal Medicine, General University Hospital of Alexandroupolis, Dragana 68100, Alexandroupolis, Greece, tel:+306944162647, fax:+302551074723, e-mail: gter41@otenet.gr

Introduction

Sepsis-associated acute kidney injury (SAAKI) appears to complicate a great percentage of patients hospitalized in Intensive Care Units (ICU), contributing to high in-hospital mortality[1-3]. Although the exact mechanisms leading to SAAKI remain elusive, recent studies suggest that it is a unique and distinct pathophysiological entity[4], resulting not only from a classical ischemic acute tubular necrosis but, rather from a combination of immunological, toxic and inflammatory insults[5]. Among these, renal tubular apoptosis emerges as the prominent process of renal dysfunction[4,6]. The early recognition of acute kidney injury (AKI) has become today a "clinical priority"[7]. Nevertheless, despite the effort that has been invested on the research for a promising early AKI biomarker, the results so far do not favor a clear candidate molecule satisfying the requirements of the perfect early biomarker[8-9].

Alpha-1-microglobulin (α1m) is a low-molecular-weight protein that is synthesized in the liver, freely filtered by glomeruli and reabsorbed by renal proximal tubular cells where it is catabolized[10]. Under normal conditions very little filtered α1m appears in the final excreted urine[11-13]. Therefore, urine levels above the reference values can indicate proximal tubular damage[14]. On the other hand, beyond the potential role as a renal biomarker, re-

cent studies revealed that α1m exhibits several immunosuppressive functions and acts as a radical reductase and scavenger. These findings support the assumption that α1m may serve as a protector of cells and tissues against apoptotic damage[15-17].

The aim of this study was to assess the utility of urine concentrations of α1m as biomarker of early SAAKI diagnosis in critically ill patients managed in an ICU.

Patients and Methods

The study was conducted in a nine-bed multidisciplinary ICU at the General University Hospital of Alexandroupolis, in Greece and lasted for one year. Patients who met any of the criteria of the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) classification were classified as acute kidney injury patients[18]. We used the change in serum creatinine level and urine output to classify patients with renal dysfunction according to the RIFLE criteria. Baseline creatinine was taken from preadmission values. When no true preadmission creatinine value existed, the lowest value of the initial creatinine on entry to the ICU was used as baseline creatinine value. The diagnosis of sepsis was made according to the International Sepsis Definition Conference criteria[19]. Eligible for inclusion were all patients older than 18 years who admitted to the ICU due to sepsis or developed sepsis during their hospitalization in the ICU. Exclusion criteria were history of renal transplantation and known renal failure of any stage or prior renal disease. Patients were withdrawn from the study, if they developed AKI in less than 72 hours after inclusion or if they were discharged from the ICU in less than 72 hours. The study protocol was approved by the local Institutional Review Board and Ethical Committee. Before enrollment, informed consent was obtained from patients' next-of-kin.

Patients were followed daily for sepsis and AKI development. Urine and blood samples were collected every day, for each patient enrolled in the study, from the day of enrollment until the day of AKI development. Urine samples were taken after thorough mixing of 24 hour urine collections, centrifuged at 3,000 rpm for 10 minutes to remove cellular debris and then stored at -40ºC. Blood samples centrifuged at 3.500 rpm for 10 minutes and serum stored at -40ºC. Alpha1-microglobulin was measured in pooled urine samples, in a blinded fashion, using the α1-Microglobulin ELISA Kit, of the Immundiagnostik AG (Immundiagnostik AG, Stubenwald-Allee 8a, D 64625 Bensheim, Germany). A1m levels were measured in all samples taken at the day of sepsis development (Sepsis-Day). In patients who finally developed SAAKI, α1m was determined in samples taken at the day when SAAKI occurred (Day-0) and in samples taken 24 hours (Day-1) and 48 hours (Day-2) before SAAKI development. In patients who did not develop SAAKI, α1m was measured in three consecutive urine samples after the episode of sepsis (Day-2, Day-1, Day-0).

