Antithrombin III Predicts Acute Kidney Injury in Septic Elderly Patients

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Abstract

Background The elderly are the primary age group of acute kidney injury (AKI). The predictive value of Antithrombin III (ATIII) level in preventing AKI among septic elderly patients has not been studied. The purpose of this study was to evaluate the value of ATIII in predicting AKI nondevelopment and prognosis in septic elderly patients under ICU settings. **Materials and methods** This is a retrospective study enrolling 107 elderly patients with sepsis who were admitted to ICUs from October 2015 to March 2018. Assessment of renal function was performed daily by measuring serum creatinine level and urine output. The ATIII level was obtained within the first 48 hours of the diagnosis of sepsis (ATIII1). **Results** Among all enrolled patients, 29 (27.1%) developed AKI. The ATIII level was a predictor of AKI nondevelopment (AUC-ROC =0.729, and sensitivity 0.700 and specificity 0.714). The ATIII/Cr ratio was also a predictor of AKI nondevelopment (AUC-ROC =0.971, and sensitivity 0.900 and specificity 1). The accuracy of ATIII and ATIII/Cr in predicting survival was intermediate, with AUC-ROC of 0.681 and 0.804 respectively, sensitivity ranging between 0.802 and 0.596, and specificity between 0.542 and 0.875. The ATIII level demonstrated excellent ability in predicting AKI nondevelopment in septic elderly patients in ICUs. Patients were divided into low ATIII group and high ATIII group using 66.95 or 55.7 as cutoff value. In comparison, ICU stay was significantly lower in the high ATIII group ($p=0.020$ and 0.049 , respectively). Off mechanical ventilation time, off CRRT time, and survival time were significantly higher in high ATIII group ($p=0.049, 0.048, 0.014$ using 66.95 as cutoff and $0.041, 0.036, 0.021$ using 55.7 as cutoff). **Conclusion** This study suggests that ATIII predicts acute kidney injury in septic elderly patients. Lower ATIII predicts worse prognosis.

Introduction

Sepsis is defined as infection with multiple organ dysfunction. Acute kidney injury (AKI) is common among early complications of sepsis. Its incidence ranges from 11% to 42%. In addition, the occurrence of AKI in sepsis patients also indicates poor prognosis and significantly increased mortality [1,2]. The elderly are the primary age group of AKI. Therefore, early detection of sepsis induced AKI and timely treatment can improve the clinical prognosis of elderly patients with sepsis.

Although a large number of studies have been conducted in the past, the exact mechanism of sepsis inducing AKI remains unclear. However, the inflammatory response to sepsis is considered to be a leading factor in kidney injury. Inflammatory responses in sepsis lead to the release of pro-inflammatory cytokines into the circulation, which then leads to systemic inflammatory responses (SIRS). Now a lot of research has shown that relationships with kidney oxygenation, metabolism, inflammation, and function, where they trigger leukocyte aggregation that leads to renal inflammation [3-6]. In addition, clinical studies have shown that we need new biomarkers to detect acute kidney injury before creatinine and urine volume [7], which with high susceptibility and can also predict prognosis.

ATIII, not only does it play a vital role in the body's anticoagulation, it also plays an crucial role in its anti-inflammatory effects [8-10]. Studies have shown that in animal models, ATIII was found to have a protective effect on the kidney, mainly through anti-inflammatory. Endogenous ATIII dysfunction worsens

renal injury in animal models. In clinical studies, low ATIII levels also increased the incidence of AKI in some patients[11,12].However, further studies are needed to confirm the protective effects of ATIII in sepsis-induced AKI. Although in fact Cr and urine output and be used to diagnose AKI development.It is too late to discover AKI. This study proposes to predict the occurrence of AKI in infectious elderly patients by ATIII level or combination of ATIII and creatinine.

Methods

Study Population

This was an observational study. We enrolled patients 60 years of age or older who had sepsis according to “Sepsis 3.0” [13]. This retrospective study included data derived from one teaching hospital (Shanghai General Hospital). This retrospective observational study was conducted between October 2015 and March. We reviewed the medical records of patients with sepsis who were admitted to the intensive care unit (ICU) of Shanghai General Hospital. This study was approved by the institutional review board of the Shanghai General Hospital. Since the data collected was anonymous, the need for informed consent was waived.

Inclusion and Exclusion Criteria

The elderly was defined as age equal to or over 60 years old based on Chinese laws . AKI was defined as increase of serum creatinine or decrease of urine output based on Kidney Disease Improving Global Outcomes (KDIGO) criteria [14]. The inclusion criteria was patients between 60 to 85 years old who presented with sepsis; sepsis was diagnosed based on the “Survival Sepsis Campaign 2012” [13]. Exclusion criteria were as follows: We excluded stages 4 or 5 chronic kidney disease (CKD) patients (clearance de creatinine < 30 ml/min), kidney transplantation patients, patients with ICU stay < 24 h, and patients already admitted to ICU with AKI.End-stage diseases(Malignant tumor, leukemia, cirrhosis, NYHA class IV, and severe COPD), written “do not resuscitate” form , history of allergies to antibiotics or other drugs.

