Impaired T Lymphocyte Subsets Early Predict Acute Kidney Injury in Sepsis Patients

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Research

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Abstract

Objective: Acute kidney injury (AKI) is a frequent complication of sepsis patients and is associated with high morbidity and mortality. Early recognition of sepsis-associated AKI (SA-AKI) is crucial to provide supportive treatment and improve prognosis. Thus, the objective is to analyze the early discriminative predictive information regarding T lymphocyte subsets of SA-AKI.

Methods: We evaluated the relationships of T lymphocyte subsets and clinical parameters of sepsis patients, and assessed their potential roles in SA-AKI diagnosis. The following T lymphocyte subsets were studied: total T lymphocyte (CD3+), helper T lymphocyte (T helper, CD3+CD4+), cytotoxic T lymphocyte (CTL, CD3+CD8+), totally activated T lymphocyte (CD3+HLADR+), early activated T lymphocyte (CD4+CD69+, CD8+CD69+), regulatory T lymphocyte (Treg, CD4+CD25+, CD8+CD25+).

Results: A total of 171 patients with sepsis were enrolled. The incidence of AKI was 80.1%. The percentages of total T lymphocyte, CTL, and totally activated T lymphocyte of SA-AKI patients were lower than those of sepsis patients without AKI (61.95±19.65 % vs 68.80±18.57 %, 19.95±17.22 % vs 26.48±18.31 %, 19.00±14.21 % vs 30.88±28.86 %, respectively, $P<0.05$). There were no significant differences in the percentages of T helper, early activated T lymphocyte, and Tregs between SA-AKI group and non-SA-AKI group. Univariate logistic regression analysis showed that percentages of total T lymphocyte, CTL, and totally activated T lymphocyte were protective factors for SA-AKI. Multivariate logistic regression analysis revealed that percentage of totally activated T lymphocyte had a negative association with SA-AKI independently (OR: 0.952, 95% CI: 0.926-0.978, $P=0.000$). Moreover, ROC analysis showed that total T lymphocyte, CTL, and totally activated T lymphocyte had discriminatory abilities, with areas under the curve (AUC) value of 0.638, 0.615, and 0.661, respectively ($P<0.05$).

Conclusions: Impaired total T lymphocyte, CTL, and totally activated T lymphocyte could contribute to early diagnosis for SA-AKI.

Introduction

Acute kidney injury (AKI) is a common clinical condition in hospitalized patients [1], which can be caused by inflammation, nephrotoxicity or ischemia-reperfusion injury [2]. In critical care patients, sepsis was the most common cause of AKI, accounting for nearly half of all AKI events [3]. Moreover, sepsis associated AKI (SA-AKI) had a higher mortality compared with non-sepsis associated AKI, and sepsis patients who did not recover from AKI had worse outcomes than patients who developed reversible AKI or improved AKI [4, 5]. Therefore, early detection of SA-AKI and targeted treatment measures are important to reduce the mortality.

Sepsis is characterized by an initial intense inflammatory response or “cytokine storm” that evolves into a subsequent low inflammatory state with significant immunosuppression [6, 7]. T lymphocytes play central roles in adaptive immunity, driving appropriate immune responses to invading pathogens of diverse types. Major T lymphocyte subsets are including helper T lymphocyte (T helper, CD3 + CD4+),

cytotoxic T lymphocyte (CTL, CD3 + CD8+), activated T lymphocyte, regulatory T lymphocyte, memory T lymphocyte and etc., depending on the activation and different function [8]. A study proved that T lymphocytes could be induced by sepsis for immune paralysis [9]. Lee SY reported that the development of acute kidney injury during sepsis was associated with apoptosis, and immune suppression [10]. However, immune parameters associated with SA-AKI have not yet been fully elucidated. Therefore, we designed this study to explore the changes of T lymphocyte subsets in the early phase of AKI in sepsis patients, along with their predictive value for early diagnosis.

Materials And Methods

Study design

This is a retrospective study conducted between 2016 and 2020 in Guangdong General Hospital. The study involving human participants was approved by the Ethical Committee of Guangdong General Hospital.

Inclusion criteria

Patients were included who met the following criteria: (1) Age > 18 years old; (2) Diagnosis of sepsis.