Statistical analysis

Program MedCalc for Windows XP version 12.2.1.0 software (MedCalc Software, Mariakerke, Belgium) was used for all statistical analyses. Predictive value of urine α1m for SAAKI development was assessed using the nonparametric calculation of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Since studies on the accuracy of α1m in early detection of septic renal failure are lacking, we considered that the ROC AUC should be higher than 0.9 for the detection of urine α1m to be clinically important. A total sample size of 30 patients was calculated to be sufficient, using a significance level of 0.05 (two-sided) and a power of 0.8[20].

Results

Among 286 critically ill adult patients admitted to our ICU, 42 patients had renal failure at admission and 146 patients stayed in ICU less than 72 hours and they are excluded from the study. From the remaining 98 patients, 45 patients met strict inclusion criteria for severe sepsis or septic shock and composed the study population. Renal failure developed in 16 septic patients (35.6%), after a median of 8 days [interquartile range (IQR) 5.75-9.25)] from the episode of sepsis. Initial RIFLE-stage was Injury in 11 patients (68.75%) and Failure in 5 patients (31.25%). Four patients with RIFLE-stage Injury (25%) progressed to Failure in a median of 5.5 days (IQR 4.75-6.5). Among survivors SAAKI patients, four patients exhibited complete recovery of renal function at the time of their ICU discharge, while one remained in RIFLE-stage Failure. Patients' characteristics are summarized in Table 1 and Table 2.

In all urine samples examined, α1m was found to be above the normal range (average value of all samples on the day of sepsis onset: 46.02 ± 7.17 mg/l). No difference observed in urine α1m levels measured on the first day that sepsis developed between the two patient groups (p=0.42). In septic patients who did not developed SAAKI, urine α1m levels were maintained persistently elevated without notable variation. In patients who eventually developed SAAKI, urine α1m levels exhibited an increase over time, as glomerular filtration rate (GFR) gradually decreased. Levels of urine α1m found to differ significantly between the two patient groups 24 hours before AKI development (p=0.014) (Figure 1).

Urine α1m performed well as a diagnostic marker for SAAKI development 24 hours before the event [(ROC AUC 0.739, 95% confidence intervals (CI) 0.587-0.859)], but did not exhibit any prognostic value on sepsis onset and 48 hours before SAAKI development (Table 3). For the prediction of SAAKI 24 hours before its development, urine α1m sensitivity and specificity were optimal at the 48 mg/l cut-off (Figure 2). Analysis revealed that urine α1m levels behaved as a sensitive marker rather than a specific one. At the same time, they presented a more valuable negative than positive predictive value in septic-AKI detection.

To assess the added value of urine α1m levels 24-hours before SAAKI development to other clinical and laboratory

Table 1: Demographic characteristics, causes ofintensive care unit admission, sepsis etiology and severity scores among critically ill patients according to the development of acute kidney injury.

	Sepsis and AKI (n=16)	Sepsis without AKI (n=29)	p value
Male gender	11 (68.7 %)	18 (62 %)	0.6
Age (years)	63 ± 16.85	51 ± 19.5	0.04
Cause of primary admission			
- trauma	5 (31.25 %)	11 (38 %)	0.9
- respiratory	6 (37.5 %)	6 (21 %)	0.4
- neurologic	2 (12.5 %)	7 (24 %)	0.6
- digestive	2 (12.5 %)	5 (17 %)	0.1
vascular	1 (6.25 %)	-	0.8
Sepsis etiology			
- VAP/pneumonia	9 (56.25 %)	8 (27.6 %)	0.1
- CVC-related infection	4 (25 %)	13 (44.8 %)	0.3
- trauma infection	2 (12.5 %)	4 (13.8 %)	0.7
- peritonitis	1 (6.25 %)	4 (13.8 %)	0.7
SAPS3 PIRO	40.6 ± 9.8	31.6 ± 7.5	0.005
APACHE II (on sepsis onset)	25.6 ± 6	20.2 ± 4	0.005
SOFA (on sepsis onset)	9.4 ± 2.4	8.1 ± 1.9	0.08

Data are expressed as mean ± standard deviation or number (percentage). ICU: intensive care unit, AKI: acute kidney injury, VAP: ventilator associated pneumonia, CVC: central venous catheter, PIRO score: Predisposition, Insult and Response/Organ dysfunction in sepsis, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment.

