· 临床研究 ·

NLR和SII对抗MDA5抗体阳性皮肌炎伴快速进展型肺炎的预后价值

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［摘　要］ **目的**：评估中性粒细胞与淋巴细胞比值（neutrophil-to-lymphocyte ratio，NLR）和全身免疫炎症指数（systemic immune-inflammation index，SII）在预测抗黑色素瘤分化相关基因5阳性皮肌炎（anti-melanoma differentiation-associated gene 5-positive dermatomyositis，抗MDA5$^+$ DM）患者发展为快速进展型间质性肺病（rapidly progressive interstitial lung disease，RPILD）的预测价值。**方法**：回顾性分析2019年3月—2023年9月南京医科大学第一附属医院124例抗MDA5$^+$ DM患者的临床和实验室资料，采用Cox回归分析确定与RPILD发展和病死率相关的独立危险因素。进行受试者工作特征（receiver operating characteristic，ROC）曲线分析，以确定预测不良结局的最佳临界值。**结果**：124例患者中，36例（29.03%）发生RPILD，39例（31.45%）在随访期间死亡。多因素Cox回归分析发现NLR升高是RPILD的独立危险因素，而SII升高与病死率独立相关。根据ROC曲线确定，NLR>6.12是RPILD的预测因子，SII>875.79时死亡风险增加。**结论**：NLR和SII是抗MDA5$^+$ DM患者简单、经济、可靠的预后指标，为临床管理和风险分层提供了有价值的指导。

［关键词］ 抗黑色素瘤分化相关基因5阳性皮肌炎；中性粒细胞与淋巴细胞比值；快速进展型间质性肺病；全身免疫炎症指数
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The predictive value of NLR and SII in anti-MDA5 antibody-positive dermatomyositis with rapidly progressive interstitial lung disease

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［**Abstract**］ **Objective:** To evaluate the predictive value of the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) in predicting patients with anti-melanoma differentiation-associated gene 5-positive (anti-MDA5$^+$) dermatomyositis (DM) develop into the rapidly progressive interstitial lung disease (RPILD). **Methods:** We retrospectively analyzed the clinical and laboratory data of 124 anti-MDA5$^+$ DM patients from the First Affiliated Hospital of Nanjing Medical University between March 2019 and September 2023. We identified independent risk factors associated with the development and mortality of RPILD with the Cox regression analysis, and determined the optimal cut-off values for predicting adverse outcomes with the receiver operating characteristic (ROC) curve analysis. **Results:** Among the 124 patients, 36 patients (29.03%) developed RPILD, and 39

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patients（31.45%） died during the follow-up period. The results of multivariate Cox regression analysis showed that the elevated NLR was an independent risk factor for RPILD development, while the elevated SII expression was independently associated with the increased mortality of RPILD. Based on the ROC curve analysis, NLR>6.12 was a predictor for RPILD, and SII >875.79 was associated with increased mortality risk of RPILD. **Conclusion:** Both NLR and SII are accessible, cost-effective, and reliable prognostic indicators for the prognosis of patients with anti-MDA5$^+$ DM, providing a valuable guidance for clinical management and risk stratification of the disease.

[**Key words**] anti-melanoma differentiation-associated gene 5-positive dermatomyositis; neutrophil-to-lymphocyte ratio; rapidly progressive interstitial lung disease; systemic immune-inflammation index

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Anti-melanoma differentiation-associated gene 5-positive（anti - MDA5$^+$）dermatomyositis（DM）is a unique subtype of idiopathic inflammatory myositis characterized by a high risk of developing interstitial lung disease（ILD）[1]. Among these patients, approximately 38%−71% of patients develop into rapidly progressive interstitial lung disease（RPILD）[2-3], a severe and life-threatening complication that is often resistant to current treatment. Despite aggressive therapy, the all-cause mortality rate within six months of the patients remains as high as 40%−60%[4-6]. Several biomarkers, including the elevated expression of serum ferritin（SF）[7-8], Krebs Von den Lungen-6（KL-6）[9], and lactate dehydrogenase（LDH）[10], as well as the presence of anti-Ro52 antibodies[11-12], have offered valuable insights into the progression of anti-MDA5$^+$ DM. However, because of the complexity and inherent variability of these markers, it highlights the urgent need for other novel and more reliable biomarkers that better predict RPILD of anti-MDA5$^+$ DM patients in clinical practice.

The neutrophil - to - lymphocyte ratio（NLR）is a cost-effective and readily available indicator of systemic inflammation, which is increasingly recognized in various inflammatory and autoimmune diseases, including sepsis, pneumonia, corona virus disease 2019（COVID-19）, rheumatoid arthritis（RA）, systemic lupus erythematosus, etc.[13-14]. High NLR was associated with poor prognosis in conditions like idiopathic pulmonary fibrosis, primary Sjögren's syndrome, and RA - associated ILD[10,15-20].

