

Original Article

Correlation between sTREM-1 and serum sTM in patients with AKI and the predictive value of their joint evaluation in AKI occurrence and patients' death

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Abstract: Objective: To explore the correlation between soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and serum soluble thrombomodulin (sTM) in patients with acute kidney injury (AKI) and the predictive value of their joint evaluation in AKI occurrence and patients' death. Methods: This is a perspective case-control study, which recruited 173 severe patients who underwent treatment in intensive care unit (ICU) of Tangshan People's Hospital. Patients were divided into the AKI group (N=71) and Non-AKI group (N=102) according to AKI diagnostic criteria in the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline. Meanwhile, patients in the AKI group were divided into the Survival group (N=54) and Death group (N=17) according to the survival status 28 days after admission. The differences of urine sTREM-1, serum sTREM-1, sTM as well as routine indexes, such as serum creatinine (SCr), serum inflammatory factors [C-reactive protein (CRP), Procalcitonin (PCT), Cystatin-C (Cys-C)] and Acute Physiology, Age, Chronic Health Evaluation II (APACHE II), were compared between the AKI group and Non-AKI group. Pearson correlation was used to analyze the correlations between sTREM-1 and sTM. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of urine sTREM-1, serum sTREM-1 and sTM in AKI occurrence and AKI patients' death. Results: Serum SCr, CRP, PCT, Cys-C, APACHE II scores, serum sTREM-1, sTM and urine sTREM-1 in the AKI group were significantly higher than those in the Non-AKI group (all $P < 0.001$). As for the comparison of subgroups of patients in the AKI group, there were no significant differences in SCr, CRP, PCT, Cys-C and APACHE II scores between the Death group and Survival group (all $P > 0.05$). However, urine sTREM-1, serum sTREM-1 and sTM in the Death group were significantly higher than those in the Survival group (all $P < 0.05$). Pearson correlation showed positive correlation coefficients ($r > 0$) between serum sTREM-1, urine sTREM-1 and sTM in the AKI/Non-AKI group, as well as Death/Survival group. The results of ROC curve analysis indicated that the joint evaluation of urine sTREM-1, serum sTREM-1 and sTM showed higher clinical reference value in the prediction of AKI occurrence (AUC=0.879) and patients' death (AUC=0.084). Conclusion: Urine sTREM-1, serum sTREM-1 and sTM were significantly increased in patients with AKI, and the changes of above indexes in patients who died within 28 days after admission were more significant. There were correlations among urine sTREM-1, serum sTREM-1 and sTM. The joint evaluation of these indexes had a high clinical value for the prediction of the AKI occurrence and patients' death.

Keywords: Acute kidney injury, sTREM-1, sTM, correlation evaluation

Introduction

AKI is a common clinical syndrome that occurs mainly in patients after cardiac surgery. Due to the functional decline of organs in elderly patients, the risk of complicated AKI is greatly increased after surgery [1, 2]. The early symptoms of AKI are not obvious and hard to detect. It is mostly on acute attacks. AKI is defined as an abrupt and persistent (>24 h) decline in renal function within 7 days, which leads to a sharply decreased urine output and can be

manifested as systemic symptoms such as water-electrolytes imbalance and azotemia [3]. Some studies have reported that the fatality rate of hospital-acquired AKI can be as high as 50%. Even if the patients survive, some survival patients may suffer from renal dysfunction, and severe patients may even develop renal failure, for which continuous renal replacement therapy is required [1, 4, 5].

Currently, the main indexes for evaluation the occurrence and progression of AKI are the

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changes in urine output and SCr, but these indexes are susceptible to interference by other factors, and they don't have timely response to the changes in glomerular filtration rate (GFR) [6]. The detection of endogenous biomarkers is a new method for the diagnosis and evaluation in patients with AKI. Their levels can reflect the changes in renal function earlier, and the evaluation effect of these indexes is better than PCT, Cys-C and other traditional detection indexes [7-9]. With the continuous development of molecular biology, more biomarkers have been discovered. Triggering receptor expressed on myeloid cells-1 (TREM-1) and Thrombomodulin (Tm) are the typical representatives [10, 11], but their roles in the evaluation of AKI occurrence and progression are still lack of clinical studies.