Exclusion criteria

To eliminate the potential confounding effects of immunosuppressive drugs or underlying diseases on the immune phenotype of patient's lymphocytes, patients who met the following criteria were excluded from the study: (1) Patients who had undergone organ transplantation; (2) Patients on immunosuppressive medications (3) Patients with autoimmune diseases; (4) Patients with malignant tumor.

The diagnosis of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock: life-threatening organ dysfunction caused by a dysregulated host response to infection [11].

Once the patient was diagnosed with sepsis, 2012 KDIGO AKI guidelines (an increase in serum creatine (SCr) by 0.3mg/dL within 48 hours or a 50% increase in SCr within 7 days) was used to diagnose AKI [12].

For all sepsis patients, clinical data were obtained from electronic records in Guangdong General Hospital.

Flow Cytometry Analysis (Fcm)

Peripheral blood samples were collected in EDTA anticoagulant. The whole blood 100μl were incubated with antibodies at 4℃ for 30 min in the dark. Before staining to each tube, a total of 2ml of red blood cell

lysis buffer was added and incubated for 10 min at room temperature in the dark. The cells were then washed twice with phosphate buffer saline (PBS), and the supernatant was discarded. The cell pellet was dissolved in 300μl of 1% paraformaldehyde. Lymphocytes were identified by side scatter (SSC) and forward scatter (FSC) properties. T lymphocyte subpopulations were further identified by CD3+, CD8+, or CD4 + immunostaining. Additional immunostaining was performed on CD3+, CD8+, and CD4 + T lymphocyte to identify the following: HLADR, CD25, and CD69 (Fig. 1).

Statistical Analysis

Statistical analysis was performed using SPSS (version 25.0; SPSS Inc., Chicago, IL, USA). Normally distributed data were reported with means ± standard deviation and were compared by using the Student t test. Non-normally distributed data were expressed as medians and interquartile ranges (IQR) and were analyzed with the Mann-Whitney U test. Categorical variables were presented as numbers and percentages and were compared by using the $\chi 2$ test. Variables with $P < 0.05$ in the univariate analysis were further analyzed by multivariate logistic regression analysis to determine the independent risk factors for AKI.

Receiver operating characteristic (ROC) analysis was used to determine the discriminatory ability of immune parameters for predicting the incidence of SA-AKI. Youden's index was defined for points along the ROC curve. The reliabilities of the diagnostic tests were assessed based on their sensitivity and specificity.

Results

Patient characteristics

A total of 171 patients with sepsis were enrolled and detected T lymphocyte subsets in Guangdong Provincial People's Hospital from 1 January 2016 to 31 December 2020. Among them, 137 (80.1%) patients (102 males and 35 females) developed AKI with a median age of 87 years. In our study, males were more likely to develop SA-AKI (74.5% vs 50.0%, $P = 0.006$). No statistically significant differences were found in median age and basic diseases (including diabetes, hypertension, chronic kidney disease) between SA-AKI group and non-SA-AKI group. The absolute neutrophil count was similar between the two groups (9.99 ± 6.99 $\times 10^9$/L vs 11.94 ± 9.16 $\times 10^9$/L, respectively, $P > 0.05$). And procalcitonin was also similar between the two groups (2.29 ± 7.06 ng/ml vs 2.05 ± 7.25 ng/ml, respectively, $P > 0.05$). Serum creatinine was much higher in patients with SA-AKI than in those without SA-AKI (159.50 ± 112.58μmol/L vs 80.34 ± 168.13μmol/L, respectively, $P = 0.000$). The clinical characteristics are summarized in Table 1.

Table 1
The baseline characteristics of sepsis patients with AKI and without AKI.

