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Original Article

Imbalance of peripheral blood Th17/Treg increases neutrophil-to-lymphocyte ratio in patients with dermatomyositis

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Abstract: Objective: To explore and analyze the association between peripheral blood Th17/Treg balance and neutrophil-to-lymphocyte ratio (NLR) in patients with dermatomyositis (DM). Methods: Data of 83 DM patients hospitalized between January 2020 to April 2022 were collected, including 43 patients in the active phase (DM active-phase group) and 40 in the remission phase (DM remission-phase group). Additionally, data of 50 healthy subjects who underwent physical examinations and immunologic function testing in the same period were taken as a control group. We detected the percentage of Th17 and Treg cells by flow cytometry, calculated patient's NLR and laboratory test indicators, and analyzed the correlation of Th17/Treg balance with NLR and laboratory indicators. Results: Th17 percentage and Th7/Treg ratio in the DM active-phase group were higher than those in the DM remission-phase group ($P<0.05$), while Treg percentage was lower in the active-phase group than in the remission-phase group ($P<0.05$). The creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), erythrocyte deposition rate (ESR), and NLR in DM patients were significantly higher than those of the control group ($P<0.05$), and were associated with the disease activity of DM. The ratio of Th17/Treg was positively correlated with CK, LDH, AST, ALT, ESR, and NLR ($P<0.05$). NLR was positively correlated with CK, LDH, AST, ALT, and ESR ($P<0.05$). Conclusion: DM patients exhibit changes in immune balance of Th17/Treg and an increase in the NLR. The Th17/Treg ratio in the patients is closely associated with the NLR, which suggests that the immune balance mechanism may interact with the inflammatory response of the body, collectively contributing to the progression of DM.

Keywords: Dermatomyositis (DM), Th17/Treg, AMPK/mTOR autophagy pathway, correlation analysis

Introduction

Dermatomyositis (DM) is a non-suppurative inflammatory condition that affects striated muscles, leading to lymphocyte infiltration. It is an autoimmune disorder characterized by symmetrical muscle weakness in the extremities, neck, or pharynx [1]. It is generally believed that the etiology of DM is associated with genetics, infection, drug, tumor, or environment [2]. T lymphocytes play an important role in innate and acquired immunity, and are considered biological markers for infectious disease. They were also shown to be markers for a systemic inflammatory response. A previous study revealed that a decrease of T lymphocyte count in patients with DM was negatively correlated with the disease activity [3]. Another study showed that DM patients exhibited significantly lower T lymphocyte counts in comparison to healthy controls, and the disease activity increased with the decrease of T lymphocyte counts [4]. As common indicators of inflammation, erythrocyte deposition rate (ESR) and C-reactive protein (CRP) are frequently used to assess the disease activity of autoimmune conditions. However, about half of DM patients have normal ESR and CRP, and only 20% of them have an ESR over 50 mm/h in active phase. This suggests that ESR and CRP levels do not parallel the DM activity [5]. An abnormal count of T lymphocytes may reflect severity of the systemic inflammatory response and immune-related damage. Therefore, compared to other inflammatory markers such as ESR and CRP, T lymphocytes may better reflect the dis-

ease activity in patients. In addition, a decrease in T lymphocytes is a common complication. For instance, steroids and immunosuppressants may cause decreased levels of T lymphocytes in various autoimmune diseases.

A large infiltrate of lymphocytes, especially T cells, occurs in the muscle tissues of the patients. Among them, activated CD4+ T cells (CD3+CD4+) and CD8+ T cells (CD3+CD8+) are the primary types. CD8+ T cells secrete a cytotoxic protein called perforin. This protein can destroy the integrity of the serous membrane, allowing lysosomes to infiltrate and release lysosomes, resulting in the dissolution of muscle fiber bundles and the onset of symptoms [6]. Decreased peripheral blood regulatory T cells are found in a variety of connective tissue diseases, including DM. This suggests that apart from drug factors, the number of T lymphocytes is also reduced in the peripheral blood of patients with DM [7]. Regulatory T cells (Tregs) and Th17 cells are two distinct subsets of immune cells found in peripheral blood. They are characterized by specific membrane surface molecules and nuclear transcription factors. These cell subsets play crucial roles in autoimmune diseases, tumors, and inflammatory diseases [8].