Table 2: Differences in laboratory parameters, physiology values and medicines used on sepsis between critically ill patients who developed or not acute kidney injury.

	Sepsis and AKI (n=16)	Sepsis without AKI (n=29)	p value
WBC (10^9/ml)	12.07 ± 6.23	15.22 ± 9	0.17
PLT (10^9/ml)	190.8 ± 100	295.85 ± 2.3	0.04
Hct (%)	31.74 ± 4.6	32.3 ± 7.7	0.9
Fib (mg/dl)	458.2 ± 198	522 ± 193	0.34
AST (U/l)	128.43 ± 271	50.17 ± 71	0.27
ALT (U/l)	102.8 ± 192	97.89 ± 184	0.93
Albumin (g/dl)	2.56 ± 0.56	3.4 ± 0.6	0.04
CPK (U/l)	723 ± 995	620 ± 1445	0.78
Sodium (mmol/l)	146.18 ± 7.89	143.7 ± 7	0.3
Potassium (mmol/l)	4.28 ± 0.62	4.07 ± 0.61	0.28
Urea (mg/dl)	66.25 ± 26.73	46.42 ± 23	0.01
Creatinine (mg/dl)	1.13 ± 0.32	0.77 ± 0.24	0.001
CRP (mg/dl)	16.86 ± 6.92	17 ± 7	0.94
PCT (ng/ml)	13.95 ± 27.51	4.44 ± 15.5	0.21
pH	7.37 ± 0.11	7.44 ± 0.08	0.04
Bicarbonate (mmol/l)	23.18 ± 5.54	26.62 ± 5.32	0.05
Lactate (mmol/l)	1.54 ± 1.08	1.76 ± 1.66	0.57
Temperature (^{o}C)	37.76 ± 1.62	38.13 ± 1.43	0.45
PO_2/FiO_2 ratio	173.12 ± 81.4	204.42 ± 104	0.27
MAP (in mmHg)	70 (60-81.25)	72.5 (65-80)	0.4
CVP (in mmHg)	11.5 (10-13)	12 (8-12.5)	0.2
Urine output (ml/24h)	119.4 ± 42.34	141.93 ± 69.85	0.11
Vasopressors (%)	12 (75%)	19 (65%)	0.85
- nonadr (γ/kg/min)	0.5 ± 0.34	0.36 ± 0.4	0.3
Diuretic use (%)	9 (56.25%)	20 (69%)	0.55
Aminoglycoside use (%)	8 (50%)	8 (27.6%)	0.23

Data are expressed as mean ± standard deviation, number (percentage) or median (interquartile range). AKI: acute kidney injury, WBC: white cell count, PLT: platelets, Hct: hematocrit, Fib: fibrinogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CPK: creatine kinase, CRP: C-reactive protein, PCT: procalcitonin, HR: heart rate, MAP: mean arterial pressure, CVP: central venous pressure, noradr: noradrenaline.

