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Original Article

Prediction of Th17/Treg cell balance on length of stay in intensive care units of patients with sepsis

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ABSTRACT

Background: Prolonged length of stay (LOS) of sepsis can drain a hospital's material and human resources. This study investigated the correlations between T helper type 17 (Th17) and regulatory T (Treg) balance with LOS in sepsis.

Methods: A prospective clinical observational study was designed in Changhai Hospital affiliated to Naval Medical University in Shanghai, China, from January to October 2020. The patients diagnosed with sepsis and who met the inclusion and exclusion criteria were recruited and whether the levels of cytokines, procalcitonin, subtypes, and biomarkers of T cells in the peripheral blood were detected. We analyzed the correlation between these and LOS.

Results: Sixty septic patients were classified into two groups according to whether their intensive care unit (ICU) stay exceeded 14 days. The patients with LOS ≥14 days were older ([72.6±7.5] years *vs.* [63.3±10.4] years, P=0.015) and had higher Sequential Organ Failure Assessment (SOFA) (median [interquartile range]: 6.5 [5.0–11.0] *vs.* 4.0 [3.0–6.0], P=0.001) and higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores (16.0 [13.0–21.0] *vs.* 8.5 [7.0–14.0], P=0.001). There was no difference in other demographic characteristics and cytokines, interleukin-6, tumor necrosis factor-α, and interleukin-10 between the two groups. The Th17/Treg ratio of sepsis with LOS <14 days was considerably lower (0.48 [0.38–0.56] *vs.* 0.69 [0.51–0.98], P=0.001). For patients with LOS ≥14 days, the area under the receiver operating characteristic curve for the Th17/Treg ratio was 0.766. It improved to 0.840 and 0.850 when combined with the SOFA and APACHE II scores, respectively.

Conclusions: The Th17/Treg ratio was proportional to septic severity and can be used as a potential predictor of ICU stay in sepsis, presenting a new option for ICU practitioners to better care for patients with sepsis.

Introduction

Sepsis is a significant public health concern. Compared with previous estimates, the estimated global annual number of sepsis cases has doubled, now totaling almost 49 million.[1] Sepsis refers to the life-threatening organ dysfunction caused by the dysregulation of the host's response to infection, especially immune dysregulation with pro-inflammatory and anti-inflammatory imbalance.[2] The complicated and collapsed immune caused by severe infection was considered the central pathogenesis of sepsis.[3–5] There is a clear link between the length of stay(LOS) in intensive care unit (ICU) stay for patients with sepsis and their prognosis and healthcare expenses. Moreover, the LOS in the ICU is an essential indicator for the diagnosis of persistent inflammatory-immunosuppressive and catabolic syndrome (PICS) (≥14 days).[6] Limited studies on ICU hospitalization costs show that early intervention can reduce hospitalization expenditures. The practice of early mobility in the ICU

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is associated with reduced total expenses and medical issues.[7] There are, however, no clinically established determinants of ICU duration of stay for sepsis patients.

T lymphocytes are one of the critical immune cells that regulate antimicrobial phagocytic and cytotoxic activity. T cells can be divided into many subtypes, and the proportion of each subtype differs by the stages of T cell immunity.[8] Among such subtypes, regulatory T cells (Treg) and the cluster of differentiation (CD)4^+IL-17^+ T helper cells (Th17) share a common precursor cell and change appearance with disease progression.[9,10] The balance between Th17 and Treg has emerged as a prominent factor in regulating autoimmunity.[11] Accumulated evidence suggests that the imbalance of Th17 and Treg is associated with the development of many diseases,[12] such as primary Sjögren's syndrome,[13] experimental autoimmune encephalomyelitis,[14] human graft-versus-host disease,[15] and asthma.[16]

This study explored the hypothesis that Th17/Treg cell homeostasis may predict LOS of sepsis patients in the ICU.