Similarly, the systemic immune - inflammation index（SII）, calculated as（platelet count × neutrophil count）/lymphocyte count, is another promising biomarker that reflects the balance between immune response and inflammation[13, 21- 24]. The SII expression was associated with disease activity of RA, adult-onset Still's disease, and ankylosing spondylitis, and it also served as a prognostic indicator in conditions such as psoriasis, psoriatic arthritis, and anti - neutrophil cytoplasmic antibody ANCA-associated vasculitis[22-27].

Studies found that the cytokine profiles of lung tissues observed in patients with anti-MDA5$^+$ DM-associated RPILD had similarities to those seen in severe cases of COVID - 19, where both NLR and SII were proven to be reliable predictors of disease severity and mortality[28-31]. These similarities suggest that NLR and SII may be valuable and easily integrated markers in routine clinical practice for monitoring inflammation and predicting outcomes in anti - MDA5$^+$ DM patients, which remains to be further explored. Therefore, the current study investigated the potential of both NLR and SII in predicting the prognosis of patients with anti-MDA5$^+$ DM.

1 Materials and methods

1.1 Study subjects

The current single - center retrospective study was conducted at the First Affiliated Hospital of Nanjing Medical University and enrolled patients with anti - MDA5$^+$ DM who received inpatient treatment between March 2019 and September 2023. All DM cases met the diagnostic criteria of Bohan - Peter 1975 or Sontheimer[32- 33] and were positive for MDA5 antibodies. The diagnosis of ILD was based on respiratory symptoms, physical examination, and high - resolution CT（HRCT）findings[34]. RPILD was defined as a progres-

sive worsening of respiratory distress over one month, along with one of the following conditions[35-36]: ① acute worsening of dyspnea requiring hospitalization or supplemental oxygen; ② a decrease in forced vital capacity (FVC) of more than 10% or a decrease in diffusing capacity of the lungs for carbon monoxide (DLCO) with FVC greater than 15%; ③ an increase in the extent of interstitial lung lesions over 20% based on chest HRCT; ④ respiratory failure or a decrease in partial pressure of oxygen over 10 mmHg based on the arterial blood gas analysis. Two professional radiologists evaluated all HRCT images. All patients enrolled in the study were sampled for laboratory test prior to receiving systemic drug therapy from the center. The current study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University (Jiangsu Provincial Hospital) (ethics No.2020-SR-265).

1.2 Data collection

Demographic, clinical, and laboratory data as well as baseline glucocorticoid doses were collected and analyzed. Baseline laboratory data included white blood cell count (WBC), absolute neutrophil count (NEU), absolute lymphocyte count (LYC), absolute monocyte count (MON), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum ferritin (SF), fibrinogen (FIB), D-dimer (D-D), myositis-specific antibodies (MDA5 antibodies), and myositis-associated antibodies (Ro52 antibodies). All glucocorticoids were converted to prednisone-equivalent doses. Follow-up time was calculated from the first visit to our center to death or the last follow-up. NLR was defined as the NEU divided by LYC. SII was defined as (PLT×NEU)/LYC[37].

1.3 Statistical analysis

All data analyses were performed using R version 4.1.3. The Shapiro-Wilk test was used for normality testing. The *t*-test or Wilcox rank-sum test was applied for continuous variables with skewed distributions, and the Chi-square test or Fisher's exact test was used for categorical variables. The data were presented as follows: mean ± standard deviation ($\bar{x} \pm s$) for normally distributed continuous variables, median and interquartile range [$M(P_{25}, P_{75})$] for non-normally distributed continuous variables, and numbers (percentages) [n (%)] for categorical variables. The univariate Cox analysis was performed followed by multivariate analysis. Stepwise regression was used to screen variables based on univariate analysis ($P < 0.100$) to identify independent risk factors affecting RPILD and survival. The diagnostic and prognostic values of NLR and SII were calculated using the receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). Survival analysis was calculated using the Kaplan-Meier method, and the log-rank test was used to compare survival curves. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered statistically significant.

2 Results

2.1 Baseline clinical characteristics

A total of 126 patients were initially enrolled in the current study, while two cases with gastric adenocarcinoma and pancreatic adenocarcinoma (no new tumor events observed during the follow-up period) were included, two cases excluded because of missing core data. The mean follow-up duration in the current study was 13.23 months, with a median disease duration of 5.36 months. The mean age of the patients was (51.82±13.33) years, and 49 cases (49/124, 39.52%) were male. During the follow-up period, 12 patients (12/124, 9.68%) did not develop ILD, 75 patients (75/124, 60.48%) developed ILD but not RPILD, and 37 patients (37/124, 29.84%) developed RPILD. The mortality rate in patients with RPILD was 78.38%, whereas in the non-RPILD patients, it was 21.62% ($P < 0.001$). Meanwhile, the 3-month, 6-month and 12-month all-cause mortality rate were found to have significantly significant differences between the two groups ($P < 0.001$) (Table 1).