Variables	AKI group	Non-AKI group	*P* Value
Cases	137	34	
Age (years)	87.00 ± 11.00	85.50 ± 22.00	0.289
Men, n (%)	102 (74.5)	17 (50.0)	0.006*
Past history n (%)			
Diabetes	43 (31.4)	12 (35.3)	0.662
Hypertension	83 (60.6)	15 (44.1)	0.082
Chronic kidney disease	31 (22.6)	13 (38.2)	0.062
Coronary heart disease	54 (39.4)	11 (32.4)	0.448
Chronic liver disease	4 (2.9)	1 (2.9)	0.995
Chronic pulmonary disease	28 (20.4)	12 (35.3)	0.067
Cerebrovascular disease	39 (28.5)	14 (41.2)	0.151
Neutrophil (10^9/L)	9.99 ± 6.99	11.94 ± 9.16	0.312
Lymphocytes (10^9/L)	0.71 ± 0.55	0.81 ± 0.71	0.591
Monocytes (10^9/L)	0.62 ± 0.68	0.81 ± 0.58	0.334
Serum albumin (g/L)	31.90 ± 7.43	29.56 ± 8.12	0.211
Alanine aminotransferase (U/L)	22.00 ± 39.00	16.50 ± 39.25	0.414
Aspartate transaminase (U/L)	44.00 ± 61.50	32.00 ± 47.00	0.397
Serum creatinine (μmol/L)	159.50 ± 112.58	80.34 ± 168.13	0.000*
Blood urea nitrogen (mmol/L)	21.40 ± 15.57	10.46 ± 15.15	0.000*
Brain natriuretic peptide (pg/ml)	4353.00 ± 9090.50	3536.00 ± 16870.25	0.807
Troponin T (μg/L)	147.90 ± 223.30	110.80 ± 142.33	0.135
Procalcitonin (ng/ml)	2.29 ± 7.06	2.05 ± 7.25	0.454
C-reactive protein (mg/L)	98.60 ± 108.15	82.10 ± 88.67	0.316
AKI: Acute kidney injury; Non-AKI: Sepsis patients without AKI. *P< 0.05			

Comparison of T lymphocyte subsets between SA-AKI and non-SA-AKI patients

Flow cytometry analysis showed that the percentages of total T lymphocyte (CD3+), CTL (CD3 + CD8+), and totally activated T lymphocyte (CD3 + HLADR+) were lower in sepsis patients with AKI than in those without AKI (61.95 ± 19.65 % vs 68.80 ± 18.57 %, 19.95 ± 17.22 % vs 26.48 ± 18.31 %, 19.00 ± 14.21 % vs 30.88 ± 28.86 %, respectively, $P < 0.05$). There were no significant differences in the percentages of T helper (CD3 + CD4+), early activated T lymphocyte (CD4 + CD69+, CD8 + CD69+), and Tregs (CD4 + CD25+, CD8 + CD25+) between SA-AKI group and non-SA-AKI group (Table 2).

Table 2
T lymphocyte subsets between AKI and non-AKI patients

Percentage (%)	AKI group (n = 137)	Non-AKI group (n = 34)	*P* Value
CD3+	61.95 ± 19.65	68.80 ± 18.57	0.013*
CD3 + CD4+	35.43 ± 13.34	34.24 ± 14.02	0.645
CD3 + CD8+	19.95 ± 17.22	26.48 ± 18.31	0.039*
CD3 + CD4+/CD3 + CD8+	1.65 ± 2.30	1.28 ± 1.31	0.078
CD3 + HLADR+	19.00 ± 14.21	30.88 ± 28.86	0.004*
CD4 + CD25+	18.25 ± 11.81	14.02 ± 14.90	0.149
CD8 + CD25+	1.20 ± 1.69	1.07 ± 1.14	0.460
CD4 + CD69+	2.58 ± 3.46	2.68 ± 3.16	0.954
CD8 + CD69+	3.80 ± 4.05	4.28 ± 6.48	0.220
AKI: Acute kidney injury; Non-AKI: Sepsis patients without AKI. *$P < 0.05$			

Risk Factors For Sa-aki

We performed logistic regression analysis of risk factors for AKI in sepsis patients. Univariate logistic regression analysis showed that percentage of total T lymphocyte (CD3+), percentage of CTL (CD3 + CD8+), and percentage of totally activated T lymphocyte (CD3 + HLADR+) were protective factors for SA-AKI ($P < 0.05$). Multivariate logistic regression analysis was then performed for the significant variables in the univariate analysis. The results indicated that percentage of totally activated T lymphocyte showed a negative association with SA-AKI independently (OR: 0.952, 95% CI: 0.926–0.978, $P = 0.000$) (Table 3).