The neutrophil-to-lymphocyte ratio (NLR) is a readily available laboratory measurement. In inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, and autoimmune thyroiditis, NLR can serve as a cost-effective surrogate marker. This study analyzed the correlation between peripheral blood Th17/Treg balance and NLR in DM patients, in order to further understand the immune and inflammatory changes in the patients and provide evidence for early diagnosis and effective treatment of DM from the aspects of immunity and inflammation.

Materials and methods

Case selection and ethical approval

Data of 83 patients with DM hospitalized between January 2020 to April 2022 were collected, including 43 patients in the active phase (DM active-phase group) and 40 patients in the remission phase (DM remission-phase group). Additionally, data of 50 healthy volunteers who underwent physical examinations and immunologic function testing in same period were taken as a control group. This study was approved by the Ethics Committee of Cangzhou Central Hospital. All subjects had provided an informed consent.

Inclusion criteria: ① Patients who met the diagnostic criteria for DM proposed by the European neuromuscular disease center and the American muscle research collaboration group in 2004 [8]; ② Patients who were at least 18 years old; ③ Patients who had not received glucocorticoids, immunosuppressants, or immunomodulatory drugs within 3 months.

Exclusion criteria: ① Patients with comorbidities of mental illness or malignancy; ② Female patients during pregnancy or lactation; ③ Patients with serious primary diseases in liver, kidney, cardiovascular, cerebrovascular, or hematopoietic system; ④ Patients with rheumatic immune diseases, such as systemic lupus erythematosus or rheumatoid arthritis; ⑤ Patients who have recently used glucocorticoids and/or immunosuppressants; ⑥ Patients with incomplete clinical data.

Data collection

Patients' clinical data such as gender, age, and body mass index (BMI) were collected. The percentage of Th17 cells, percentage of Treg cells, and the Th17/Treg ratio in peripheral blood were calculated. The biochemical values, such as ESR, neutrophil counts, lymphocyte counts, creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were collected, and the NLR was calculated accordingly.

The test reagents were purchased from Roche, Switzerland. The percentage of Th17 and Treg cells was detected by BD flow cytometry, and the antibodies included murine anti-human CD25-FITC (Invitrogen, 11-0257-41), CD4-FITC (Invitrogen, 11-0041-82), mouse anti-human IgG1-PE (Abcam company, ab99776), and IgG1-FITC (Abcam company, ab98692). The biochemical indicators were detected by an XE-2100 automatic blood cell analyzer from Sysmex, Japan.

Table 1. Comparison of basic data

Clinical data	DM active-phase group (n=43)	DM remission-phase group (n=40)	Control group (n=50)	F/X^2	P
Gender (n, %)					
Male	20 (46.51)	16 (40.00)	24 (48.00)	0.625	0.732
Female	23 (53.49)	24 (60.00)	26 (52.00)		
Age (years, $\bar{x}\pm s$)	49.28±6.01	48.73±9.36	48.90±7.22	0.059	0.305
BMI (kg/m^2, $\bar{x}\pm s$)	23.18±2.16	23.54±2.97	23.09±3.04	0.305	0.738

Note: BMI, body mass index; DM, Dermatomyositis.

Follow-up check

The 83 DM patients were followed up until March 31, 2023 or the death of patients. Follow-up methods included revisits to the hospital, telephone, WeChat, and email.

Statistical analysis

Data processing and analysis was conducted using SPSS 25.0. The measured data were expressed as ($\bar{x}\pm s$). Comparison of the measured data among three groups was performed by variance analysis, and the post-hoc comparison was performed by LSD-t test. Counted data were expressed as percentages and compared by χ^2 test. Correlation analysis was performed by Pearson correlation analysis. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of Th17/Treg and NLR in the active stage of DM, as well as their predictive value of poor prognosis. P<0.05 was considered significant.

