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ORIGINAL ARTICLE

Th17/Treg Imbalance in Acute Kidney Injury

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SUMMARY

Background: **Helper T cell 17 (Th17) and regulatory T cells (Treg) play an important role in the inflammatory response. However, the role of Th17/Treg imbalance in acute kidney injury is not yet established. The aim of the study was to analyze Th17/Treg imbalance in acute kidney injury caused by sepsis or other reasons.**

Methods: **An observational prospective study was conducted. We enrolled adult patients admitted to the intensive care unit (ICU) with acute kidney injury caused by sepsis or other reasons and then followed up until 28 days or discharge. Healthy volunteers were followed during the same period as the control group. We investigated the differences in renal injury markers and inflammatory indicators between acute kidney injury (AKI) patients and the control group. The clinical data and peripheral blood samples of all patients were collected immediately after enrollment. An analysis of the data was conducted to determine if the Th17/Treg ratio could serve as a predictive marker of sepsis induced acute kidney injury (SAKI) in AKI patients.**

Result: **A total of 104 AKI patients were enrolled in the study, including 60 SAKI, 44 AKI without sepsis, while 10 healthy volunteers served as the control group. Infections, especially thoracoabdominal infection leading to sepsis, were the major cause of AKI in the study population (58%). Th17/Treg ratio, the proportion of Th17 cells, the concentration of interleukin-10 (IL-10), and the concentration of interleukin-17 (IL-17) of AKI patients showed a significant increase compared to that in the control group. The proportion of Th17 cells and Treg cells as well as the Th17/Treg ratio of the SAKI group were higher than those of the AKI without sepsis group. Chronic kidney disease (CKD) and Th17/Treg ratio were independent risk factors for SAKI. The AUC demonstrated that the Th17/Treg ratio measured 0.775 (95% CI 0.683 - 0.851, $p < 0.0001$). The cutoff value of Th17/Treg ratio for predicting SAKI was 0.033. When the Th17/Treg ratio was > 0.033, the sensitivity of predicting SAKI was 0.967, and the specificity was 0.500. The 28-day mortality and renal function recovery rate between the SAKI group and the AKI without sepsis group did not differ.**

Conclusions: **There was an imbalance of Th17/Treg in acute kidney injury. Compared with AKI caused by other factors, Th17/Treg ratio was higher in SAKI patients. There was no difference in 28-day mortality and renal function recovery rate among AKI patients with different etiologies.**

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Supplementary Data

Table S1. Comparison of clinical characteristics between SAKI and AKI without sepsis group after exclusion of patients with CKD.