Table 3
Univariate and multivariate analyses of risk factors for AKI in sepsis patients.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CD3+ (%)	0.967 (0.940–0.995)	0.022*		
CD3 + CD4+ (%)	1.007 (0.979–1.035)	0.643		
CD3 + CD8+ (%)	0.966 (0.937–0.996)	0.024*		
CD3 + CD4+/CD3 + CD8+	1.299 (0.977–1.726)	0.072		
CD3 + HLADR+ (%)	0.957 (0.933–0.983)	0.001*	0.952 (0.926–0.978)	0.000*
CD4 + CD25+ (%)	1.025 (0.984–1.069)	0.236		
CD8 + CD25+ (%)	1.064 (0.888–1.276)	0.500		
CD4 + CD69+ (%)	1.028 (0.914–1.155)	0.647		
CD8 + CD69+ (%)	0.946 (0.883–1.012)	0.109		
Hypertension	1.947 (0.912–4.158)	0.085		
Diabetes	0.839 (0.380–1.849)	0.663		
Chronic kidney disease	2.117 (0.952–4.707)	0.066		
Coronary heart disease	1.360 (0.614–3.016)	0.449		
Chronic liver disease	0.992 (0.107–9.177)	0.995		
Chronic pulmonary disease	0.471 (0.208–1.066)	0.071		
Cerebrovascular disease	0.569 (0.261–1.237)	0.154		
Age (years)	1.014 (0.989–1.041)	0.269		
Neutrophil (10^9/L)	0.954 (0.909–1.001)	0.055		
Lymphocytes (10^9/L)	0.956 (0.563–1.625)	0.869		
Monocytes (10^9/L)	0.703 (0.435–1.137)	0.151		
ALB (g/L)	1.037 (0.968–1.112)	0.302		
ALT (U/L)	1.000 (0.999–1.002)	0.694		

AKI: Acute kidney injury; ALB: Serum albumin; ALT: Alanine aminotransferase; AST: Aspartate transaminase; BNP: Brain natriuretic peptide; TNT: Troponin T; PCT: Procalcitonin; CRP: C-reactive protein. *$P < 0.05$

Variables	Univariate analysis		Multivariate analysis
AST (U/L)	1.000 (0.999-1.000)	0.829	
BNP (pg/ml)	1.000 (1.000–1.000)	0.304	
TNT (μg/L)	1.000 (1.000-1.001)	0.638	
PCT (ng/ml)	1.006 (0.991–1.021)	0.440	
CRP (mg/L)	1.003 (0.997–1.010)	0.286	
AKI: Acute kidney injury; ALB: Serum albumin; ALT: Alanine aminotransferase; AST: Aspartate transaminase; BNP: Brain natriuretic peptide; TNT: Troponin T; PCT: Procalcitonin; CRP: C-reactive protein. *P< 0.05			

Diagnostic Value For Sa-aki

Based on the above results, ROC analysis was performed. The results showed that total T lymphocyte (CD3+), CTL (CD3 + CD8+), and totally activated T lymphocyte (CD3 + HLADR+) had discriminatory abilities (P< 0.05), with areas under the curve (AUC) value of 0.638, 0.615, and 0.661, respectively; sensitivity of 66.4%, 59.9%, and 80.3%, respectively; specificity of 61.8%, 64.7%, and 52.9%, respectively; and cutoff values of 66.75%, 23.24%, and 30,64%, respectively (Fig. 2 and Table 4).

Table 4
ROC Curve analysis of parameters predicting incidence of AKI.

Variables	Cutoff value	AUC	Sensitivity	Specificity	*P* Value
CD3+ (%)	66.75	0.638	66.4%	61.8%	0.013*
CD3 + CD8+ (%)	23.24	0.615	59.9%	64.7%	0.039*
CD3 + HLADR+ (%)	30.64	0.661	80.3%	52.9%	0.004*
AKI: Acute kidney injury. *P< 0.05					