Methods

Patient characteristics

Sepsis patients admitted to the ICU in Shanghai Changhai Hospital from January to October 2020 were recruited, and the study was approved by the human ethics committee of Changhai Hospital (CHEC2019-133). We obtained informed consent from all subjects or their relatives before enrollment. The diagnostic criteria of sepsis were based on the definitions for sepsis and septic shock defined in The Third International Consensus (Sepsis-3).[17] Eligibility criteria for enrollment in this study included patients aged 18–80 years with a diagnosis of sepsis (Sequential Organ Failure Assessment [SOFA] ≥2 points) and systolic blood pressure <90 mmHg who have not been resuscitated with corticosteroids, blood, or blood products. The severity of the patient's disease was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II, and the extent of organ dysfunction was assessed using the SOFA score (range, 0–24). Exclusion criteria included: (1) age <18 years; (2) severe acute head injury (Glasgow Coma Scale score<5); (3) presentation at terminal stage that could not be resuscitated; (4) autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, asthma, and multiple sclerosis; (5) acquired immunodeficiency syndrome; (6) acute stroke, myocardial infarction, or recent viral hepatitis; (7) use of hormones or immunosuppressors within 3 months before hospitalization; (8) transplant surgery; (9) unexpected termination of continuous blood purification treatment; (10) patients resuscitated with anti-inflammatory drugs or corticosteroids; and (11) septic patients whose blood sample was not taken within the first 8 h after the definition of sepsis.

Reagents

Tumor necrosis factor-α (TNF-α), interleukin (IL)-17A, IL-10, IL-6 enzyme-linked immunosorbent assay (ELISA) kits, fluorescent-labeled monoclonal antibodies anti-CD4-fluorescein isothiocyanate (FITC), anti-IgG1-FITC, anti-CD25-Phycoerythrin (PE), anti-IgG1-PE, anti-FoxP3-Allophycocyanin (APC), anti-Interferon (IFN)-gamma-PE, anti-IgG1-APC, and anti-IL-17-APC were bought from eBiosciences (San Jose, CA, USA). FIX & PERM medium was obtained from Invitrogen (California, USA). Leukocyte Activation Cocktail was obtained from BD (New York, USA), Catalog No.550583, containing phorbol 12-myristate 13-acetate (PMA), a calcium ionophore (ionomycin), and the protein transport inhibitor BD GolgiPlug™ (Brefeldin A, New York, USA).

Blood samples

Venous blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) tubes within 24 h after the patients were diagnosed with sepsis. Blood samples were refrigerated at 4 °C after EDTA anticoagulation. Density gradient centrifugation was conducted at 2000 revolutions per minute (rpm) for 20 min to isolate peripheral blood mononuclear cells (PBMCs), which were used to detect the expression of membrane markers. Additionally, plasma was obtained and stored at −80 °C for subsequent cytokine detection. The concentration of PBMCs was adjusted to 1×10^6/mL in Roswell Park Memorial Institute (RPMI) 1640 (Gibco, Thermo Fisher, Dublin, Ireland)culture solution supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin, 2 mmol/L glutamine, and 10% fetal calf serum (Gibco, Thermo Fisher, Dublin, Ireland). The cell suspension was seeded onto 12-well cell culture plates. Cells were treated with 1 μL Leukocyte Activation Cocktail, BD GolgiPlug (BD, New York, USA), and incubated in darkness at 37 °C under a 5 %- carbon dioxide atmosphere for 6 h.