	Total (n = 76)	SAKI group (n = 50)	AKI without Sepsis group (n = 26)	Test value	p-value
Male [n (%)]	50 (65.8)	32 (64.0)	18 (69.2)	0.208	0.648
Age - year (median [Q1, Q2])	69.00 (54.00, 79.00)	66.00 (52.50, 77.25)	72.00 (63.75, 79.00)	-0.789	0.430
BMI - kg/m^2 (mean ± SD)	23.37 ± 4.49	22.92 ± 4.03	24.24 ± 5.23	-1.221	0.226
Comorbidities					
Hypertension [n (%)]	48 (63.2)	30 (60.0)	18 (69.2)	0.626	0.429
Diabetes [n (%)]	24 (31.6)	22 (44.0)	2 (7.7)	10.436	0.001**
Chronic cardiovascular disease [n (%)]	36 (47.4)	18 (36.0)	18 (69.2)	7.577	0.006 **
Chronic lung disease [n (%)]	10 (13.2)	8 (16.0)	2 (7.7)	1.033	0.309
Chronic liver disease [n (%)]	2 (2.60)	2 (4.0)	0 (0)	1.068	0.301
Nervous system disease [n (%)]	16 (21.1)	10 (20.0)	6 (23.1)	0.097	0.755
Malignant tumor [n (%)]	16 (21.1)	12 (24.0)	4 (15.4)	0.764	0.382
Physiological parameters					
APACHEII - score (mean ± SD)	20.50 ± 7.91	20.32 ± 7.10	20.85 ± 9.42	-0.273	0.785
NAGL - ng/mL (median [Q1, Q2])	65.79 (58.67, 75.94)	72.99 (55.34, 77.57)	64.75 (59.49, 67.92)	-0.898	0.369
Urine output - L/24hours (median [Q1, Q2])	1.21 (0.38, 2.24)	1.65 (0.51, 2.37)	0.43 (0.04, 1.64)	-3.176	0.001 **
Cr - µmol/L (median [Q1, Q2])	130.55 (99.10, 190.50)	125.90 (96.40, 193.05)	152.50 (103.30, 199.10)	-1.029	0.303
BUN - mmol/L (median [Q1, Q2])	12.89 (7.69, 18.55)	13.13 (9.30, 19.07)	15.42 (12.31, 24.08)	-0.986	0.324
PCT - ng/mL (median [Q1, Q2])	13.59 (1.92, 31.92)	19.26 (2.95, 33.84)	8.00 (0.68, 23.80)	-1.998	0.046 *
Lac - mmol/L (median [Q1, Q2])	2.05 (1.30, 3.20)	1.80 (1.18, 2.40)	2.90 (2.08, 5.05)	-2.914	0.004 **
OI (median [Q1, Q2])	258.00 (180.00, 350.00)	266.00 (184.50, 357.00)	230.00 (159.50, 338.00)	-0.657	0.511
WBC - x 10^9/L (median [Q1, Q2])	12.43 (7.11, 18,68)	12.20 (8.11, 19.85)	12.65 (6.17, 17.79)	-0.591	0.554
GR - x 10^9/L (median [Q1, Q2])	11.08 (5.87, 17.25)	11.35 (7.29, 18.18)	11.06 (4.27, 15.44)	-0.986	0.324
LY - x 10^9/L (median [Q1, Q2])	0.69 (0.50, 1.08)	0.70 (0.49, 1.03)	0.65 (0.57, 1.21)	-0.942	0.346
NLR (median [Q1, Q2])	15.10 (7.56, 24.55)	16.79 (10.30, 33.34)	12.06 (6.68, 15.29)	-2.387	0.017 *
Immune indexes					
T lymphocyte ratio - % (median [Q1, Q2])	67.84 (55.49, 75.16)	68.73 (53.17, 75,28)	67.50 (57.74, 74.73)	-0.052	0.959
CD4+ T lymphocyte ratio - % (median [Q1, Q2])	37.73 (27.25, 48.55)	39.09 (26.37, 47.35)	37.13 (35.88, 48.55)	-0.728	0.466
Treg cell ratio - % (median [Q1, Q2])	1.40 (0.67, 2.60)	1.38 (0.53, 2.49)	1.44 (0.93, 3.29)	-1.468	0.142
Th17 cell ratio - % (median [Q1, Q2])	0.13 (0.09, 0.19)	0.14 (0.11, 0.24)	0.08 (0.04, 0.12)	-4.909	0.000 ***
Th17/Treg ratio (median [Q1, Q2])	0.09 (0.04, 0.19)	0.11 (0.07, 0.26)	0.03 (0.02,0.09)	-4.447	0.000 ***

Table S1. Comparison of clinical characteristics between SAKI and AKI without sepsis group after exclusion of patients with CKD (continued).

	Total (n = 76)	SAKI group (n = 50)	AKI without Sepsis group (n = 26)	Test value	p-value
IL10 - pg/mL (median [Q1, Q2])	40.16 (25.47, 71.00)	32.99 (24.04, 80.51)	42.62 (28.24, 96.17)	-0.548	0.584
IL17 - pg/mL (median [Q1, Q2])	4.86 (1.95, 12.18)	4.89 (2.10, 14.19)	3.88 (1.86, 6.61)	-0.876	0.381
TNF-α - pg/mL (median [Q1, Q2])	9.16 (4.05, 22.06)	7.87 (3.67, 13.08)	54.89 (38.83, 69.94)	-3.074	0.002 **

BMI Body mass index, APACHE II Acute physiology and chronic health evaluation 2, KDIGO The Kidney Disease: Improving Global Outcomes, Cr Serum creatinine, BUN Blood urea nitrogen, NAGL Neutrophil gelatinase-associated lipocalin, PCT Procalcitonin, Lac Lactic acid, OI Oxygenation index, WBC White blood cell, GR Neutrophil granulocyte, LY Lymphocyte, NLR Neutrophil/lymphocyte ratio, Th17 Helper T cell 17, Treg Regulatory T cell, IL-10 Interleukin-10, IL-17 Interleukin-17, TNF-α Tumor necrosis factor alpha, RRT renal replacement therapy. p-value: * 0.05 - 0.01, ** 0.01 - 0.001, * < 0.001.**

Table S2. Risk factor analysis for SAKI after exclusion of patients with CKD.