Discussion

In the last few decades, sepsis has been recognized as an important complication of critical illness, which was associated with considerably high morbidity, mortality and increased medical costs [13]. The development of AKI during sepsis further increases morbidity and mortality [14]. Therefore, early diagnosis of AKI and appropriate adjustment of follow-up treatment strategy are very important to improve the prognosis. 2012 KDIGO guideline for AKI present the most recent consensus definition, which was based on increases in serum creatinine or decreases in urine output [12]. However, serum creatinine and urine output have some limitations. On one hand, the definition that relies on change in serum creatinine is establishing a baseline serum creatinine. No consensus method exists to establish pre-AKI

baseline serum creatinine in the absence of previous values (recent or distant). One the other hand, it requires the results of change in serum creatinine which needs at least two days, and changes in serum creatinine are often delayed owing to renal reserve and the kinetics of AKI [15]. In addition, the use of diuretics resulted in insignificant changes in urine volume. Therefore, newer methods are needed to detect AKI in sepsis patients. Lymphocyte subtyping is an appropriate method because of the ease of collecting peripheral blood samples and the short duration of results available.

In our study, a total of 171 sepsis patients were included. Among them, 137 patients developed AKI with a median age of 87 years. Flow cytometry analysis showed that the percentages of total T lymphocyte (CD3+), CTL (CD3 + CD8+), and totally activated T lymphocyte (CD3 + HLADR+) were lower in sepsis patients with AKI than in those without AKI. Univariate logistic regression analysis found that percentages of total T lymphocyte, CTL, and totally activated T lymphocyte were protective factors for AKI. And multivariate analysis indicated that percentage of totally activated T lymphocyte was an independent protective factor for AKI. Moreover, ROC analysis showed that total T lymphocyte, CTL, and totally activated T lymphocyte had discriminatory abilities for SA-AKI.

AKI is common in sepsis, a prospective cohort study of 1177 sepsis patients from 198 ICUs in 24 European countries reported a 51% incidence of AKI [16]. Bagshaw SM et al found that 64.4% of patients with septic shock developed early AKI [17]. In contract, our data showed that the incidence of SA-AKI was 80.1%, which was higher than previously reported. The reason may be that our patients were older, with a median age of 86 years, while the median ages of patients in the above study were 65 and 62 years old, respectively. Furthermore, Bagshaw SM et al showed that the age of SA-AKI patients was older than that of non-SA-AKI patients ($P < 0.05$) [17]. These results suggest that elderly patients with sepsis are more likely to develop AKI.

CD3 is the characteristic surface marker of mature T lymphocytes and total T lymphocyte is defined by marker of CD3. Sepsis often results in an immunosuppressed state [18], Monserrat J showed that CD3 + T lymphocyte was significantly lower in patients with septic shock [19]. Furthermore, Drewry AM reported that persistent lymphopenia was associated with poor outcome in sepsis patients [20]. In this study, our results revealed that SA-AKI patients had lower percentage of total T lymphocyte than that of non-SA-AKI patients with novelty. Moreover, we found that total T lymphocyte was a protective factor for SA-AKI and ROC analysis showed it had discriminatory ability for diagnosis of SA-AKI. These evidences indicated decreased total T lymphocyte was associated with AKI induced by sepsis and could be an immune marker to early diagnose SA-AKI.

CD4 + T lymphocyte (T helper) and CD8 + T lymphocyte (CTL) are the two major types of T lymphocytes involved in the cell-mediated immunity [21]. There are many studies on their role in ischemic AKI, but their role in SA-AKI is less. One study showed that SA-AKI was driven through IL-17 released by CD4 + T lymphocyte. However, our data found that impaired T helper does not mediate the occurrence of AKI or play a protective role. More research is needed to explore the role of T helper in SA-AKI. In addition, our study found that the CTL percentage was significantly lower in sepsis patients with AKI than in those

without AKI. We originally reported CTL was impaired in sepsis associated AKI, thus CTL could be a new immune marker of SA-AKI. Previous studies reported that CTL apoptosis was rapidly increased in blood of patients in septic shock, which lead to a profound and persistent lymphopenia associated with poor outcome [22, 23]. Singbartl K et al showed that dysfunction of immune cells can contribute to immune dysfunction and impaired bacterial clearance during AKI [24]. Moreover, one study reported that few T lymphocytes were seen in human kidney biopsy specimens during AKI [21]. These results are consistent with ours, and together they indicate that SA-AKI is closely related to the level and function of CTL.