Flow cytometry

All antibodies listed were obtained from eBioscience (San Diego, CA, USA). A total of 5 μL labeled antibodies was added in each procedure. Because the PMA culture stimulates PBMC, it produces endocytosis of CD4 on the cell surface, which interferes with CD4 flow cytometric staining. As a result, $CD3^+CD8^-$ T cells were employed to counter-select $CD4^+$ T cells in this investigation. Stimulated and cultured mononuclear cells were collected, pre-incubated for 15 min with unlabeled isotype control Abs (IgG1 or IgG2b), and then incubated with anti-CD3-FITC, anti-CD8-PE, or anti-CD4-FITC and anti-CD25-PE. A parallel control group was treated with their isotype controls. Then, mononuclear cells were treated with 100 μL FIX & PERM medium A and B (Invitrogen). Then, anti-IL-17-APC or anti-FoxP3-APC was added to PBMCs. A parallel control group was treated with isotype controls. Both suspensions were incubated at 4 °C away from light for one night. The markers for Treg cells and Th17 cells were $CD4^+CD25^+FoxP3^+$, $CD4^+IL17^+$(unstimulated with PMA), or $CD3^+CD8^-IL17^+$ (stimulated with PMA), respectively.

Plasma cytokines

The plasma of patients with sepsis was collected, as described above, to measure the content of TNF-α, IL-17, IL-10, and IL-6 in the plasma from the patients using ELISA according to the manufacturer's recommendations (Thermo Fisher).

Statistics

All analyses were done using SPSS, version 22.0 (IBM Corp. Armonk, New York, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were reported as mean ± standard deviation or median (interquartile range [IQR]) after assessing their normal distribution using the Kolmogorov–Smirnov test. To compare the two groups, the independent samples *t*-test was used for normally distributed data, and the Mann–Whitney test was used for non-normally distributed data. For the comparisons across multiple groups, the one-way analysis of variance and the Kruskal–Wallis test were used to analyze normally and non-normally distributed data, respectively. Categorical data were summarized using numbers (percentage) and were compared using the chi-squared or Fisher's exact test. Spearman's rank correlation was applied to determine the correlation between variables. The area under the receiver operating characteristic (ROC) curve was calculated to evaluate the diagnostic and prognostic value of the tested parameters. A value of P <0.05 was considered statistically significant.

Results

Demographic data of the septic patients

Sixty-five adult patients with sepsis were admitted, encompassing 41 males and 24 females. Five patients died in the ICU; three were admitted < 14 days, and two ≥ 14 days. According to whether they had been in ICU ≥ 14 days, 60 surviving patients were divided into two groups. Patients who had been in ICU ≥ 14 days were older ([72.6±7.5] years *vs.* [63.3±10.4] years, P=0.015) and had higher SOFA (median=6.5 [IQR:5.0–11.0] *vs.* median=4.0 [IQR:3.00–6.00], P=0.001) and APACHE II scores (median=16.0 [IQR:13.0–21.0] *vs.* median=8.5 [IQR:7.0–14.0], P=0.001). There were no significant differences in other demographic data between the two groups (Table 1).

Table 1
Demographic data of septic patients with different LOS in ICU.

Parameter	Total	ICU LOS <14 days (n=36)	ICU LOS ≥14 days (n=24)	P-value
Age (years)	67.1±10.4	63.3±10.4	72.6±7.5	0.015
Gender (M/F)	39/21	24/12	15/9	0.742
Height (cm)	166.7±9.5	166.8±9.2	166.7±10.0	0.862
Body weight (kg)	67.7±13.1	65.6±13.2	70.7±12.7	0.516
White blood cells (10^6/L)	16.6 (11.1–23.7)	18.4 (12.4–24.3)	16.6 (8.3–21.0)	0.165
Lymphocytes (10^6/L)	0.7 (0.4–1.0)	0.7 (0.4–0.9)	0.7 (0.3–1.1)	0.868
SOFA score	5.0 (4.0–9.0)	4.0 (3.0–6.0)	6.5 (5.0–11.0)	0.001
APACHE II score	13.0 (8.0–17.0)	8.5 (7.0–14.0)	16.0 (13.0–21.0)	0.001

Data expressed as mean±SD or median (interquartile range).
APACHE II: Acute physiology and chronic health evaluation II; ICU: Intensive care units; LOS: Length of stay; M/F: Male/female; SD: Standard deviation; SOFA: Sequential organ failure assessment.

Table 2
Inflammatory cytokines in patients with sepsis by LOS in the ICU.