Results

Comparison of clinical data

There was no significant difference in gender, age, or BMI among the DM active-phase group, the DM remission-phase group, and the control group (all P>0.05; **Table 1**).

Comparison of peripheral blood Th17/Treg ratio among the DM patients

The Th17 percentage and Th7/Treg ratio in the DM active-phase group were higher than those of the DM remission-phase group (both *P< 0.05*), while the Treg percentage was lower in the active-phase group than that in the remission-phase group (*P<0.05*; **Figure 1**).

Comparison of biochemical indicators among the three groups

There were significant differences in CK, LDH, AST, ALT, ESR and NLR among the DM active-phase group, the DM remission-phase group, and the control group (all *P<0.05*). CK, LDH, AST, ALT, ESR and NLR in the DM groups were significantly higher than those in the control group (all P<0.05). Moreover, CK, LDH, AST, ALT, ESR, and NLR in the DM active-phase group were significantly higher than those in the DM remission-phase group (all P<0.05). See **Table 2**.

Correlation analysis of Th17/Treg ratio with CK, LDH, AST, ALT, ESR, and NLR

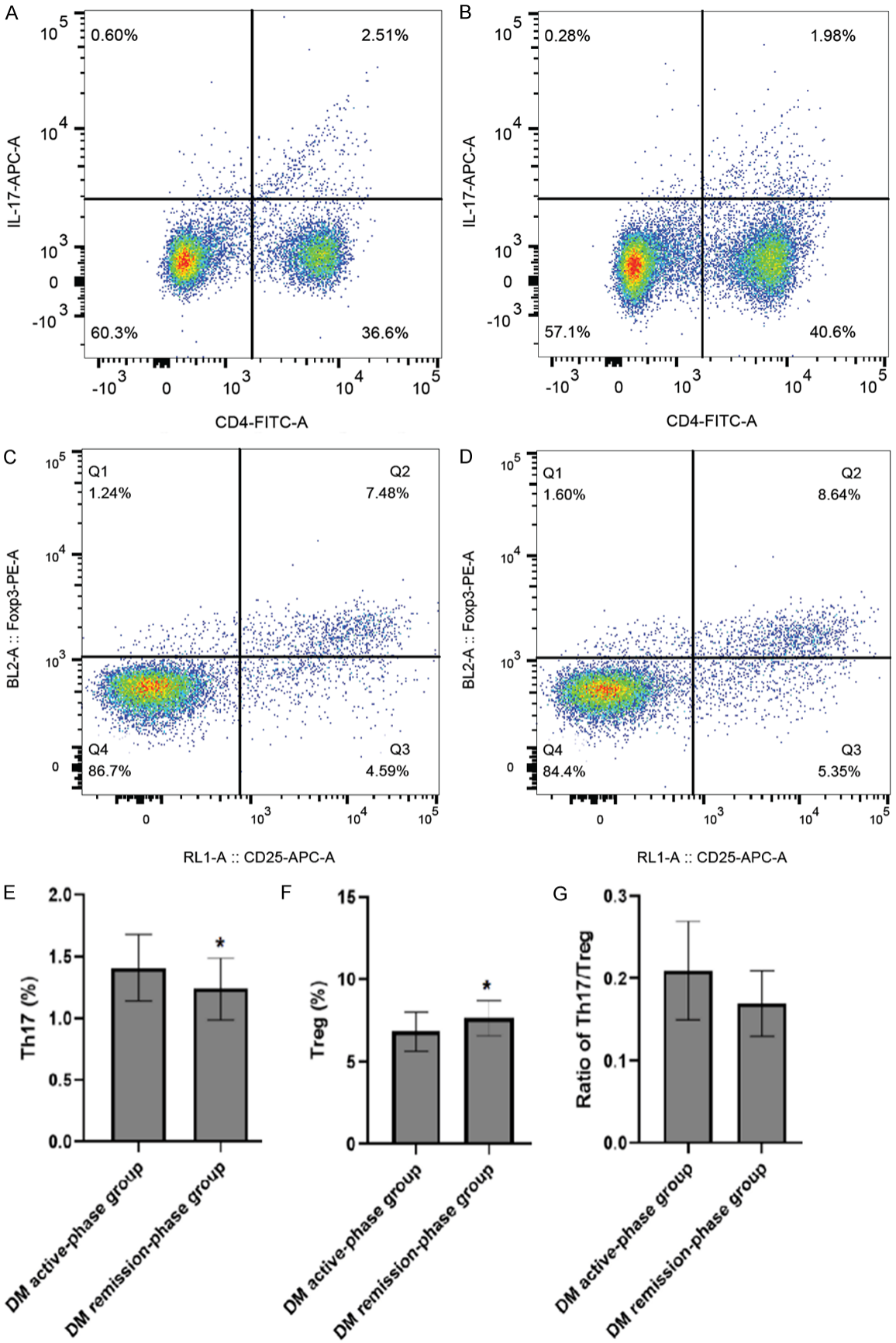
The results of correlation analysis showed a significant positive correlation (all *P<0.05*) between the Th17/Treg ratio and CK, LDH, AST, ALT, ESR, and NLR, respectively, as shown in **Figure 2**.