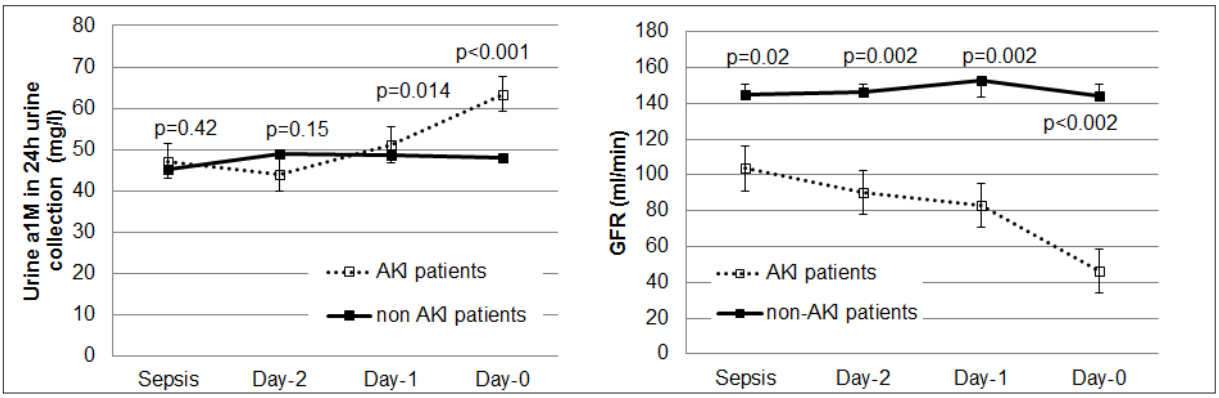

Figure 1: Time course of alpha1-microglobulin (α1m) levels and renal function (Glomerular Filtration Rate, GFR) in septic critically ill patients with or without acute kidney injury (AKI) development. Assessment of GFR was made by using 24-hour collections for estimating creatinine clearance expressed in ml/min. Creatinine clearance was calculated from the equation: [Cr urine (mg/dl)] x urine volume (ml) x 1.73 / Cr serum (mg/dl) x minutes]. Serum creatinine was measured at the start of the observation and at the end of every 24-hour period. The mean of the two measurements was used for serum creatinine determination. Values are expressed as mean ± standard deviation.

Table 3: Diagnostic significance of 24-hour urine alpha1-microglobulin concentration in sepsis-associated acute kidney injury (AKI) across three time intervals

	AUC	Cut-off value (mg/l)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	*p*
Sepsis	0.574	-	93.75 % (69.8-99.8)	34.48 % (17.9-54.3)	44.1 %	76.9 %	0.4
48h before AKI	0.523	-	31.25% (11-58.7)	89.66% (72.6-97.8)	57.1%	68.4 %	0.8186
24h before AKI	0.739	>47.9	87.5 % (61.7-98.4)	62.07 % (42.3-79.3)	56 %	90 %	0.0020

AKI: acute renal injury, AUC: area under the ROC curve, PPV: positive predictive value, NPV: negative predictive value.

parameters at sepsis, we performed a multivariate logistic regression analysis. All variables that were found by univariate analysis to display a p<0.1 were included into the model. According to the univariate model, eight parameters were predictive of SAAKI: urine α1m levels 24-hours before SAAKI [odds ratio (OR):1.16 (1.02-1.31), p=0.01], age [OR:1.03 (0.99-1.07), p=0.05], Acute Physiology and Chronic Health Evaluation II (APACHE II) [OR:1.24 (1.06-1.44), p=0.004] and Sequential Organ Failure Assessment (SOFA) scores calculated on sepsis onset [OR:1.34 (0.97-1.85), p=0.07], serum creatinine [OR:59.27 (4.15-845), p=0.002] and urea serum concentrations [OR: 1.03 (1.005-1.061), p=0.02] on sepsis, fluid balance on sepsis [OR:1 (1-1.008), p=0.06] and the worst pH at the episode of sepsis [OR: 0.0002(0-0.23), p=0.01]. However, by multiple stepwise regression analysis, only α1m, serum creatinine and APACHE II score emerged as the most powerful independent predictors. Adding α1m to creatinine and APACHE II improved the prediction significantly and increased AUC from 0.849 (95% CI 0.709-0.939) to 0.944 (95% CI 0.831-0.991) (Table 4).