This study innovatively analyzed the correlation between the sTREM-1 and sTM in patients with AKI and their joint predictive value, in order to provide clinical references for the occurrence of AKI in ICU patients and the prediction of patients' death.

General information and methods

General information

This study recruited 173 severe patients who underwent treatment in ICU of Tangshan People's Hospital from January 2016 to January 2019. According to AKI diagnostic criteria in the KDIGO clinical practice guideline, they were divided into the AKI group (N=71) and Non-AKI group (N=102). According to the survival status 28 days after admission [12], patients in the AKI group were divided into the Survival group (N=54) and Death group (N=17) in order to study the differences in test indexes of patients with AKI between the two groups and to provide clinical reference for the death prediction of the patients.

Inclusion criteria [13]: The patients' diagnoses were clear, and patients in the AKI group met the AKI diagnostic criteria in the KDIGO clinical practice guideline; patients were no less than 18 years old; clinical and follow-up data were complete. Clinical data included test indexes, and follow-up data included patients' survival and death status; patients volunteered to participate in the study and signed informed consent forms.

Exclusion criteria [14, 15]: Patients were combined with end-stage renal disease at admission; patients who stayed in ICU for less than 48 hours, including half-way death and other reasons for withdrawal studies; patients were combined with autoimmune diseases, malignant tumors or other major diseases; patients were pregnant or lactating; patients were combined with severe infectious diseases such as human immunodeficiency virus (HIV).

This study has been approved by medical ethical committee of Tangshan People's Hospital. All patients (or their families) signed informed consent forms.

Recruitment of patients

This study recruited critically ill patients treated in ICU of Tangshan People's Hospital from January 2016 to January 2019. During the study period, total 870 patients were recruited, of which 193 patients were suspected to have AKI, and the remaining 677 patients were excluded. Patients were diagnosed with AKI according to the KDIGO clinical practice guideline. The survival status was determined by patients' follow-up visit 28 days after admission. Patients were divided into the AKI group (N=71) and Non-AKI group (N=102). Patients in the AKI group were divided into two subgroups: Survival group (N=54) and Death group (N=17). See **Figure 1**.

Test indexes

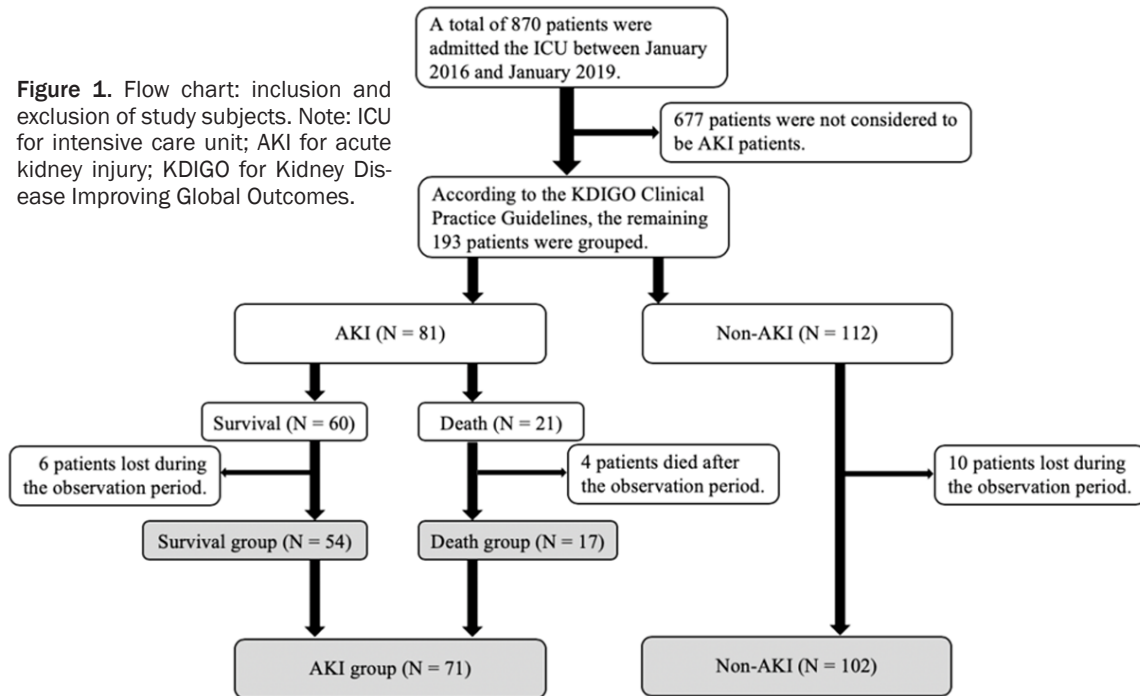
The basic vital indexes were tested after admission, including electrocardiogram and blood cell analysis. The test specimens were collected, which included venous blood specimens taken through the procoagulant tube and urine specimens retained through the catheter. The observation period cut-off date was 28 days after admission. Patients' survival status during the observation period and test results of related indexes were recorded and statistically analyzed.