Correlation analysis of NLR with CK, LDH, AST, ALT, and ESR

The results of correlation analysis demonstrated a significant positive correlation (*P<0.05*) between NLR and CK, LDH, AST, ALT, and ESR, respectively, as shown in **Figure 3**.

ROC curve analysis of the diagnostic value of Th17/Treg and NLR in active DM

The diagnostic value of Th17/Treg ratio and NLR in active DM was analyzed by ROC curve. The results showed that the area under the curves (AUCs) of Th17/Treg ratio and NLR were 0.940 (P=0.000, 95% CI: 0.900~0.979) and 0.977 (P=0.000, 95% CI: 0.947~1.000), respectively. See **Figure 4**.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DM remission-phase group
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Treg (%)
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DM remission-phase group
G
Ratio of Th17/Treg
DM active-phase group
DM remission-phase group

Figure 1. Percentage of Th17/Treg cells in peripheral blood. A: Th17 cells in DM active-phase group; B: Th17 cells in DM remission-phase group; C: Treg cells in DM active-phase group; D: Treg cells in DM remission-phase group; E: Comparison of Th17 cells between the two DM groups; F: Comparison of Treg cells between the two DM groups; G: Comparison of Th17/Treg ratio between the two DM groups. Compared to DM active-phase group, $^{*}P<0.05$. DM, Dermatomyositis.

Table 2. Comparison of biochemical indexes among the three groups

Index	DM active stage group (n=43)	DM remission stage group (n=40)	Control group (n=50)	F	P
CK (U/L)	218.39±60.49	179.47±35.20*	35.43±7.95$^{*,\#}$	276.579	0.000
LDH (U/L)	329.52±95.48	276.70±61.27*	169.58±48.59$^{*,\#}$	62.699	0.000
AST (U/L)	62.93±12.52	31.50±9.25*	19.85±3.47$^{*,\#}$	277.164	0.000
ALT (U/L)	53.96±7.96	29.06±7.26*	16.52±3.28$^{*,\#}$	407.574	0.000
ESR (mm/h)	16.48±5.10	14.47±3.97*	11.28±3.04$^{*,\#}$	19.332	0.000
NLR	4.72±1.25	3.64±0.98*	1.49±0.47$^{*,\#}$	144.516	0.000

Note: Compared to DM active stage group, $^{*}P<0.05$; Compared to DM remission stage group, $^{\#}P<0.05$. DM, Dermatomyositis; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte deposition rate; NLR, neutrophil-to-lymphocyte ratio.