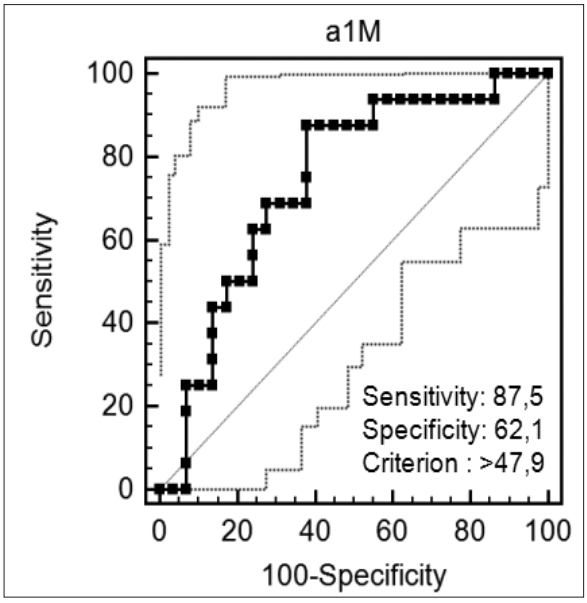

Figure 2: Receiver operator characteristic (ROC) curve for prediction of sepsis-associated acute kidney injury (AKI) in critically ill patients by urine alpha1-microglobulin (a1m) levels measured 24-hours before AKI develops.

Discussion

In this study we sought to evaluate the predictive value of urine α1m levels on SAAKI development in

Table 4: Multiple logistic regression models for the prediction of sepsis-associated acute kidney injury (AKI) in critically ill patients.

	Simple model			Biomarker model		
	OD (95% CI)	***p***	**Model performance**	**OD (95% CI)**	***p***	**Model performance**
APACHE	1.18 (1-1.3)	*0.0386*	*AUC: 0.849 Accuracy: 81.82%*	1.36 (1-1.7)	*0.012*	*AUC: 0.944 Accuracy: 86.36%*
S-Cr	43,87 (2.4-777.6)	*0.009*		271.47 (2.9-25268)	*0.015*	
α1m				1.54 (1-2.2)	*0.027*	

AKI: acute renal injury, OD: odds ratio, AUC: Area under the ROC curve, APACHE: APACHE II score on sepsis day, S-Cr: serum creatinine levels on sepsis day (mg/dl), α1m: 24-hour urine alpha1-microglobulin levels 24 hours before AKI development (mg/dl).

patients admitted to an ICU. We suggest that there are two results of relevance: the elevated levels of α1m in all septic patients and the progressive increase of α1m in patients who finally developed SAAKI.

Increased levels of urine α1m in sepsis

There are only a few studies investigating the levels of urine α1m in septic critically ill patients[4,21-23]. Martersson et al, found a trend towards higher peak levels of urine α1m with increasing sepsis severity and the presence of AKI[21]. In addition, Magid et al reported an 8-98 fold relative increase in α1m/creatinine ratio among septic critically ill patients studied[22]. The finding of the increased urine α1m levels far beyond normal values in all septic patients enrolled - even before SAAKI develops - could have a double explanation. First, since it is already established that α1m is a renal tubular marker, the increased urine levels of the protein could mirror an early subclinical renal proximal tubular dysfunction, which, however, does not reach the limit of AKI, according to the current definitions. It has been suggested that sepsis can cause renal impairment that is not obvious by changes in creatinine clearance but documented by an early tubular proteinuria[24]. A second explanation of the high urine α1m levels in all septic patients could be an increased production of the protein during sepsis. This could result in increased plasma levels, with overflow of the reabsorption capacity in tubular cells, leading to an increase in urine secretion, without however, the presence of any tubular dysfunction or renal damage. Unfortunately, overproduction of α1m during sepsis is difficult to be proved because the determination of the α1m concentration in human plasma or serum is complicated by the presence of different forms of the protein, resulting in a widely variation of reports on normal blood α1m concentrations[10]. However, several studies have shown that α1m might be implicated in septic processes. A1m has a number of immunoregulatory properties such as inhibition of neutrophils' oxidative burst[25] and inhibition of antigen-induced lymphocyte cell proliferation and cytokine secretion[26-28]. A1m acts as a reductase and a radical scavenger and protects against pathological oxidation of tissue components by binding and degradating heme and free radicals, and by enzymatically reducing oxidants and oxidation products[29-32]. Most importantly α1m is implicated in the protection of the mitochondria against oxidative insult during cell death, assisting mitochondria to maintain their energy delivery during cell death and, at the same time, counteract and eliminate the reactive oxygen species (ROS) generated by the mitochondrial respiration in order to prevent oxidative damage to surrounding healthy tissue[32-33]. These redox properties make α1m a novel and previously unknown defense mechanism against pathologic oxidation, cell necrosis and apoptosis.