The patients were divided into the non-RPILD and RPILD groups. We found statistically significant differences between the two groups in terms of age, LYC, PLT, AST, LDH, CRP, SF, NLR and SII. Specifically, compared with those in the non-RPILD group, patients in the RPILD group were older [(55.73 ±

12.57）years *vs.*（50.16±13.36）years，*P*=0.03］，had lower LYC levels（median：0.73×10^9/L *vs.* 0.98×10^9/L，*P*=0.003），lower PLT levels（median：168.00×10^9/L *vs.* 179.00×10^9/L，*P*=0.023），higher NLR levels（6.74 *vs.* 3.92，*P*=0.003），higher SII levels（1 206.81 *vs.* 716.83，*P*=0.014），higher AST levels（median：62.40 U/L *vs.* 48.60 U/L，*P*=0.005），higher LDH levels（median：344.00 U/L *vs.* 288.00 U/L，*P*=0.012），higher CRP levels（median：9.15 mg/L *vs.* 3.96 mg/L，*P*=0.001），and higher SF levels（median：977.70 mg/mL *vs.* 547.20 mg/mL，*P*=0.001）（Table 1）.

Furthermore，we observed a significant difference in myositis-associated antibodies，with a higher rate of anti-Ro52 antibody positivity in the RPILD group than in the non-RPILD group（86.49% *vs.* 67.82%，*P*=0.044）. Baseline data of glucocorticoid（GC）usage also differed significantly between the two groups（*P*=0.014）. In the non-RPILD group，27 cases（31.03%）used no GC at baseline，26 cases（29.89%）used high-dose GC，and only 1 case（1.15%）used mega-dose GC. In contrast，in the RPILD group，17 cases（45.95%）used no GC at baseline，16 cases（43.24%）used high-dose GC，and none used mega-dose GC. There were no statistically significant differences between the two groups regarding the percentage of males as well as the levels of WBC，NEU，MON，ALT，CK，ESR，FIB，D-D，baseline average dose of GC and anti-MDA5 antibodies（Table 1）.

2.2 Risk factor analysis for RPILD and mortality in anti-MDA5$^+$ DM

In the current study，we analyzed the risk factors for developing RPILD and mortality in patients with anti-MDA5$^+$ DM，respectively. Univariate analysis revealed that age and serum biomarkers（i.e.，NLR，PLR，SII，SIRI，and AISI）were positively correlated with the risk of developing RPILD［hazard ratio（HR）>1，*P* < 0.05，respectively］. A higher LMR was identified as a protective factor against RPILD（Table 2）. In the multivariate Cox regression analysis，a high NLR remained the strongest independent risk factor for RPILD［HR=1.11，95% confidence interval（CI）：1.03-1.18，*P*=0.003］（Table 2）.

To assess the risk of mortality，variables that showed significant differences in the univariate analysis（i.e.，age，NLR，LMR，SII，SIRI，AISI，and myasthenia）were included in the multivariate model. The multivariate Cox regression analysis indicated that a high SII was an independent risk factor for mortality（HR=1.00，95% CI：1.00-1.00，*P* < 0.05）. Increasing age was also a significant determinant of mortality risk（Table 3）.

2.3 Analysis of the value of NLR and SII on the prognosis of anti-MDA5$^+$ DM

NLR and SII were identified as independent risk factors for poor prognosis，specifically for the development of RPILD and overall survival，respectively. The ROC curve analysis was used to determine the optimal cut-off values for predicting RPILD and survival（Figure 1A，B）. The AUC for NLR in predicting RPILD was 0.67，with a cut-off value of 6.12. This cut-off value indicated a sensitivity of 56.76% and a specificity of 77.01%，suggesting moderate accuracy. Similarly，the AUC for NLR in predicting survival was 0.73，with the same cut-off value of 6.12，reflecting a sensitivity of 62.16% and a specificity of 79.31%，indicating a good accuracy. Regarding SII，the AUC for predicting RPILD was 0.64，with a cut-off value of 1 200.82，demonstrating a sensitivity of 51.35% and a specificity of 78.16%. The AUC for SII predicting survival was 0.69，with the cut-off value of 875.79，reflecting a sensitivity of 72.97% and a specificity of 62.07%，indicating that SII was a moderately accurate predictor（Table 4）.

2.4 Survival analysis of anti-MDA5$^+$ DM

Among patients with anti-MDA5$^+$ DM，there was a significant association between SII，NLR and RPILD（*P*=0.001 and *P* < 0.001）. When stratified by the optimal cut-off value of SII，the Kaplan-Meier survival curve revealed that patients with SII>1 200.82 had a significantly lower incidence of non-RPILD within one year，compared to those with SII≤1 200.82（*P*=0.001，Figure 2A）. Figure 2B showed that patients with an NLR≤6.12 had a significantly lower incidence of non-RPILD than those with an NLR>6.12（*P* < 0.001）.