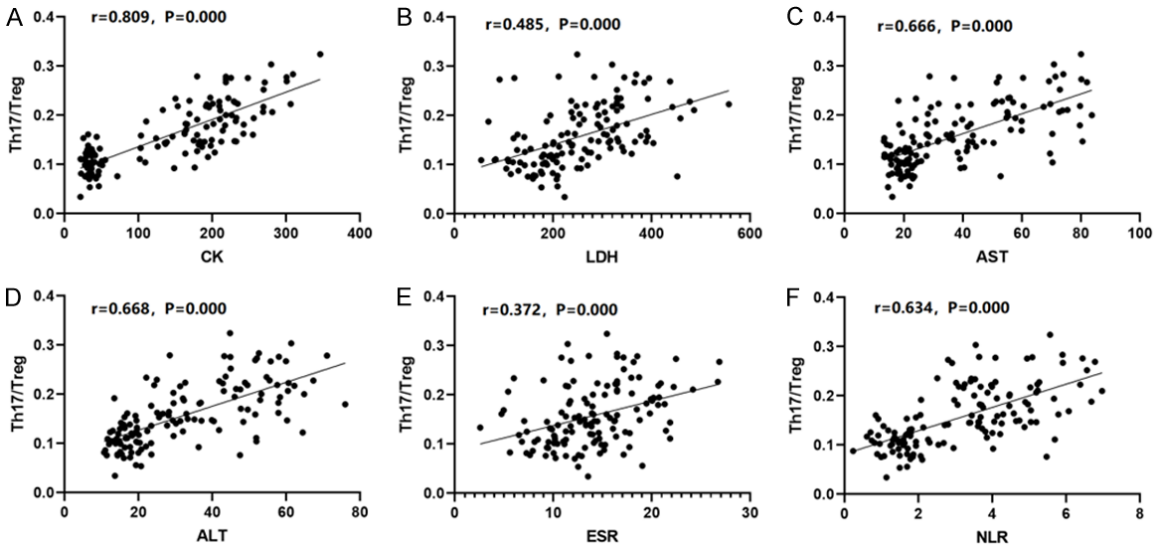

Figure 2. Correlation analysis between Th17/Treg ratio and CK, LDH, AST, ALT, ESR, and NLR. A: There was a significant positive correlation between CK and Th17/Treg ratio; B: There was a significant positive correlation between LDH and Th17/Treg ratio; C: AST was positively correlated with Th17/Treg ratio; D: ALT was positively correlated with Th17/Treg ratio; E: There was a significant positive correlation between ESR and Th17/Treg ratio; F: NLR was positively correlated with Th17/Treg ratio. CK, Creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio.

ROC curve analysis of the predictive value of Th17/Treg and NLR for death in patients with DM

Eight of the 83 DM patients died during the follow-up period. The predictive value of Th17/Treg and NLR for death in DM patients was analyzed by ROC curve, which exhibited that the AUCs of Th17/Treg ratio and NLR were 0.819 (P=0.001, 95% CI: 0.712~0.927) and 0.738 (P=0.015, 95% CI: 0.594~0.928), respectively. See **Figure 5**.

Discussion

The pathogenesis of DM is complex, and current studies suggest that the main mechanisms of DM involve a combination of immune