Parameter	Total	ICU LOS <14 days (n=36)	ICU LOS ≥14 days (n=24)	P-value
IL-6 (pg/mL)	163.5 (44.5–374.6)	125.5 (44.0–301.0)	213.0 (66.0–376.0)	0.154
TNF-α (pg/mL)	23.9 (13.6–34.0)	19.0 (13.0–34.3)	27.0 (17.0–34.0)	0.484
IL-10 (pg/mL)	20.3 (8.6–50.8)	18.5 (8.0–35.5)	25.5 (10.3–57.3)	0.327
IL-17 (pg/mL)	140.8 (107.6–188.9)	125.9 (98.5–162.8)	173.4 (131.9–206.9)	0.020
PCT (pg/mL)	6.9 (1.4–16.5)	5.2 (1.1–10.0)	7.4 (3.1–23.3)	0.097

Data are expressed as median (interquartile range).
ICU: Intensive care units; IL: Interleukin; LOS: Length of stay; PCT: Procalcitonin; Th17: T helper type 17; TNF-α: Tumor necrosis factor-α; Treg: Regulatory T.

Comparison of Th17 and Treg in patients with sepsis between two groups

The proportion of Th17 and Treg among $CD4^+$ T lymphocytes and Th17/Treg was compared between patients with sepsis and LOS less or longer than 14 days. There was a significant difference in the proportion of Treg between the two groups of patients (median = 4.21 [IQR: 3.66–5.26] *vs.* median = 3.50 [IQR 2.85–4.37], P=0.020) (Figure 1). The proportion of Th17 in patients with sepsis who stayed in the ICU for more than 14 days was significantly increased (median = 2.47 [IQR: 2.01–3.03] *vs.* median = 2.19 [IQR: 1.56–2.46], P=0.005) (Figure 2).

Cytokines in patients with sepsis and ICU LOS longer than 14 days

As shown in Table 2, despite the more severe condition of patients with sepsis who had been in the ICU ≥14 days, the conventional cytokines, including IL-6, TNF-α, and IL-10, were not significantly different from those in the patients who had been in the ICU < 14 days. However, the IL-17 levels in the patients with sepsis who had been in the ICU ≥ 14 days were significantly increased compared with those in patients who had been in the ICU < 14 days (median= 125.94 [IQR: 98.53–162.81] *vs.* median = 173.36 [IQR: 131.86–206.94], P=0.02).

The Th17/Treg ratio and relevance with the LOS, SOFA, and APACHE II scores

The ratio of Th17/Treg in patients with sepsis who had been in the ICU ≥14 days was significantly increased compared with those who had been in the ICU <14 days (median = 0.48 [IQR:0.38–0.56] *vs.* median= 0.69 [IQR: 0.51–0.98], P=0.001) (Figure 3A), indicating that Th17/Treg may be a detection index of the LOS of patients with sepsis in the ICU. The ratio of Th17/Treg in patients with sepsis was positively correlated with the LOS (Figure 3B), SOFA score (Figure 3C), and APACHE II score (Figure 3D) in the ICU.

Predictive roles of Th17/Treg ratio, SOFA score, and APACHE II score on LOS in ICU

A ROC analysis was performed to investigate the predictive roles of the Th17/Treg ratio, SOFA score, APACHE II score, Th17/Treg ratio combined with SOFA score, and Th17/Treg ratio combined with APACHE II score for LOS in the ICU (Table 3 and Figure 4).