Furthermore，SII and NLR were found to be significantly associated with mortality（*P* < 0.001）. Patients with SII>875.79 had a significantly lower survival rate within one year，compared to those with SII≤875.79（Figure 3A）. While，patients with NLR>6.12 had a lower survival rate than those with NLR<6.12（Figure

表1　Anti-MDA5$^+$ DM患者的临床特征

Table 1　Clinical characteristics of anti-MDA5$^+$ DM patients

Variable	Total(n=124)	Non-RPILD(n=87)	RPILD(n=37)	P	Survival(n=87)	Death(n=37)	P
Age(years,$\bar{x} \pm s$)	51.82 ± 13.33	50.16 ± 13.36	55.73 ± 12.57	0.030	49.32 ± 13.32	57.70 ± 11.47	0.001
Male[n(%)]	49.00(39.52)	32.00(36.78)	17.00(45.95)	0.451	33.00(37.93)	16.00(43.24)	0.724
WBC[10^9/L,$M(P_{25},P_{75})$]	5.08(3.85,7.10)	5.06(3.89,6.84)	5.87(3.60,7.39)	0.561	4.89(3.82,6.69)	6.01(4.13,8.39)	0.121
NEU[10^9/L,$M(P_{25},P_{75})$]	3.68(2.56,5.19)	3.58(2.45,4.84)	4.21(2.84,5.52)	0.277	3.36(2.35,4.59)	4.96(2.85,7.15)	0.006
LYC[10^9/L,$M(P_{25},P_{75})$]	0.85(0.56,1.10)	0.98(0.63,1.17)	0.73(0.44,0.87)	0.003	0.98(0.63,1.19)	0.73(0.45,0.85)	0.002
MON[10^9/L,$M(P_{25},P_{75})$]	0.47(0.32,0.60)	0.47(0.32,0.60)	0.47(0.29,0.59)	0.844	0.46(0.32,0.60)	0.50(0.32,0.59)	0.723
PLT[10^9/L,$M(P_{25},P_{75})$]	178.00(140.75,223.25)	179.00(148.00,224.00)	168.00(134.00,221.00)	0.023	179.00(143.00,223.00)	171.00(134.00,223.00)	0.563
ALT[U/L,$M(P_{25},P_{75})$]	50.70(27.90,94.97)	46.80(26.10,87.70)	51.20(29.75,126.75)	0.337	45.70(24.90,79.70)	58.80(31.00,134.00)	0.042
AST[U/L,$M(P_{25},P_{75})$]	53.40(31.60,83.40)	48.60(30.65,73.15)	62.40(38.25,130.75)	0.005	44.30(29.20,67.90)	69.60(45.80,135.00)	0.004
LDH[U/L,$M(P_{25},P_{75})$]	304.50(253.75,389.00)	288.00(248.00,353.50)	344.00(280.00,425.50)	0.012	287.00(247.00,346.00)	344.00(270.00,462.00)	0.005
CK[U/L,$M(P_{25},P_{75})$]	45.50(27.25,1 080.00)	42.00(27.00,104.50)	71.00(31.00,119.50)	0.113	40.00(27.00,77.00)	74.00(33.00,168.00)	0.017
ESR[mm/h,$M(P_{25},P_{75})$]	34.50(22.00,51.00)	34.00(22.00,51.00)	36.00(21.00,62.00)	0.773	33.00(22.00,50.25)	41.50(19.50,62.00)	0.334
CRP[mg/L,$M(P_{25},P_{75})$]	4.60(2.57,10.43)	3.96(2.22,7.39)	9.15(3.88,23.50)	0.001	4.02(2.20,7.39)	8.70(3.16,20.10)	0.003
SF[ng/mL,$M(P_{25},P_{75})$]	687.00(295.75,1 176.03)	547.20(227.50,873.60)	977.70(738.65,1 636.05)	0.001	543.65(196.53,875.25)	1 030.75(732.62,1 697.10)	<0.001
FIB(g/L,$\bar{x} \pm s$)	3.24 ± 0.98	3.15 ± 0.87	3.43 ± 1.20	0.220	3.02(2.54,3.65)	3.38(2.42,3.94)	0.572
D-D[mg/L,$M(P_{25},P_{75})$]	0.77(0.48,1.40)	0.67(0.45,1.17)	1.07(0.52,1.76)	0.099	0.67(0.43,1.25)	0.95(0.59,1.62)	0.046
SII[$M(P_{25},P_{75})$]	847.00(478.80,1 363.50)	716.83(454.71,1 169.00)	1 206.81(634.36,1 916.57)	0.014	694.55(445.02,1 131.77)	1 278.43(746.85,1 994.61)	0.001
NLR[$M(P_{25},P_{75})$]	4.25(3.03,7.15)	3.92(2.72,5.44)	6.74(4.06,10.78)	0.003	3.82(2.57,5.38)	6.89(4.24,11.73)	<0.001
GC[mg/d,$M(P_{25},P_{75})$]	16(0,40)	16(0,32)	8(0,60)	0.980	12(0,32)	32(0,60)	0.071
GC[n(%)]				0.014			0.029
0 mg/d	44.00(35.48)	27.00(31.03)	17.00(45.95)		31.00(35.63)	13.00(35.14)	
0−15 mg/d	16.00(12.90)	13.00(14.94)	3.00(8.11)		14.00(16.09)	2.00(5.41)	
15−30 mg/d	21.00(16.94)	20.00(22.99)	1.00(2.70)		18.00(20.69)	3.00(8.11)	
30−100 mg/d	42.00(33.87)	26.00(29.89)	16.00(43.24)		24.00(27.59)	18.00(48.65)	
>100 mg/d	1.00(0.81)	1.00(1.15)	0.00(0)		0.00(0)	1.00(2.70)	
Anti-MDA5				0.370			0.972
+++	72.00(58.06)	49.00(56.32)	23.00(62.16)		51.00(58.62)	21.00(56.76)	
++	22.00(17.74)	14.00(16.09)	8.00(21.62)		15.00(17.24)	7.00(18.92)	
+	30.00(24.19)	24.00(27.59)	6.00(16.22)		21.00(24.14)	9.00(24.32)	
Anti-Ro52$^+$[n(%)]	90.00(72.58)	59.00(67.82)	32.00(86.49)	0.044	59.00(67.82)	31.00(83.78)	0.109
RPILD[n(%)]	37.00(29.83)	−	−	−	8.00(1.15)	29.00(78.38)	0.006
Death[n(%)]	37.00(29.83)	8.00(21.62)	29.00(78.38)	<0.001			
3-month mortality rate[n(%)]	14.00(11.29)	2.00(2.30)	12.00(37.50)	<0.001			
6-month mortality rate[n(%)]	27.00(21.77)	4.00(4.55)	23.00(63.89)	<0.001			
12-month mortality rate[n(%)]	34.00(27.42)	7.00(8.05)	27.00(72.97)	<0.001			