Baseline glomerular filtration rate was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation [15]. Baseline creatinine was defined as the lowest serum creatinine value in the last 6 months before onset of AKI, or, for those without this measurement, the lowest value achieved during hospitalization in the absence of dialysis [16]. Complete data on inclusions and exclusions are shown in Figure 1.

Outcome

The primary outcome was AKI, the secondary outcomes include use of CRRT, 28-day mortality, 90-day mortality, incidence of MODS, shock, length of hospital stay (days), duration of mechanical ventilation (days), use of vasoactive agent.

Data collection

All data were retrospectively collected. Baseline data, including demographics, medical history, and disease severity, were collected retrospectively on each patient by reviewing patients' medical records. Laboratory data were collected for the first ICU day. Vital signs, hemodynamic and laboratory data were collected each day during ICU stay. Renal function was assessed daily by creatinine levels and urine output. Serial Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score were calculated on the first ICU day. AKI was staged according to KDIGO stage 7 days after AKI diagnosis.

Blood samples were collected and tested for AT III and Cr level within the first 48 hours before treatment of sepsis in ICU after admission. The samples were centrifuged and stored at minus 80-degree Celsius and were analyzed subsequently. ATIII was measured by enzyme linked immunosorbent assay (ELISA). Serum Cr was measured by the enzymatic colorimetric test based on Jaffé reaction (alkaline picrate).

Statistical analysis

Statistical analysis was performed using SPSS 13.0. Quantitative data was expressed as mean $\pm$ standard deviation. For data with normal distribution, independent sample t-test was used to compare the differences between two sets of data. For data with non-normal distribution, non-parametric tests were used to compare the differences. Chi-square test or Fisher's test were used for qualitative data. Logistical regression analysis was used to evaluate the outcomes based on risk factors selected by univariate analysis. Diagnostic values of ATIII in predicting AKI and death were assessed by calculating the area under the receiver operating characteristic curve (AUC-ROC). AUCROC analysis was performed by comparing AKI patients with non-AKI patients and by comparing survivor patients with non-survivor patients. The optimal cutoff values were determined by the highest values of sensitivity and specificity showed in AU-ROC analysis. $P < 0.05$ was considered statistically significant.

Results

Patient demographics and baseline characteristics

Study enrollment began in January 2015 and ended in June 2018. During the 3-year period, a total of 130 patients were selected for this study. 23 patients were excluded based on exclusion criteria on ICU admission. 107 (82.3%) patients were included (Figure 1).

Patient demographics and baseline characteristics were presented in Table 1. 65 patients (60.7%) were male and 42 (39.3%) patients were female, All the 107 patients were included in the final data analysis (Fig. 1). Mean age was 69.76 ± 4.773 years old and most of them had comorbidities (87.8%). Hypertension,

cardiovascular disease, and diabetes mellitus were the most common comorbidities. APACHE II score was 17.42 ± 2.28 , SOFA score was 6.757 ± 3.10 . The need for mechanical ventilation and noradrenalin use in the first 24 hours after admission to ICU was 63.5% and 51.4%, respectively. The main source of infection was lung infection (57%), followed by the abdominal cavity infection (43.0%) and urinary tract infection (24%). twenty-seven patients (27.1%) developed AKI, most of whom were classified as KDIGO 3 (63.0%). KDIGO 1 occurred in 11.1% and KDIGO 2 in 33.3% patients. Acute renal replacement therapy was indicated in 17.8%, and mortality rate was 37.3%.

Characteristics of non-AKI(n=78) and AKI group (n=29) were similar regarding age, diabetes, immune disease, liver disease and COPD. Male, hypertension and cardiovascular disease were higher in AKI. Mortality was higher in AKI patients (89.6% vs 30.8%, $p = 0.026$). Table 1 shows the clinical and laboratory characteristics of the population based on AKI. The two groups were statistically different in need for mechanical ventilation(79.3% vs 57.7%, $p=0.044$), need for noradrenalin use(79.3%vs 41%, $p<0.0001$), APACHE II score(21.69 ± 7.04 vs 15.83 ± 5.86 , $p<0.0001$), and SOFA score(9.448 ± 3.611 vs 5.756 ± 2.960 , $p<0.0001$), all of which were significantly higher in AKI patients. (Table 1).