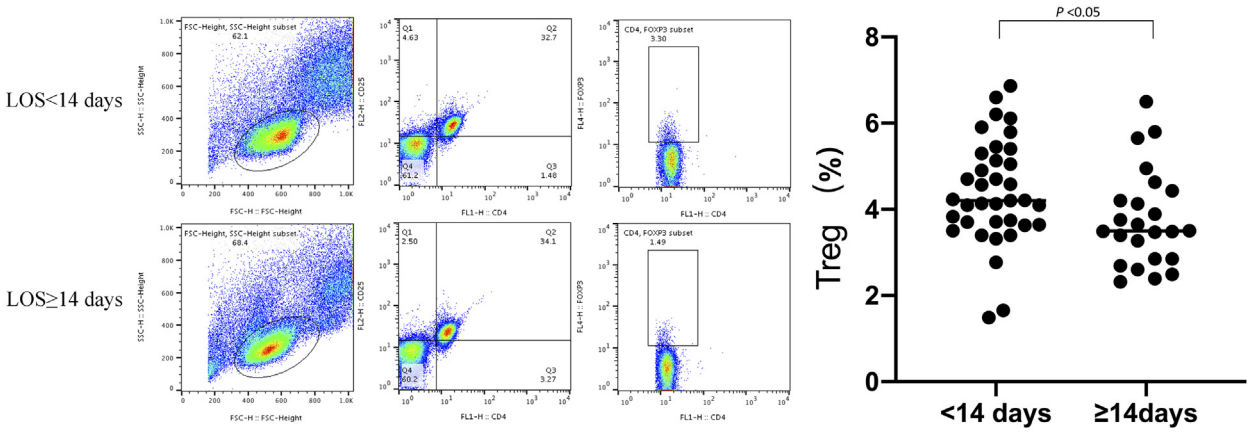

Figure 1. The proportion of Treg cells in patients with sepsis and LOS less or longer than 14 days. A: The flow cytometry of Treg cells in patients with sepsis. The flow cytogram has CD4 as the horizontal coordinate and CD25 and Foxp3 as the vertical coordinates, respectively. B: Comparison of Treg cells' proportion between patients with an ICU LOS ≥ 14 days (n=24) and < 14 days (n=36).
FSC: Forward scatter; ICU: Intensive care units; LOS: Length of stay; SSC: Side scatter; Treg: Regulatory T.

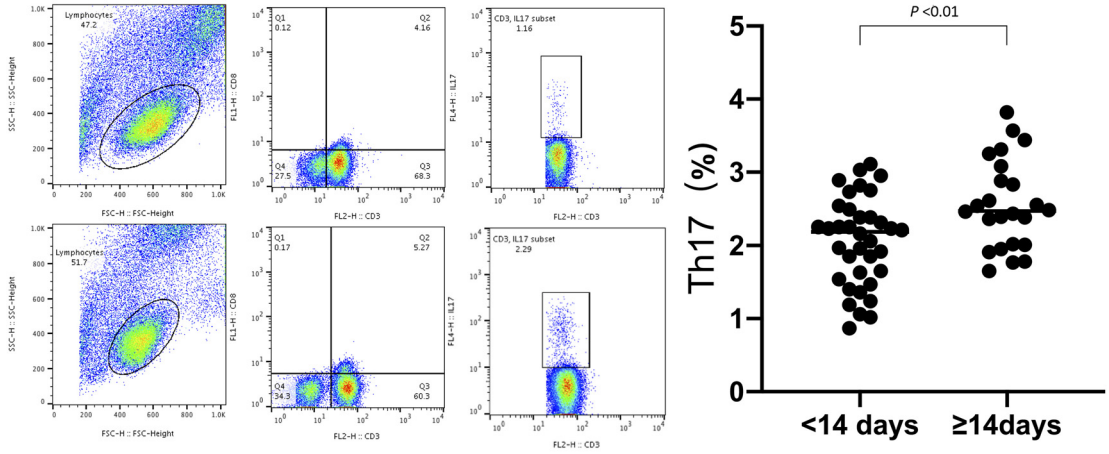

Figure 2. The proportion of Th17 cells in patients with sepsis and LOS less or longer than 14 days. A: The flow cytometry of Th17 cells in patients with sepsis. The flow cytogram has CD3 as the horizontal coordinate and CD8 and IL-17 as the vertical coordinates, respectively. B: Comparison of Th17 cells' proportion between patients with an ICU LOS ≥ 14 days (n=24) and < 14 days (n=36).
FSC: Forward scatter; ICU: Intensive care units; IL: Interleukin; LOS: Length of stay; SSC: Side scatter; Th17: T helper type 17.