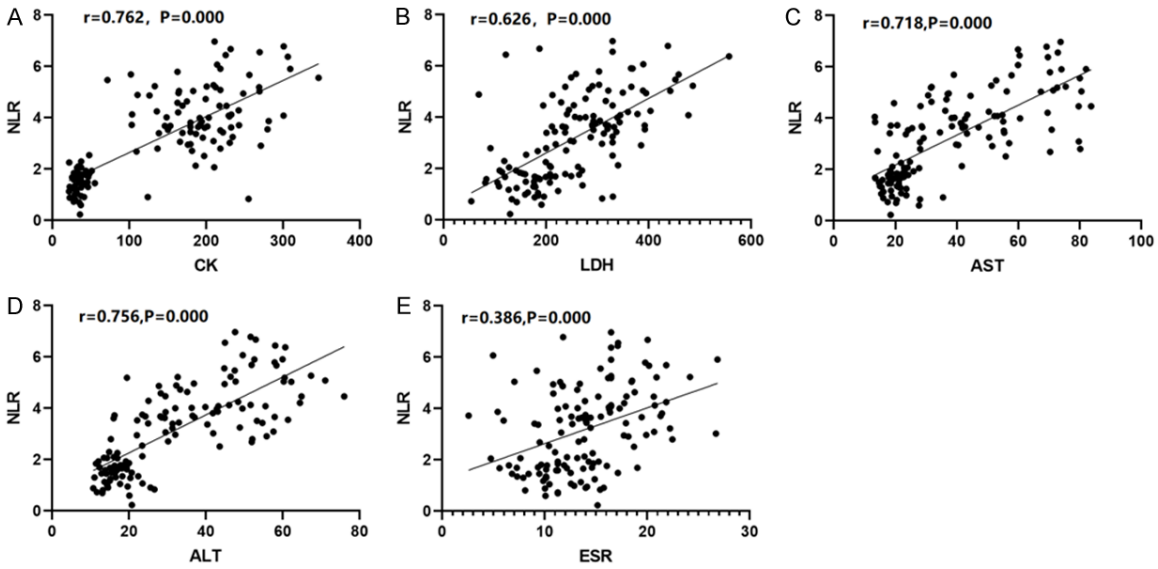

Figure 3. Correlation analysis between NLR and CK, LDH, AST, ALT, and ESR. A: CK was positively correlated with NLR, r=0.762, *P<0.05*; B: LDH was positively correlated with NLR, r=0.626, *P<0.05*; C: AST was positively correlated with NLR, r=0.718, *P<0.05*; D: ALT was positively correlated with NLR, r=0.756, *P<0.05*; E: ESR was positively correlated with NLR, r=0.386, *P<0.05*. CK, Creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte deposition rate; NLR, neutrophil-to-lymphocyte ratio.

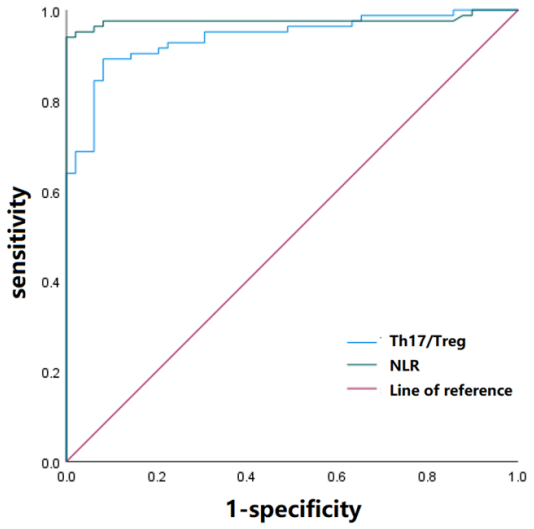

Figure 4. ROC curve analysis of the diagnostic value of Th17/Treg and NLR for DM. DM, Dermatomyositis; ROC, Receiver operating characteristic.

and non-immune factors [9]. The immune mechanism is critical. According to the traditional view, DM is an autoimmune disease which caused by the excessive activation of effector T cells. In recent years, immune tolerance caused by the imbalance of the quantity and functionality of Treg cells has been considered to play a key role in autoimmune diseases [10, 11]. The CD4+ lymphocyte subset includes cells such as Th17 and Treg. Th17 cells are derived from CD4+ T cells induced by IL-23 and IL-6, and can secrete the cytokine IL-17. Treg cells can differentiate TGF-β and play immunosuppressive and immunomodulatory roles. Under normal circumstances, Th17 and Treg cells are in a state of dynamic balance, and the imbalance of their ratio is often associated with the development of various diseases [12, 13]. Research has shown that the Th17 and Treg cells are increased in peripheral blood of children with active systemic juvenile idiopathic arthritis. The imbalance of Th17 and Treg is involved in the immune regulation mechanism of children, and is closely associated with the severity of the disease [14, 15]. In addition, studies have shown that the proportion of peripheral blood Treg, Th17, and Th9 is abnormal in patients with immune thrombocytopenia. Such patients have abnormal expression levels of cytokines TGF-β, IL-17, and IL-9, suggesting that Treg, Th17, and Th9 cells may play an important role in immune pathogenesis [16, 17].