Characteristics of non-survivors(n=40) and survivors group (n=67) were similar regarding age, hypertension, diabetes, cardiovascular disease, immune disease, liver disease and COPD. AKI was higher in non-survivors (40% vs. 19.4%, $p = 0.02$). Mortality was higher in AKI patients (55.17% vs. 30.77.9%, $p = 0.02$). Table 1 shows the clinical and laboratory characteristics of the population based on the hospital outcome. The two groups were statistically different in need for mechanical ventilation(82.5% vs 52.2, $p=0.002$), need for noradrenalin use(92.5%vs26.9%, $p<0.0001$), APACHE II score(21.97 ± 6.282 vs 14.70 ± 5.359 , $p<0.0001$), and SOFA score(9.15 ± 3.051 vs 5.328 ± 3.012 , $p<0.0001$), all of which were significantly lower in survivor patients. (Table 2).

Multivariable analysis for AKI and death risk

Male(OR= 0.140, 95% CI 0.030 -0.643, $p=0.011$),hypertension(OR= 4.744, 95% CI 1.207 – 18.643, $p=0.026$), Cardiovascular disease(OR= 5.364, 95% CI 1.234 – 23.311, $p=0.025$) and ATIII (OR=0.961, 95% CI 0.935-0.988, $p=0.005$) were identified as independent risk factors for AKI in multivariable regression analysis (Table 3).

ATIII values based on development of acute kidney injury and patient outcome.

Both ATIII and ATIII/Cr were higher in non-AKI group than AKI group: ATIII(73.43 ± 23.42 vs 54.01 ± 25.46 g/l; $p=0.003$), ATIII/Cr (1.10 ± 0.751 vs 0.212 ± 0.099 g/ μ mol; $p<0.0001$). Similarly, both ATIII and ATIII/Cr were higher in survival group than non-survival group: ATIII (73.14 ± 22.55 vs. 56.99 ± 27.87 g/l, $p=0.019$), ATIII/Cr(1.06 ± 0.812 vs 0.398 ± 0.304 g/ μ mol; $p=0.0003$). (Figure 2)

ROC analysis of ATIII in elderly septic patients with AKI vs non-AKI.

Figure 3 shows that ATIII was a predictor of AKI nondevelopment(AUC-ROC =0.729, and sensitivity 0.700 and specificity 0.714). The ATIII/Cr was also a predictor of AKI nondevelopment(AUC-ROC =0.971,

and sensitivity 0.900 and specificity 1). The accuracy of ATIII and ATIII/Cr as predictors of survival was intermediate (AUC-ROC were 0.681 and 0.804, respectively. sensitivity were 0.802 and 0.596, specificity were 0.542 and 0.875). Both ATIII and ATIII/Cr were excellent predictors of AKI nondevelopment within the 48 h after ICU admission.

Regarding ATIII as a predictor of survival, the areas under the curve for ATIII and ATIII/Cr were 0.681 and 0.804, respectively (Fig. C-D). The optimal cutoff value of each one of them had sensitivity between 0.802 and 0.596 and specificity between 0.542 and 0.875 (Table 4).

ATIII cutoff =66.95 or 55.7, patient outcome data.

ATIII cutoff in predicting AKI nondevelopment in elderly septic patients was 66.95 g/l. (Table 4). ATIII cutoff in predicting survival of elderly septic patients was 55.7 g/l. (Table 5). When patients were divided into low ATIII group and high ATIII group using 66.95 or 55.7 as cutoff value. In comparison, ICU stay was significantly lower in the high ATIII group ($p=0.020$ and 0.049 , respectively). Off mechanical ventilation time, off CRRT time, and survival time were significantly higher in high ATIII group ($p=0.049, 0.048, 0.014$ using 66.95 as cutoff and $0.041, 0.036, 0.021$ using 55.7 as cutoff) (Table 6,7).

Discussion

We have performed a retrospective study evaluating the associations between ATIII levels and clinical outcomes in septic elderly patients. We find associations between decreases in ATIII levels and acute kidney injury, mortality and other morbidities. It is well known that morbidity and mortality in sepsis is associated with decreases in ATIII levels. This has been described many times. There have been over 30 prospective randomized trials of ATIII replacement in critical illness. A systemic review and meta-analysis of ATIII prospective randomized trials, showed no effect on mortality and increased bleeding[22]. But our study found that ATIII was associated with prediction acute kidney injury in elderly septic patients. Patients with higher ATIII level were found to have shorter ICU stay, longer no mechanical ventilation time, longer no CRRT time, and longer survival time.