WBC: white blood cell count; NEU: absolute neutrophil count; LYC: absolute lymphocyte count; MON: absolute monocyte count; PLT: platelet count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; CK: creatine kinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SF: serum ferritin; FIB: fibrinogen; D-D: D-dimer; GC: glucocorticoid.

表2 anti-MDA5$^+$ DM患者发生RPILD独立危险因素的单因素和多因素分析

Table 2 Univariate and multivariate analysis of the independent risk factors of RPILD in anti-MDA5$^+$ DM patients

Variable	Univariate		Multivariate	
	P	HR（95%CI）	*P*	HR（95%CI）
Age	0.022	1.03（1.01-1.06）	0.141	1.02（0.99-1.05）
Sex	0.364	1.35（0.71-2.58）	-	-
NLR	<0.001	1.13（1.06-1.20）	0.003	1.11（1.03-1.18）
PLR	0.012	1.00（1.00-1.00）	-	-
LMR	0.037	0.66（0.44-0.98）	-	-
SII	0.003	1.00（1.00-1.00）	-	-
SIRI	0.003	1.21（1.07-1.36）	-	-
AISI	0.015	1.00（1.00-1.00）	-	-
Myasthenia	0.179	1.56（0.82-2.98）	-	-
Gottron's sign	0.084	0.57（0.30-1.08）	0.146	0.62（0.32-1.18）
Heliotrope rash	0.068	0.54（0.28-1.05）	0.156	0.61（0.31-1.21）
V sign	0.658	0.86（0.43-1.70）	-	-
Shawl sign	0.220	0.58（0.24-1.39）	-	-
Skin erythema	0.369	0.78（0.35-1.48）	-	-
Raynaud's phenomenon	0.716	0.69（0.10-5.04	-	-
Periungual erythema	0.380	0.66（0.26-1.68）	-	-
Arthritis	0.442	0.76（0.35-1.58）	-	-
Mechanic's hand	0.239	0.66（0.32-1.33）	-	-
Heterotopic calcification	0.998	0.00（0-Inf）	-	-
Skin ulcer	0.227	0.53（0.19-1.49）	-	-
Hypertension	0.534	1.26（0.61-2.60）	-	-
Diabetes	0.423	0.62（0.19-2.01）	-	-
Malignant tumor	0.996	0.00（0-Inf）	-	-
Cardiac involvement	0.234	0.30（0.04-2.18）	-	-
ILD	0.996	79 944 617.47（0-Inf）	-	-
Glu	0.202	1.55（0.79-3.05）	-	-

PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; ILD: interstitial lung disease; Glu: glucose; Inf: infinity; CI: confidence interval.

3B).

3 Discussion

Anti-MDA5$^+$ DM is frequently associated with interstitial lung disease, particularly RPILD which has impressively high mortality[1]. The interactions of peripheral blood cells play a crucial role in regulating inflammation and immune responses. Neutrophils, lymphocytes, and platelets are vital effector cells in the inflammatory response[38-40]. Consequently, the derived inflammatory indices, such as NLR and SII, have gained attention for their ability to comprehensively assess the inflammatory status in patients with systemic autoimmune diseases, including anti-MDA5$^+$ DM[12]. In the current study, we aimed to screen prognostic factors affecting anti-MDA5$^+$ DM and highlight its potential significance in clinical practice.