Increased levels of α1m in SAAKI

The second important finding in our study was the trend of urine α1m titers to increase in patients with deterioration and SAAKI development. According to ROC curve analysis, urine α1m levels presented a relatively limited diagnostic performance, as a sole biomarker, in predicting SAAKI. On the other hand, adding α1m data to other independent predictors of SAAKI improved significantly their diagnostic ability. Many studies so far, examining other renal biomarkers, found good prognostic value of these biomarkers in predicting AKI, however, they failed to early detect AKI development in the course of a septic episode[34-35]. This shows that sepsis could probably modify the diagnostic ability of biomarkers in AKI. Even if, at the beginning of our study we assumed that SAAKI is primarily characterized by a tubular damage or dysfunction, SAAKI has proved to be a multi-pronged injury implicating mechanisms such as renal circulatory alterations, inflammation and oxidative stress injury, coagulation disturbances, endothelial cell dysfunction and apoptosis[9,36]. Thus, increased complexity of pathophysiological mechanisms might limit the diagnostic value of single biomarkers. Moreover, another inherent limitation associated with ineffectiveness of novel biomarkers in predicting SAAKI, is the difficulty in selection and enrollment of critically ill patients without renal injury precipitating factors others than sepsis. Furthermore, unlike

experimental studies, designing a study in the clinical setting carries always the difficulty of defining the time of the initial sepsis insult, as well as, the onset of deterioration of renal function.

The main strength of our study is the prospective enrolment of a relatively homogeneous population of critically ill patients, selected by strict, predefined criteria, without obvious underlying causes for AKI. Among the limitations are the relatively small number of patients included, the need for 24-hour urine collections and the absence of α1m measurements in a control subgroup of critically ill patients without sepsis or AKI.

Conclusion

In conclusion, our study suggests that sepsis and AKI contribute both in the increase of urine α1m levels. Measurement of urine α1m may help in early prediction of SAAKI. Urine α1m levels have a relatively limited diagnostic performance in predicting SAAKI but adding α1m to other parameters, like serum creatinine on sepsis onset and APACHE II score, can improve the early prediction of SAAKI significantly. Our results do not clearly support the superiority of urine α1m over traditional laboratory and clinical practices in SAAKI prediction. More studies are needed to clarify the usefulness of urine α1m as a SAAKI biomarker and many things remain to be addressed, such as the use of creatinine-adjusted spot urine samples in urine α1m measurement, the influence of other coexisting parameters or medications on urinary α1m levels, or the potential role of urine α1m in monitoring renal recovery. The additional contribution of α1m in a panel of other biomarkers that already have been studied in early AKI diagnosis, such as NGAL or KIM-1, could be also the aim of a study. On the other hand the finding of the increased urine α1m levels in all septic patients, even in those with normal or slightly raised serum creatinine, should stimulate further research to understanding the probable pathophysiological role of α1m, as an antioxidant and an immunoregulatory molecule, in sepsis and SAAKI. The biological roles and the possible implications of α1m in sepsis and SAAKI remain to be clarified.

Conflict of Interest

The authors declare no conflict of interest.

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