SCr, CRP, PCT and Cys-C

Serum SCr was detected on automatic biochemical analyzer (Beckman coulter, USA) by enzyme method [16], and creatinine assay kit was purchased from Colab, Germany. Serum CRP was detected on automatic biochemical

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Figure 1. Flow chart: inclusion and exclusion of study subjects. Note: ICU for intensive care unit; AKI for acute kidney injury; KDIGO for Kidney Disease Improving Global Outcomes.



analyzer (Beckman coulter, USA) by immunoturbidimetry [17], and the kit was provided by Wuhan Merck Biotech Co., Ltd. Serum PCT was detected on immunofluorescence analyzer (Mini-ViDas, France) by immunofluorescence technology [18], and the kit was provided by bioMérieux, France. Serum Cys-C was detected by quantitative sandwich enzyme-linked immunosorbent assay (ELISA) [19], and the kit was provided by ADL, USA.

APACHE II

APACHE II is currently the most widely used and authoritative critical illness evaluation system used in ICU. The scale is divided into the following four parts: A. Age; B. Severe organ dysfunction or immune damage; C. Physiological indexes; D. Points.

APACHE II scoring formula: $APACHE\ II = A + B + C + D$ [20].

Detection of serum sTREM-1, sTM and urine sTREM-1

The levels of sTREM-1 in serum and urine were detected by double antibody sandwich ELISA [21], and the kit was provided by CUSABIO, USA. sTM was detected by sandwich ELISA [22], and the kit was provided by Life, USA.

Correlation analysis between sTREM-1 and sTM

The bivariate Pearson correlation analysis was used to analyze the correlation between serum and sTM, as well as urine sTREM-1 and sTM. R values were calculated, of which $r > 0$ was considered as positive correlation, $r < 0$ was considered as negative correlation, and the larger the absolute r value, the stronger the correlation.

The prediction value of serum sTREM-1, urine sTREM-1 and sTM in AKI occurrence and AKI patients' death

The ROC curve analysis was used to analyze the predictive value of serum sTREM-1, sTM and urine sTREM-1 in AKI occurrence and AKI patients' death. Calculation of Youden index: $Youden\ index = Sensitivity + Specificity - 1$, and the maximum test result variable value of Youden index is the optimal critical value. According to the optimal critical value of the three indexes, the value which was higher than the optimal critical value was determined to be positive, and patients with more than two positives among the three indexes were finally diagnosed as AKI occurrence or AKI patients' death. Calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive

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Table 1. Comparison of baseline information

Baseline information	Survival group (n=54)	Death group (n=17)	t/ χ^2	P	AKI group (n=71)	Non-AKI group (n=102)	t/ χ^2	P
Age (years)	61.38±9.67	63.92±9.53	0.955	0.348	62.56±9.98	63.37±9.33	0.539	0.591
Gender [n/(%)]			0.036	0.850				
Male	30/(55.56)	9/(52.94)			39/(54.93)	58/(56.86)	0.064	0.801
Female	24/(44.44)	8/(47.06)			32/(45.07)	44/(43.14)		
BMI (kg/m ²)	22.38±3.27	21.78±4.11	0.550	0.588	22.04±3.87	22.32±3.97	0.463	0.644
Complications [n/(%)]			0.486	0.523			0.551	0.397
Coronary heart disease	5/(9.26)	2/(11.76)			7/(9.86)	13/(12.75)		
Diabetes	10/(18.52)	4/(23.53)			14/(19.72)	25/(24.51)		
Hypertension	20/(37.04)	7/(41.18)			27/(38.03)	41/(40.20)		
COPD	3/(5.56)	2/(11.76)			5/(7.04)	8/(7.84)		