We found that the NLR was the most significant prognostic biomarker for RPILD in patients with anti-MDA5$^+$ DM. According to previous studies, NLR was an important marker for evaluating the activity of RA[41-42] and predicting the risk of death[43]. Additionally, NLR was associated with the activity of leukoaraiosis syndrome[44-45] and a predictor of psoriatic arthritis[46-47]. It has also been correlated with the activity of systemic lupus erythematosus and the prediction of lupus nephritis[48]. In cases of pulmonary fibrosis in ILD, fibroblasts and myofibroblasts proliferate and deposit exces-

表3　anti-MDA5$^+$DM患者死亡独立危险因素的单因素和多因素分析

Table 3　Univariate and multivariate analysis of the independent risk factors of death in anti-MDA5$^+$DM patients

Variable	Univariate		Multivariate	
	P	HR(95%CI)	*P*	HR(95%CI)
Age	0.002	1.04(1.02-1.07)	0.039	1.03(1.00-1.06)
Sex	0.632	1.17(0.61-2.25)	-	-
NLR	<0.001	1.18(1.11-1.26)	-	-
PLR	0.076	1.00(1.00-1.00)	-	-
LMR	0.018	0.60(0.39-0.92)	0.129	0.76(0.57-1.08)
SII	<0.001	1.00(1.00-1.00)	0.002	1.00(1.00-1.00)
SIRI	<0.001	1.29(1.16-1.45)	-	-
AISI	<0.001	1.00(1.00-1.00)	-	-
Myasthenia	0.027	2.07(1.09-3.96)	0.139	1.66(0.85-3.25)
Gottron's sign	0.986	1.01(0.52-1.93)	-	-
Heliotrope rash	0.260	0.69(0.36-1.30)	-	-
V sign	0.450	0.76(0.38-1.54)	-	-
Shawl sign	0.375	0.69(0.30-1.57)	-	-
Skin erythema	0.592	0.83(0.42-1.65)	-	-
Raynaud's phenomenon	0.776	0.75(0.10-5.47)	-	-
Periungual erythema	0.451	0.71(0.30-1.72)	-	-
Arthritis	0.508	0.78(0.37-1.64)	-	-
Mechanic's hand	0.177	0.61(0.29-1.25)	-	-
Heterotopic calcification	0.997	0.00(0-Inf)	-	-
Skin ulcer	0.460	1.34(0.61-2.94)	-	-
Hypertension	0.619	1.20(0.58-2.49)	-	-
Diabetes	0.594	0.75(0.27-2.13)	-	-
Malignant tumor	0.996	0.00(0-Inf)	-	-
Cardiac involvement	0.871	0.91(0.28-2.96)	-	-
ILD	0.997	78 116 206.82(0-Inf)	-	-
Glu	0.694	1.15(0.58-2.29)	-	-

PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; ILD: interstitial lung disease; Glu: glucose; Inf: infinity; CI: confidence interval.

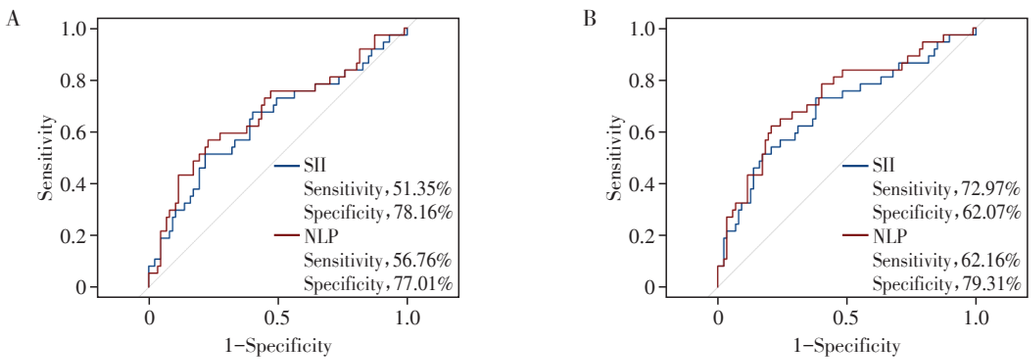

图1　NLR和SII在预测RPILD(A)与存活(B)的ROC分析

Figure 1　ROC analysis of both NLR and SII in predicting RPILD(A) and survival(B)

sive extracellular matrix (ECM) in the interstitium, leading to an impaired lung function [49]. Neutrophils play a crucial role in this process by releasing elastase and matrix metalloproteinases to degrade ECM pro-