Table 3
Predictive roles of Th17/Treg ratio, SOFA score, and APACHE II score on LOS in ICU.

Parameters	AUC	95 % CI
Th17/Treg ratio	0.766	0.627 to 0.906
APACHE II score	0.760	0.637 to 0.884
SOFA score	0.764	0.642 to 0.887
Th17/Treg ratio + SOFA score	0.840	0.735 to 0.945
Th17/Treg ratio + APACHE II score	0.850	0.747 to 0.952

APACHE II: Acute physiology and chronic health evaluation II; AUC: Area under curve; CI: Confidence interval; ICU: Intensive care units; LOS: Length of stay; SOFA: Sequential organ failure assessment; Th17: T helper type 17; Treg: Regulatory T.

Discussion

The present study found that in patients with sepsis, an initial high Th17 ratio and a decreased Treg ratio were related to a longer ICU stay. A higher Th17/Treg ratio was linked to a longer ICU stay. Its area under the ROC curve for predicting ICU length of stay longer than 14 days in patients with sepsis was 0.766, which reached 0.850 when paired with the APACHE II score. These findings imply that a Th17/Treg imbalance has a role in the pathophysiology of immunological diseases caused by sepsis.

The immune system plays a double-edged role in sepsis: it protects against invading pathogens, but its overreaction can cause organ injury.[18] During sepsis, the invasion of a large number of pathogens causes immune overreaction and the depletion of a large number of lymphocytes, inducing immune paralysis. Th17, Treg, and their balance proportion have garnered growing interest in maintaining immune homeostasis.[19] Although Treg represents less than 10 % of circulating $CD4^+$ T cells, it can limit the overreaction of effector cells, protect surrounding normal tissues from damage, and maintain immune homeostasis.[20,21] Th17 cells are terminally differentiated cells that play an opposite role to Treg, and IL-17 released by Th17 can promote inflammation in sepsis.[22] Studies have found that Th17 can appear in lung tissue to help eliminate bacteria in the bacterial infection model, including *Klebsiella* pneumonia resis-