Totally activated T lymphocyte is charactered by expression of HLADR, which has mainly been regarded as a marker of activated T lymphocytes [25]. HLA-DR molecules play a vital role in the specific immune response to infection. We found that totally activated T lymphocyte of SA-AKI patients was lower than those of sepsis patients without AKI, and it is also a protective and predictive factor for SA-AKI. A previous study showed that HLADR expression on circulating T lymphocyte was reduced in patients with severe sepsis [26]. These data suggested that totally activated T lymphocyte may play a protective role in SA-AKI and may contribute to diagnosis of SA-AKI.

Regulatory T lymphocytes, which are mainly derived from thymus, are considered to be an indispensable part of the regulation of the immune system, and CD25 + is an important marker [27]. Moreover, CD69 + is an early activation marker and involved in the regulatory function of T lymphocyte. Therefore, early activated T lymphocyte (CD69 + T lymphocyte) considered to be a new subset of regulatory T lymphocytes [28]. It has been reported that CD25 + and CD69 + lymphocytes were significantly increased in sepsis [29]. One study showed that soluble CD25 is increased in patients with sepsis induced AKI [30]. But few studies have analyzed the relationship between CD69 + lymphocytes with AKI. Our study found that SA-AKI was not associated with CD25 + and CD69 + lymphocytes. Therefore, more studies are needed to investigate the roles of them in AKI.

Our study has certain limitations. Firstly, this was a retrospective study. Secondly, the relationship between AKI severity and T lymphocyte was not explored. Further studies should be carried out to explore these results.

Conclusions

In summary, our results demonstrated that total T lymphocyte, CTL, and totally activated T lymphocyte percentages were significantly decreased in SA-AKI group compared with non-SA-AKI group. Moreover, these subsets were also protective and predictive factors for SA-AKI. These data indicated that impaired T lymphocyte subsets contributed to pathogenesis and the early diagnosis of AKI in sepsis patients. Further research is needed to elucidate T lymphocyte subsets in the immunological mechanisms of SA-AKI.

Declarations

Ethics approval and consent to participate

The study involving human participants was approved by the Ethical Committee of Guangdong General Hospital.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

HWX and HWK designed the research, obtained funding and supervised the work. LGL and ZY conducted the research and wrote the first draft of the manuscript. HGY contributed to data collection, and data interpretation. All authors read and approved the final manuscript.