表4　NLR和SII对RPILD和生存的预测价值

Table 4　表4 The predictive value of NLR and SII for RPILD and survival

Variable	AUC	95%CI	*P*	Cut-off	Sensitivity（%）	Specificity（%）	Youden index	Group
NLR	0.67	0.56-0.78	0.001	6.12	56.76	77.01	0.34	RP-ILD
SII	0.64	0.53-0.73	0.007	1 200.82	51.35	78.16	0.30	RP-ILD
NLR	0.73	0.63-0.83	<0.001	6.12	62.16	79.31	0.41	Survival
SII	0.69	0.58-0.80	<0.001	875.79	72.97	62.07	0.35	Survival

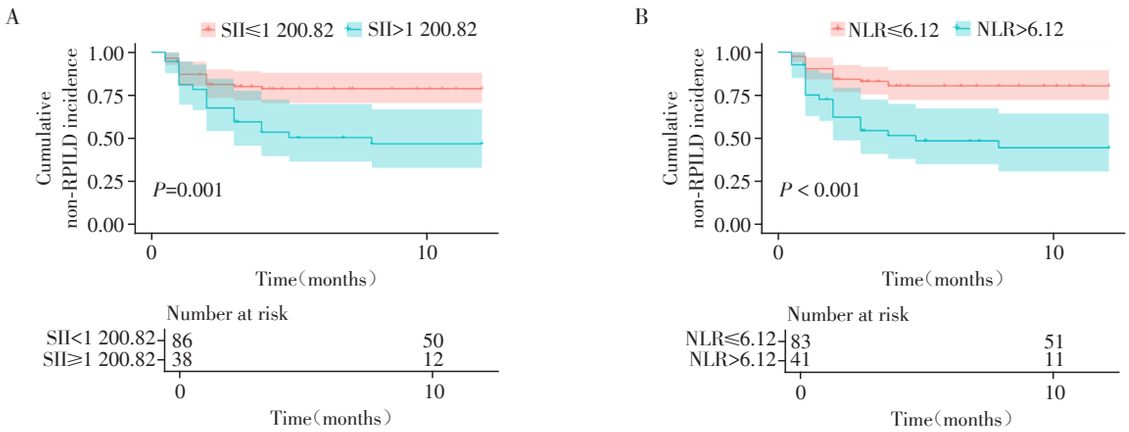

图2　低/高SII（A）、低/高NLR（B）分层的非RPILD anti-MDA5$^+$DM患者的Kaplan-Meier生存曲线

Figure 2　Kaplan-Meier survival curve of anti-MDA5$^+$DM patients with non-RPILD stratified by low/high SII（A）and low/high NLR（B）

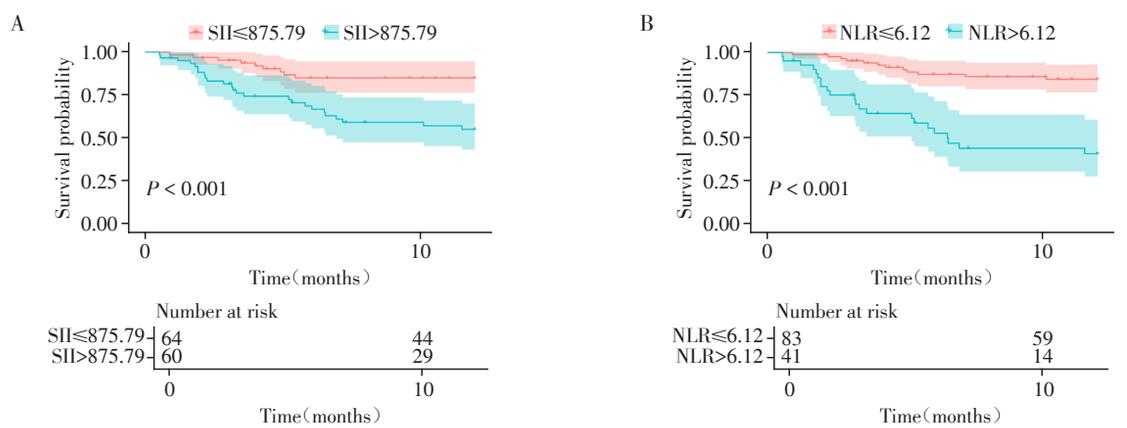

图3　低/高SII（A）、低/高NLR（B）分层的anti-MDA5$^+$DM患者总体生存的Kaplan-Meier生存曲线

Figure 3　Kaplan-Meier survival curves for overall survival of anti-MDA5$^+$DM patients stratified by low/high SII（A）and low/high NLR（B）

teins and activate transforming growth factor-β（TGF-β），thus promoting further ECM accumulation. Additionally，neutrophil extracellular traps stimulate the TGF-β production and activate myofibroblasts，leading to endothelial damage and the increased infiltration of inflammatory cells in the lungs，exacerbating interstitial inflammation and fibrosis[15]. The role of lymphocytes in this process is complex and somewhat controversial. For example，the activated human T lymphocytes inhibit the TGF-β-induced fibroblast differentiation into myofibroblasts through prostaglandin D[49]. On the other hand，Th1 cells alleviate fibrosis by secreting interleukin-12（IL-12）and interferon-γ[15].