	Univariable logistic regression		Multivariable logistic regression	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Diabetes [n (%)]	9.429 (2.008 - 44.281)	0.004 **		
Chronic cardiovascular disease [n (%)]	0.250 (0.091 - 0.689)	0.007 **		
Urine output - L/24hours (median [Q1, Q2])	0.535 (0.331 - 0.865)	0.011 *		
PCT - ng/mL (median [Q1, Q2])	0.979 (0.948 - 1.010)	0.174		
Lac - mmol/L (median [Q1, Q2])	1.367 (1.083 - 1.724)	0.008 **		
NLR (median [Q1, Q2])	0.939 (0.891 - 0.990)	0.021 *		
Th17 cell ratio - % (median [Q1, Q2])	0.000 (0.000 - 0.000)	0.000 ***	0.000 (0.000 - 0.000)	0.002 **
Th17/Treg ratio (median [Q1, Q2])	0.000 (0.000 - 0.000)	0.004 **	0.000 (0.000 - 0.328)	0.031 *
TNF-α - pg/mL (median [Q1, Q2])	1.070 (0.998 - 1.148)	0.059		

PCT Procalcitonin, Lac Lactic acid, NLR Neutrophil/lymphocyte ratio, Th17 Helper T cell 17, Treg Regulatory T cell, TNF-α Tumor necrosis factor alpha, RRT renal replacement therapy. p-value: * 0.05 - 0.01, ** 0.01 - 0.001, * < 0.001.**

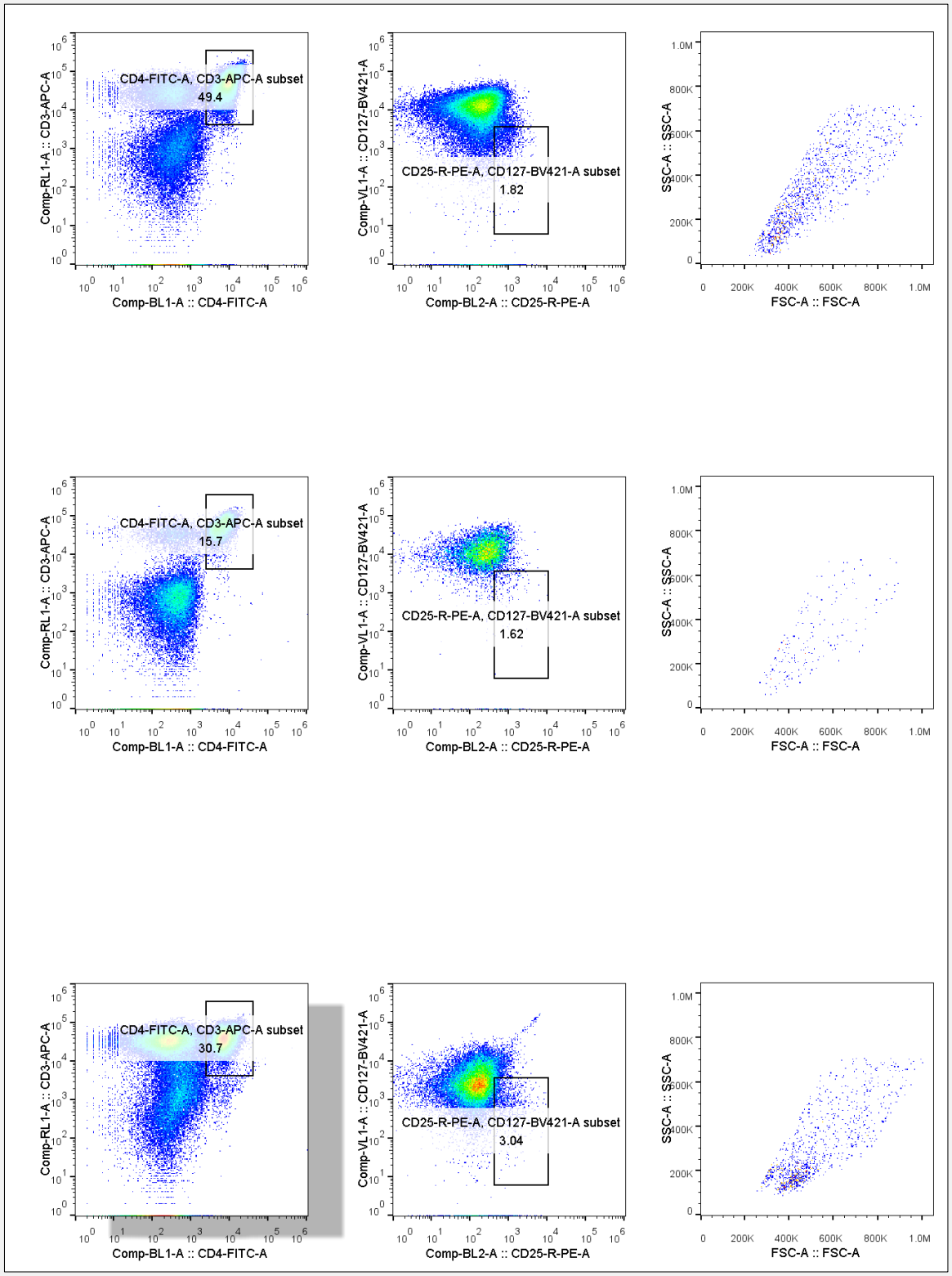

Figure S1. Flow cytometry analysis for Treg population in A the Control group, B the SAKI group, and C the AKI without sepsis group. SAKI sepsis-induced acute kidney injury, AKI acute kidney injury.