Note: BMI for body mass index; COPD for chronic obstructive pulmonary disease; AKI for acute kidney injury.

value (NPV): Sensitivity = number of true positives/(number of true positives + number of false negatives) × 100%; specificity = number of true negatives/(number of true negatives + number of false positives) × 100%; PPV = number of true positives/(number of true positives + number of false positives) × 100%; NPV = number of true negatives/(number of true negatives + number of false negatives) × 100%.

Statistical analysis

The data were analyzed by SPSS 24.0 statistical analysis software. The count data of gender and past medical history, etc. were expressed as cases number (percentage) [n (%)] and Chi-square (χ^2) test was applied. The measurement data that conformed to the normal distribution was expressed as ($x \pm sd$), and independent sample t-test was used for the comparison among groups. The measurement data that did not conform to the normal distribution was represented by M (Q1, Q3), and nonparametric test of two independent samples (Mann Whitney U test) was used for the comparison among groups. The correlation between pairwise variables was analyzed by bivariate Pearson correlation analysis. The ROC curve of serum sTREM-1 and sTM to predict AKI occurrence and AKI patients' death was drawn. AUC>0.5 was considered to have clinical diagnostic value, and the higher the AUC, the higher the clinical diagnostic value. P<0.05 was considered statistically significant.

Results

Comparison of baseline information

There were no significant differences in baseline information such as age, gender and BMI

between the AKI group and Non-AKI group (P>0.05). There were also no significant differences in baseline information between the Survival group and Death group (P>0.05). See **Table 1**.

The routine serum indexes and APACHE II scores in the AKI group and Non-AKI group

The SCr, CRP, PCT, Cys-C and APACHE II scores in the AKI group were significantly higher compared with those in the Non-AKI group (P<0.001). As for patients in the AKI group, there were no significant differences in SCr, CRP, PCT, Cys-C and APACHE II scores in the Death subgroup compared with those in the Survival subgroup (P>0.05). See **Table 2**.

Comparison of serum sTREM-1, sTM and urine sTREM-1 between the AKI group and Non-AKI group

Serum sTREM-1, sTM and urine sTREM-1 in the AKI group were significantly higher than those in the Non-AKI group (P<0.001). As for the patients with AKI, the serum sTREM-1, sTM and urine sTREM-1 in the Death subgroup were significantly higher than those in the Survival subgroup (P<0.05). See **Table 3**.

Correlation analysis between sTREM-1 and sTM

Pearson correlation analysis was performed, and the results showed that in the AKI group and Non-AKI group, the correlations between serum sTREM-1 and sTM, as well as urine sTREM-1 and sTM were positive, respectively (r>0). In the Survival group and Death group, the correlations between serum sTREM-1 and sTM, as well as urine sTREM-1 and sTM were also positive, respectively (r>0). See **Table 4**.

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Table 2. Comparisons of routine serum indexes and APACHE II scores (x±sd)

Group	SCr (mg/dL)	CRP (mg/L)	PCT (ng/mL)	Cys-C (n)	APACHE II (scores)
Survival and Death group					
Survival group (n=54)	0.80±0.14	114.91±17.59	11.35±4.76	952.33±98.56	22.72±5.39
Death group (n=17)	0.88±0.19	124.30±19.26	12.96±5.24	982.37±108.30	24.35±6.34
t	1.604	1.789	1.129	1.019	0.957
P	0.124	0.086	0.27	0.319	0.349
AKI and Non-AKI group					
AKI group (N=71)	0.83±0.15	116.76±18.44	12.06±4.55	969.77±103.25	23.82±5.77
Non-AKI group (N=102)	0.68±0.13	85.37±13.83	7.38±3.97	635.76±86.46	20.05±4.85
t	6.828	12.159	7.007	22.345	4.508
P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Note: AKI for acute kidney injury; SCr for serum creatinine; CRP for C-reactive protein; PCT for Procalcitonin; Cys-C for Cystatin-C; APACHE II for Acute Physiology, Age, Chronic Health Evaluation II.