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Figures

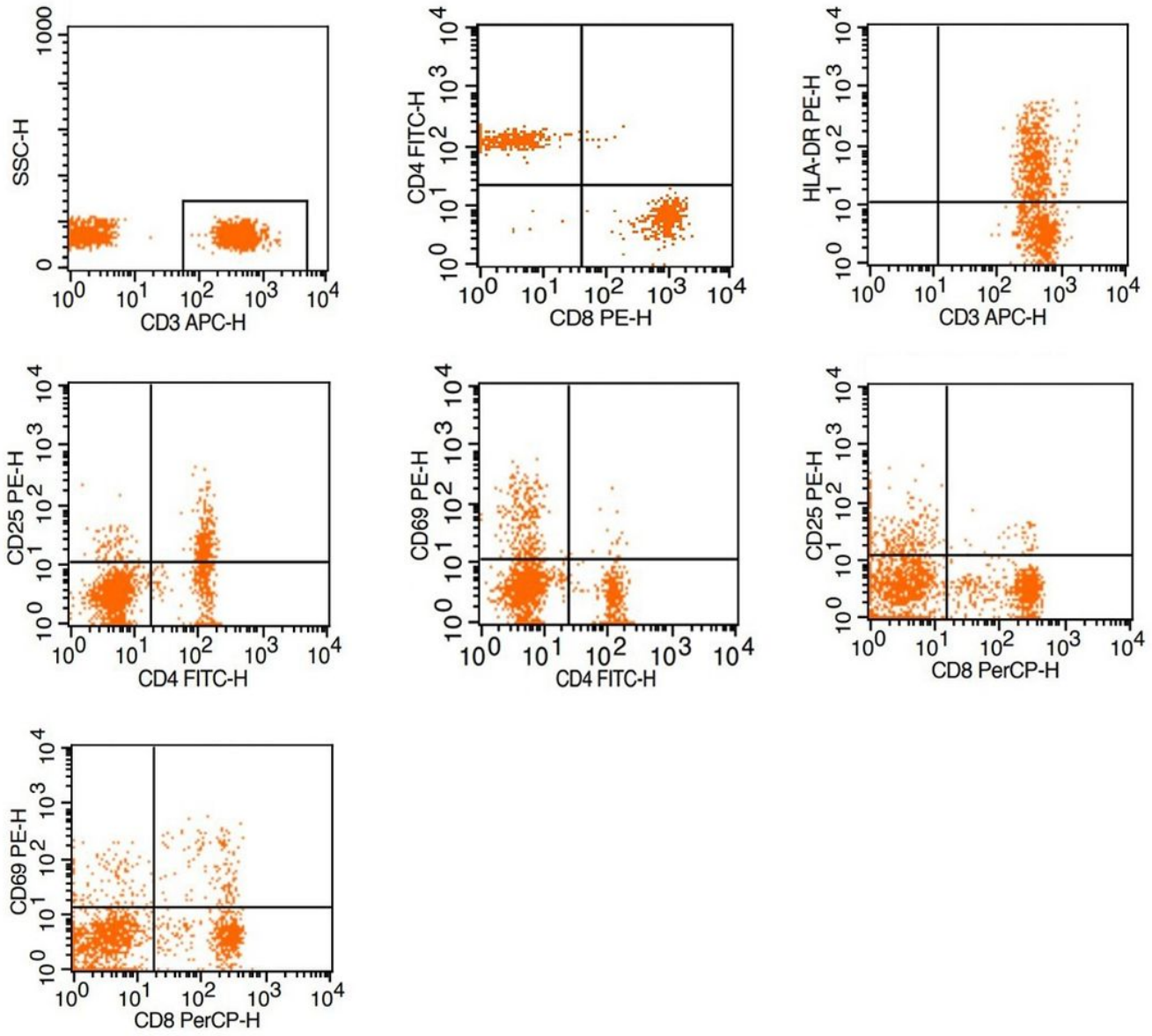

Figure 1

Flow cytometric analysis of T lymphocyte subsets, including CD3+, CD3+CD4+, CD3+CD8+, CD3+HLADR+, CD4+CD25+, CD8+CD25+, CD4+CD69+, CD8+CD69+ T lymphocyte.

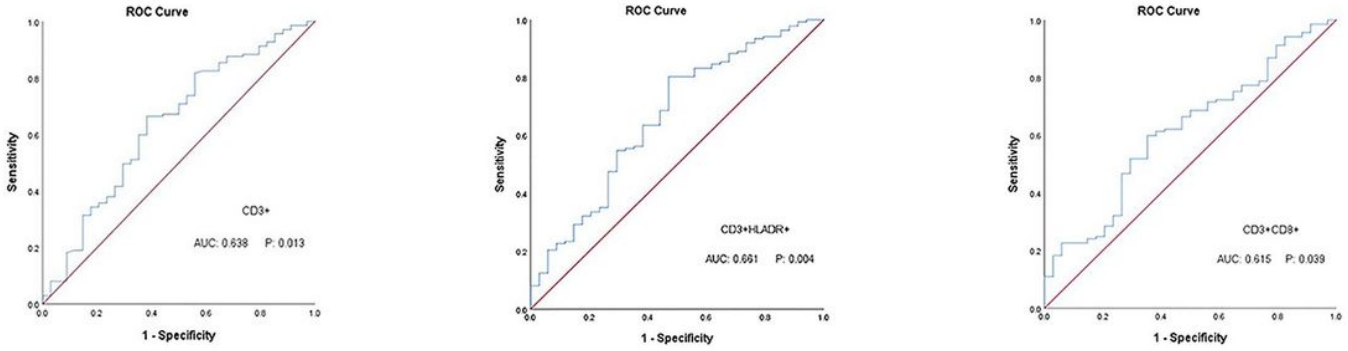

Figure 2

ROC analysis of T lymphocyte subsets predicting AKI, including CD3+, CD3+CD8+, and CD3+HLADR+ T lymphocyte.