We found that 27.1% of geriatric septic patients developed AKI and most of them had AKI stage 3. This is consistent with previous study which showed the incidence of AKI among geriatric patients ranged from 11 to 42%[1]. The in-ICU mortality of geriatric AKI patients (37.4%) was similar to other studies (16–40%) [21]. In our study, male, hypertension, cardiovascular disease and ATIII were identified as predictors of AKI in logistic regression analysis. ATIII level was a predictor of AKI-nondevelopment (AUC-ROC =0.729, sensitivity 0.700 and specificity 0.714). ATIII/Cr ratio was a predictor of AKI-nondevelopment (AUC-ROC =0.971, sensitivity 0.900 and specificity 1). The accuracy of ATIII and ATIII/Cr as predictors of survival was intermediate, with AUC-ROC of 0.681 and 0.804, sensitivity of 0.802 and 0.596, specificity 0.542 and 0.875, respectively. In the setting of ICUs, ATIII demonstrated excellent predicting value of AKI-nondevelopment in elderly septic patients.

Until today, this is the largest data on ATIII's predicting effect on AKI development in sepsis. Several recent articles described the protective effect of ATIII on kidneys, but they were animal studies[17]. ATIII has emerged as a promising single, universal predict methodology for sepsis with AKI diagnostics. In addition, ATIII will be further studied in the coming years to evaluate the prognosis of renal injury in sepsis. ATIII can assist clinicians to diagnose AKI in sepsis quickly and accurately. It is being introduced in the setting of ICUs into clinical work gradually and has the potential to change the way we used to work. However, there are also many challenges, such as lack of universal standards of results analysis and guidelines for result interpretation. Early detection of AKI in sepsis is still challenging, requiring combination of clinical judgement and other objective workups.

In this study, ATIII had a predictive effect on kidney injury caused by sepsis. Low ATIII levels are associated with an increased risk of AKI in patients with sepsis. In rat models, ATIII improves kidney injury mainly by reducing inflammation, apoptosis and oxidative stress. In addition, ATIII may play an anti-inflammatory role by inhibiting the release of inflammatory cytokines and chemical kinases mediated infiltration of immune cells [11]. Therefore, ATIII may play a predictive, preventive and protective role in sepsis induced AKI. Members of ATIII serine protease inhibitors are not only major coagulant factor inhibitors in vivo, but exhibits in many clinical anti-inflammatory properties such as disseminated intravascular coagulation(DIC) and sepsis (8, 18). Besides inhibiting inflammatory cytokines produced by endothelial cells [19], the mechanisms of ATIII anti-inflammatory effect include increased synthesis and secretion of prost, inhibition of neutrophil roll and adhesion [20], and prevention of platelet activity [8].

The limitations of this study mostly come from its retrospective design. Also, the study was performed in a single center with a small sample size. Additionally, patient's long-term survival was not well followed up. Therefore, further studies with larger sample size are needed.

The result of this study shows that ATIII can predict AKI in septic elderly patients, guide clinical management, and lastly reduce the mortality. In other words, clinics call for new methods like ATIII for the sepsis patients, to realize the aim of personalized and precision therapy while ATIII can predict the AKI quickly and is able to guide the treatment. As a promising biomarker, ATIII may change conventional management of sepsis patients.

Conclusions

In conclusion, this study suggests that ATIII predict acute kidney injury in septic elderly patients. Lower ATIII may predict worse prognosis. Findings in this study come up with new ideas on ATIII and acute kidney injury prevention. Further studies are needed to confirm the role of ATIII administration in predicting AKI and increasing survival in sepsis patients.

List Of Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation II score;SOFA, Sepsis-related Organ Failure Assessment; COPD, chronic obstructive pulmonary disease;HBP, high blood pressure.; ICU: Intensive Care Unit ; HLOS, hospital length of stay; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome ;CRRT, continuous renal replacement therapy; ATIII ,Antithrombin III; SIRS, systemic inflammatory response; KDIGO, Kidney Disease Improving Global Outcomes ; CKD, chronic kidney disease.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from Shanghai General Hospital Institutional Review Board (reference number [2018]KY004).

Consent for publication

All the authors agree to publish.

Competing interests

The authors declare that they have no competing interests.

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Data Availability

The data used to support the findings of this study are included within the article.

Authors' contributions

All the authors fulfill three authorship criteria: conception and design or analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and the final approval of the version to be published. All the authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of the research method.

Figure 2

ATIII values based on development of acute kidney injury and outcome. A) ATIII values based on development of acute kidney injury B) ATIII/Cr values based on development of acute kidney injury C) ATIII values based on outcome D) ATIII/Cr values based on outcome

Figure 3

ROC analysis of ATIII in elderly septic patients with AKI vs non-AKI. A) ROC analysis of ATIII measured on first 48 hours of admission to ICU in septic elderly patients with AKI vs non-AKI. B) ROC analysis of ATIII/Cr measured within first 48 hours of admission to ICU in elderly septic patients with AKI vs non-AKI. C) ROC analysis of ATIII measured within first 48 hours of admission to ICU in elderly septic patients, survivors vs non-survivors. D) ROC analysis of ATIII/Cr measured within first 48 hours of admission to ICU in elderly septic patients, survivors vs non-survivors.

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