Table 3. Comparison of serum sTREM-1, serum sTM and urine sTREM-1 (x±sd)

Groups	Serum sTREM-1 (ng/mL)	Urine sTREM-1 (ng/mL)	sTM (ng/mL)
Survival and Death group			
Survival group (n=54)	14.12±4.89	6.08±2.37	11.12±3.26
Death group (n=17)	17.54±4.13	7.61±2.42	13.76±3.58
t	2.844	2.285	2.708
P	0.008	0.031	0.012
AKI and Non-AKI group			
AKI group (N=71)	15.52±4.82	6.53±2.79	11.88±3.37
Non-AKI group (N=102)	9.36±2.78	2.44±1.03	7.68±2.17
t	6.049	11.805	9.251
P	<0.0001	<0.0001	<0.0001

Note: AKI for acute kidney injury; sTREM-1 for soluble triggering receptor expressed on myeloid cells-1; sTM for soluble thrombomodulin.

The predictive value of serum sTREM-1, sTM and urine sTREM-1 in AKI occurrence

The Youden index of the predictive value of serum sTREM-1, sTM and urine sTREM-1 in AKI occurrence was analyzed by ROC curve analysis, and the optimal critical value was calculated. See **Table 5**. The results indicated that serum sTREM-1, sTM and urine sTREM-1 had higher clinical reference value in the prediction of AKI occurrence (AUC>0.5). See **Figure 2A** and **Table 6**.

The reference value of serum sTREM-1, sTM and urine sTREM-1 in the prediction of AKI patients' death

The clinical value of joint evaluation was analyzed by ROC curve analysis and the results indicated that serum sTREM-1, sTM and urine sTREM-1 had higher clinical reference value in

the prediction of AKI patients' death (AUC>0.5). See **Figure 2B** and **Table 6**.

Discussion

Kidney is one of the most important metabolic organs in the human body. When the kidney undergoes organic changes such as glomerular structure changes, its filtration, secretion and excretion functions will be seriously affected, especially on the vascular endothelium, which can further lead to diffuse lesions in the body. Therefore, AKI can significantly increase

the risk of death for patients [23]. The exploration of stable biomarkers is conducive to the observation of the disease progression for patients with AKI in the clinical diagnosis and treatment, and the corresponding treatment strategy should be given as early as possible to improve the prognosis of patients. SCr, CRP and PCT are routine detection indexes for patients with AKI, which have high sensitivity but are greatly affected by other complications, so their accuracy is not high. Schneider et al. [24] showed that Cys-C and APACHE II scores had a good predictive effect on the disease course in patients with AKI, but their effect on prediction of the AKI occurrence and patients' death was still not ideal. In this study, SCr, CRP, PCT, Cys-C and APACHE II scores of patients were compared, and the results indicated that compared with patients in the Non-AKI group, SCr, CRP, PCT, Cys-C and APACHE II scores of

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Table 4. Correlation analysis between sTREM-1 and sTM levels

Indexes	r value in AKI and Non-AKI group	r value in Survival and Death group
Serum sTREM-1 (ng/mL)	0.773	0.653
Urine sTREM-1 (ng/mL)	0.689	0.571

Note: AKI for acute kidney injury; sTREM-1 for soluble triggering receptor expressed on myeloid cells-1; sTM for soluble thrombomodulin.