In addition, the Th17/Treg ratio was found to be significantly increased in patients with active DM. The results are similar to those reported by scholars [18, 19], with Th17 and Treg cells

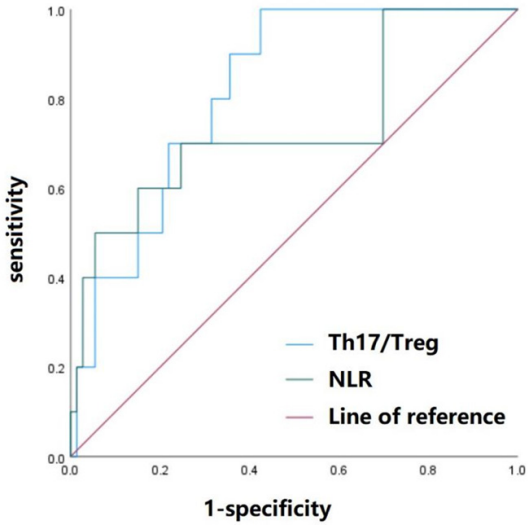

Figure 5. ROC curve analysis of the predictive value of Th17/Treg and NLR for death in DM patients. DM, Dermatomyositis; NLR, neutrophil-to-lymphocyte ratio; ROC, Receiver operating characteristic.

being two subsets found to have specific membrane surface molecules and nuclear transcription factors. In autoimmune diseases, the dynamic balance of Th17 and Treg is disrupted to the side of Th17 cells, which leads to the development of DM.

Peripheral blood NLR is a simple marker of subclinical inflammation. It is a value that can be obtained by dividing the absolute number of neutrophils (N) by the absolute number of lymphocytes (L). NLR is an indicator that can be easily obtained from routine blood tests [20, 21]. Reports have shown that abnormal NLR is associated with cardiovascular disease, liver disease, autoimmune disease, and tumors. [22, 23]. A study of 52 patients with primary Sjogren's syndrome (pSS) found that NLR was elevated in patients with pSS and positively correlated with the disease activity index of pSS ($r=0.44$, $P<0.01$) [24]. Comparison between patients with systemic lupus erythematosus (SLE) and healthy controls revealed that the difference in N count and SLE was not significant ($P=0.74$), while L count was significantly decreased ($P=0.000$), and NLR was significantly increased ($P=0.007$) [25]. Therefore, it can be inferred that NLR reflects the state of systemic inflammation, and its change may be associated with the disease activity of DM.

The results of this study showed that Th17/Treg ratio and NLR have a significant positive correlation. In addition, Th17/Treg was positively correlated with CK, LDH, AST, ALT, and ESR in DM patients, and NLR was positively correlated with CK, LDH, AST, ALT, and ESR in the patients. These results suggest that Th17/Treg and NLR are associated with the development and progression of DM. Furthermore, the influence of immune and inflammatory responses in the progression of DM may be one of the mechanisms of DM [26-28]. ROC results showed that the AUCs of Th17/Treg ratio and NLR were 0.940 and 0.977, respectively, indicating that both Th17/Treg and NLR have a good diagnostic value for DM.

However, due to the small scale of study, there may be a certain level of bias in our results. As this study is a retrospective analysis, limited clinical data were available, so the specific mechanisms of DM were not deeply discussed. In future studies, we can expand the sample size and analyze the mechanism of the development and progression of DM through prospective research. We can also obtain more significant sensitive indicators of DM, providing beneficial clinical guidance for the formulation of individualized treatment plans for patients and the observation of drug efficacy [29, 30].

In summary, DM patients exhibited changes in the immune balance of Th17/Treg and an increase in the NLR. The Th17/Treg ratio in DM patients is closely associated with the NLR, which suggests a potential interplay between immune balance mechanisms and the inflammatory response of the body, jointly driving the progression of DM.

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Disclosure of conflict of interest

None.

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