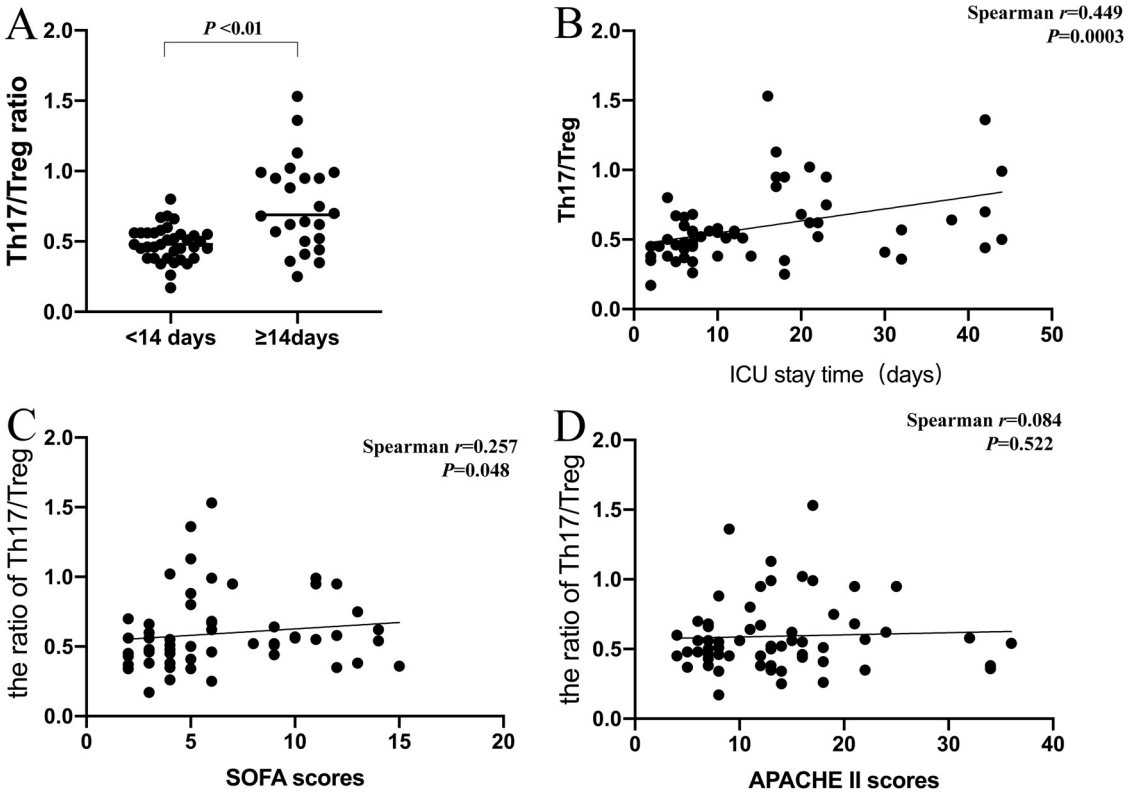

Figure 3. The Th17/Treg ratio and relevance with the LOS, SOFA, and APACHE II scores. A: Comparison of Th17/Treg ratio between patients with an ICU LOS ≥ 14 days (n=24) and < 14 days (n=36). B: Spearman's rank correlation of Th17/Treg ratio with LOS in ICU. C: Spearman's rank correlation of Th17/Treg ratio with SOFA score. D: Spearman's rank correlation of Th17/Treg ratio with APACHE II score.
APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive care units; LOS: Length of stay; SOFA: Sequential Organ Failure Assessment; Th17: T helper type 17; Treg: Regulatory T.

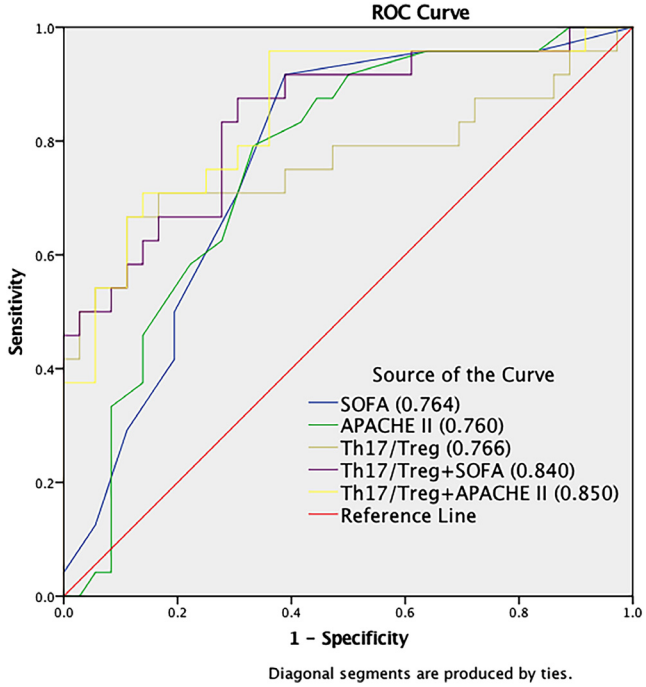

Figure 4. ROC curves for the Th17/Treg ratio. APACHE II, SOFA, Th17/Treg ratio in combination with APACHE II score, and Th17/Treg ratio combined with SOFA score in predicting the LOS in ICU for patients with sepsis.
APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive care unit; LOS: Length of stay; ROC: Receiver operating characteristic; SOFA: Sequential Organ Failure Assessment; Th17: T helper type 17; Treg: Regulatory T.