Table 5. The optimal critical value of serum sTREM-1, sTM and urine sTREM-1 in the diagnoses of AKI occurrence and AKI patients' death

Indexes	AKI and Non-AKI group	Survival and Death group
Serum sTREM-1 (ng/mL)	11.42	15.20
Urine sTREM-1 (ng/mL)	3.61	6.27
sTM (ng/mL)	9.18	11.98

Note: AKI for acute kidney injury; sTREM-1 for soluble triggering receptor expressed on myeloid cells-1; sTM for soluble thrombomodulin.

patients in the AKI group were significantly increased, which was consistent with previous studies [25, 26]. As for the comparison of subgroups of patients in the AKI group, there were no significant differences in SCr, CRP, PCT, Cys-C and APACHE II scores between the Death group and Survival group ($P > 0.05$). The main reason for the results was that most patients in the AKI group had complications, which might affect the changes of test indexes, and these test indexes could not effectively identify AKI patients' survival or death 28 days after admission.

TREM-1 is one of the members of immunoglobulin superfamily which was discovered in 2000. Its relative molecular weight is 26 KD, and its gene is located at chromosome 6p21.2. TREM-1 is mainly expressed on the surface of macrophages, neutrophils and monocytes [27]. TREM-1 is highly correlated with inflammation and autoimmune responses. Previous study has confirmed its high detection value in patients with meningitis and peritonitis [27]. sTREM-1 is an existence form of TREM-1 which is soluble. It is released by activated phagocytes and then enters the body fluid. The increased concentration of sTREM-1 in the body fluid indicates that the body may have an infection, and the concentration level is positively correlated with the degree of infection [28]. Marc and Tamaro et al. [29, 30] have proven that the sensitivity and specificity of sTREM-1 in blood and urine were higher than those of

traditional biomarkers in the diagnosis of sepsis, and the indexes had significant increment at early stage in patients with septic AKI, which suggested that sTREM-1 might also have diagnostic value in the disease progression of patients with AKI. However, the study subject of Tamaro's research was patients with septic AKI [30]. There have been no reports of sTREM-1 changes in patients with primary AKI. Tm is a transmembrane single-chain glycoprotein derived from injured vascular endothelial cells, which exists on the cell surface. Nagato et al. [31] have shown that Tm could be used as a

biomarker for vascular endothelial injury. In recent years, continuous studies have shown that Tm was correlated with disseminated intravascular coagulation (DIC), multiple organ failure (MOF) and fatality rate. sTM is Tm in the state of dissolution in the blood, and its elevated level is associated with impaired renal function in patients with AKI [31, 32]. However, it is still lack of studies on the changes of sTREM-1 and sTM levels in the disease progression of patients with AKI. The results of this study showed that compared with Non-AKI group, the serum sTREM-1, sTM and urine sTREM-1 in the AKI group were significantly increased. As for the comparison of subgroups of patients in AKI group, there were no significant differences in SCr, CRP, PCT, Cys-C and APACHE II scores between Death group and Survival group. However, serum sTREM-1, sTM and urine sTREM-1 in the Death group were significantly higher than those in the Survival group. The result suggested that serum sTREM-1, sTM and urine sTREM-1 are more sensitive than traditional biomarkers, and may have predictive value in the survival and death of patients with AKI.

Further analysis indicated that there was a correlation between serum/urine sTREM-1 and sTM, suggesting that the joint evaluation of sTREM-1 and sTM had significant effects on the identification between AKI and non-AKI ICU patients, as well as the Survival and Death groups of patients with AKI. The reason may be