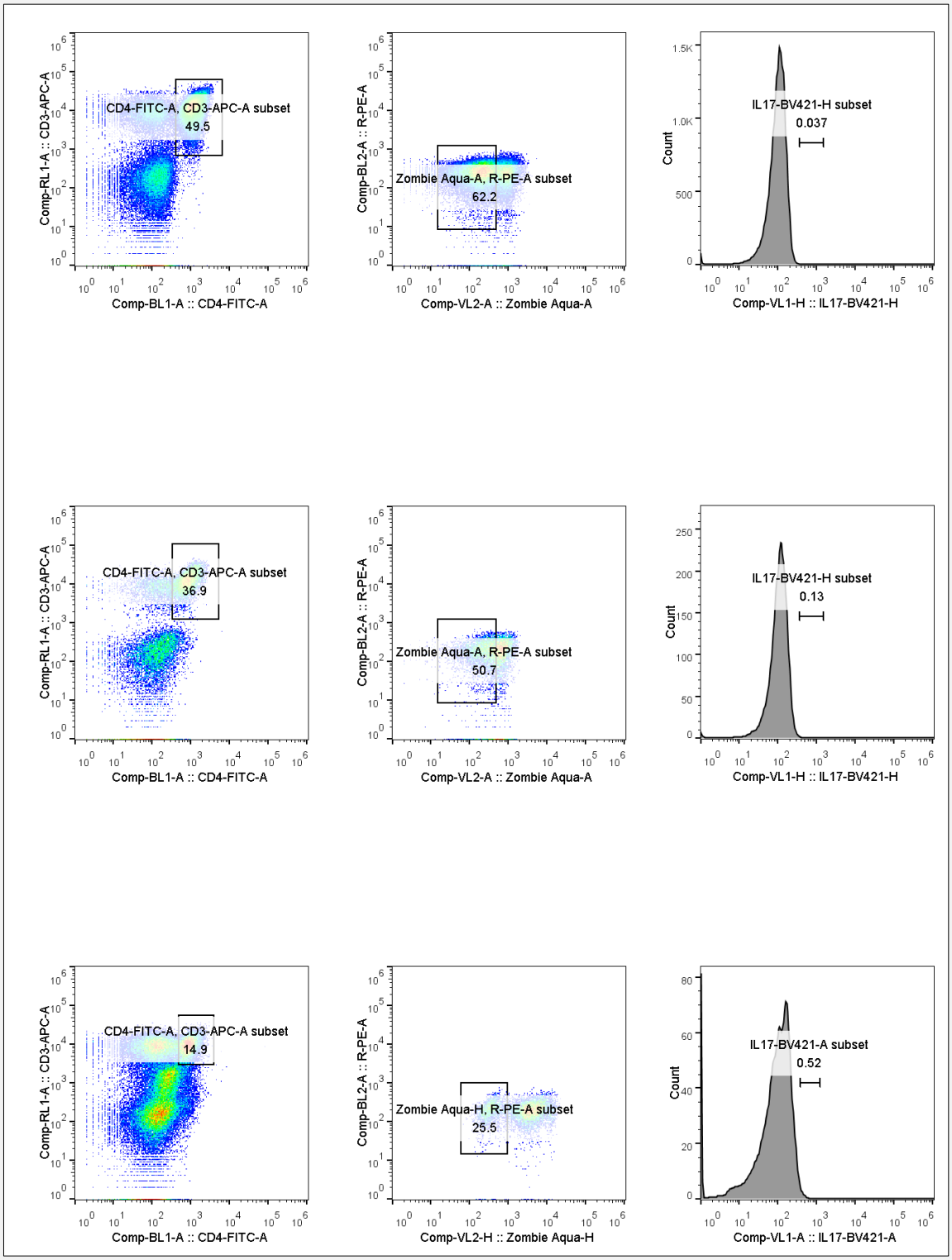

Figure S2. Flow cytometry analysis for Th17 population in A the Control group, B the SAKI group, and C the AKI without sepsis group. SAKI sepsis-induced acute kidney injury, AKI acute kidney injury.