tant to carbapenem.[23] This is critical to combating bacterial infection in sepsis. Th17 causes autoimmunity and inflammation, whereas Treg inhibits these phenomena and maintains immune homeostasis. The two are functionally antagonistic to each other but also inhibit each other in differentiation, even switching between each other.[24] Th17/Treg ratio variations reflect the immune status in sepsis, but the impact on sepsis pathogenesis and prognosis is controversial.[25] Elevated Th17/Treg ratio in sepsis is positively correlated with both organ impairment and high morbidity and mortality.[26]

One of the most extensively used indices of patient prognosis is the LOS in the ICU. A prolonged stay in the ICU can deplete a hospital's human and material resources. As a result, predicting patient LOS can assist medical practitioners in making medical decisions and evaluating the optimization of medical resources. The LOS in the ICU is an important driver of the total cost of ICU admission, with patients with sepsis accounting for a significant portion.[27] The average cost for patients with prolonged ICU stays is seven times that of patients who do not have prolonged hospitalizations.[28] Patients who stay in the hospital for an extended period develop neuroendocrine and immunological dysfunctions, become increasingly dependent on intensive care treatment, and may require organ support.[29] One of the main diagnostic indications of chronic inflammation-immunosuppression-catabolic syndrome for sepsis was the length of patient's stay in the ICU.[30] Age was found to be an independent risk factor for several diseases, and one study found that the probability of mortality in ICU patients with sepsis increased with age at the fastest rate.[31] Age affects ICU duration in patients with sepsis, and there is a positive association between age and ICU duration. Besides age, clinical ratings such as the APACHE II [32] and SOFA [33] have been widely used in clinical practice to predict outcomes in critically ill patients; early risk assessment of these patients and their prognosis; and reliable monitoring of clinical therapy effects. Limited evidence suggests that the Th17/Treg ratio is associated with the clinical severity and prognosis of sepsis.[25,34,35] The Th17/Treg ratio in sepsis patients with acute respiratory distress syndrome (ARDS), which is a serious lung condition that causes low blood oxygen, can predict 28-day mortality.[36] Currently, there appears to be a lack of accurate biomarkers for predicting ICU LOS in patients with sepsis. The present study found positive associations between the Th17/Treg ratio and ICU LOS, indicating that the greater the Th17/Treg ratio, the longer the LOS for sepsis in the ICU. In patients with sepsis, the Th17/Treg ratio, APACHE II score, and SOFA score were all independent predictors of ICU stay. The Th17/Treg ratio, when paired with the APACHE II score, improved the AUC for predicting ICU LOS. Taken together, our findings strongly imply that the Th17/Treg ratio can reflect the severity of the inflammatory response in sepsis and may be a potential predictor of ICU LOS in patients with sepsis.

Limitations

First, this was a single-center prospective clinical observational study with a small sample size. Our findings must be confirmed by additional research and more patients. Second, because we wanted to understand the early functional immune cells' influence on clinical outcomes, we only assessed the change in functional immunocompetent cells at a single time point. Many factors influence the ICU LOS in patients with sepsis, but not all of them were studied. Furthermore, we did not examine the five patients who died in the ICU. Therefore, further research is needed to incorporate more factors influencing ICU LOS among patients with sepsis.

Conclusions

The Th17/Treg ratio is proportional to the severity of sepsis and can be used to predict ICU stay in patients with sepsis, giving ICU practitioners a new strategy to better care for these patients.

Author Contributions

Yu Wu: Data curation, Writing original draft. **Guosheng Wu:** Visualization, Investigation. **Minyu Li:** Software, Validation. **Yongqing Chang:** Visualization, Investigation. **Miao Yu:** Supervision. **Yan Meng:** Writing review & editing. **Xiaojian Wan:** Conceptualization, Methodology, Software.

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Ethics Statement

This study was reviewed and approved by the Changhai Hospital Ethics Committee (CHEC2019-133). It was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients or their legal proxy before enrollment. All animal experiments were performed according to the guidelines for the Care and Use of Laboratory Animals (Ministry of Health, China, 1998).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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