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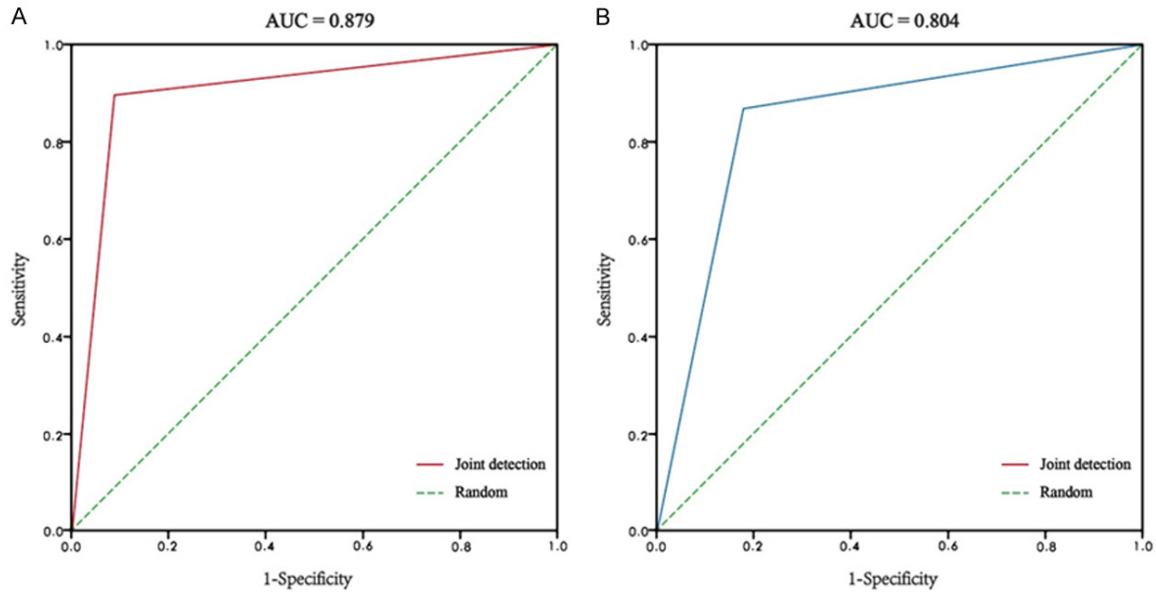


Figure 2. The prediction value of joint evaluation of three indexes in AKI occurrence and AKI patients' death. Note: A for prediction value of joint evaluation of three indexes in AKI occurrence; B for prediction value of joint evaluation of three indexes in AKI patients' death. Note: AUC for area under the curve.

Table 6. The prediction value of joint evaluation of serum sTREM-1, sTM and urine sTREM-1 in AKI occurrence and AKI patients' death

Indexes	AKI occurrence	AKI patients' death
Sensitivity (%)	91.55 (65/71)	82.35 (14/17)
Specificity (%)	88.24 (90/102)	87.04 (47/54)
PPV (%)	84.42 (65/77)	66.67 (14/21)
NPV (%)	93.75 (90/96)	94.00 (47/50)
AUC (95% CI)	0.879 (0.775, 0.937)	0.804 (0.694, 0.880)

Note: AKI for acute kidney injury; sTREM-1 for soluble triggering receptor expressed on myeloid cells-1; sTM for soluble thrombomodulin; PPV for positive predictive value; NPV for negative predictive value; AUC for Area Under the Curve; CI for confidence interval.

that serum sTREM-1, sTM and urine sTREM-1 are highly sensitive and related to the AKI occurrence and progression, which has been confirmed in previous studies [31-34]. In this study, the joint evaluation of these three indexes was used innovatively to predict the AKI occurrence and AKI patients' death. The results showed that the joint evaluation of serum sTREM-1, sTM and urine sTREM-1 not only had high reference value in the prediction of AKI occurrence, but also in the prediction of AKI patients' death. It is worth noting that the study found that the solubility of sTREM-1 in blood was higher than that in urine, and the change of sTREM-1 was more significant between AKI group and Non-AKI group. But the difference in

AKI subgroups (Survival group and Death group) was relatively smaller, which was also reflected in the final ROC curve analysis, suggesting that serum sTREM-1 might be higher than urine sTREM-1 in clinical diagnosis. This study showed that the joint evaluation of the three indexes had higher predictive value in AKI occurrence than in AKI patients' death. The possible reasons are as follows: (1) There are many complications in patients with AKI, which have an impact on the biomarkers; (2) The three biomarkers lack the specificity on AKI.

There are also some limitations in this study. (1) The serum and urine specimens in this study were not collected and tested by the same designated person, and there might be some deviations in test results. The study design needs to be further improved. (2) The small sample in this study might also result in some deviations. The results need to be further analyzed by large samples.

In conclusion, serum sTREM-1, sTM and urine sTREM-1 were significantly increased in patients with AKI, and changes of above indexes in patients who died within 28 days after admission were more significant. There were correlations among serum sTREM-1, urine sTREM-1 and sTM. The joint evaluation of these indexes

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had high clinical value in the prediction of the AKI occurrence and AKI patients' death.

Disclosure of conflict of interest

None.

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