In healthy adult non-elderly populations，normal NLR values range from 0.78 to 3.53，with a mean value of 2.8 in patients with connective tissue conditions[50].

In the current study, patients with a poor prognosis had elevated NEU, decreased LYC, and consequently elevated NLR, consistent with previous studies[44-48, 50-51]. The development of ILD is associated with the overactivation of alveolar macrophages, which triggers neutrophil activation and the release of lymphocyte chemotactic factors[52-53], further leading to an increase in NLR. For instance, in patients with systemic sclerosis, an NLR value higher than 2.59 helps predict ILD[50]; in polymyositis and dermatomyositis, NLR is significantly correlated with the presence of ILD and serves as an independent predictor of its occurrence[54]. Therefore, NLR is closely associated with ILD[50]. In the current study, the mean NLR value was 3.92 in non-RPILD patients and 6.74 in RPILD patients (P=0.003). After conducting an ROC curve analysis, the best cut-off value for NLR in predicting RPILD was consistent with that of mortality, which was 6.12, indicating a strong association with a fatal outcome, especially when combined with RPILD. Compared with recent studies, NLR higher than 4.86 was used as an independent predictor of mortality in patients with anti-MDA5$^+$ DM[14]. It is worth noting that the optimal cut-off value may differ in other studies because of factors such as sample size and analysis methods. Therefore, further research with larger sample sizes and multi-center studies is necessary to determine a more definitive prediction.

SII is a newly developed index that measures inflammation by combining peripheral lymphocytes, neutrophils, and platelets, providing a more comprehensive assessment of inflammation and immune balance in the body. SII can be used to evaluate disease activity and predict adverse outcomes. From a pathophysiological perspective, inflammation leads to an increase in neutrophil and platelet counts as well as a decrease in lymphocyte counts, which results in higher SII values that indicate stronger inflammatory responses and weaker immune responses[55]. In the assessment of cancer, an elevated SII is significantly associated with lower survival rates, and the median critical value for SII was 572[37], with a value above 600 serving as a clinical marker of inflammation[50]. Studies have shown that when the critical value exceeds 578.25, there is a significant increase in the risk of developing RA[25]. In ankylosing spondylitis patients, an SII critical value of 513.20 yielded a sensitivity of 86.84% and specificity of 83.33% for diagnosing disease activity[27]. In the current study, the mean SII value for surviving patients was 694.55, while for deceased patients, it was 1 278.43 (P=0.001). SII was significantly associated with mortality in anti-MDA5$^+$ DM patients, with a cut-off value above 895.79 indicating an increased risk of death. Additionally, the current study showed that age was an independent risk factor for predicting mortality in anti-MDA5$^+$ DM, consistent with previous findings, which may be due to older patients having more comorbidities and overall poorer health[56-57].

In summary, NLR and SII are valuable tools for clinicians in assessing disease severity, monitoring inflammation, and predicting poor prognosis in anti-MDA5$^+$ DM patients[54]. These parameters offer greater diagnostic and predictive accuracy than single indicators because they provide a more comprehensive assessment of the inflammatory response. Although the exact cause of anti-MDA5$^+$ DM remains unknown, recent studies have correlated disease prognosis with several factors, including anti-MDA5 antibody titers, high ferritin levels, serum KL-6, serum LDH levels, and the proportion of CD4$^+$CXCR4$^+$ T cells[3, 58-59]. Besides, studies have shown that peripheral LYC is correlated with RPILD and is an applicable prognostic predictor for anti-MDA5$^+$ DM[60]. Compared with these indicators, both NLR and SII are simpler, faster, and more cost-effective, making them particularly useful for dynamic monitoring in clinical practice.

However, the current study has several limitations. Firstly, the follow-up period for recently enrolled patients was relatively short, which may introduce some bias. Secondly, because of the rarity of the disease, the sample size was relatively small. Thirdly, the study was limited to a single center, and future multicenter studies are needed to validate the results. Lastly, lymphocyte, neutrophil, and platelet counts may be influenced by treatment regimens; however, most cases in the study had received steroid treatment, making it difficult to exclude this factor. Prospective studies are necessary to evaluate changes in NLR and SII at different disease stages. Future efforts should focus on design-

ing large-scale, multicenter, prospective studies to explore the application value of NLR and SII in anti-MDA5$^+$ DM patients.

Availability of data and materials:

The datasets used during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests:

The authors declare that they have no competing interest.

Author's Contributions:

TAN Wengfeng designed the study. CAI Qingqing contributed to the study design. YOU Hanxiao, LÜ Chengyin, WANG Lei, QIU Yulu, and SHI Yumeng recruited patients and obtained consent for the study. CAI Qingqing and WU Lingyun analyzed and interpreted the data. CAI Qingqing, WANG Fang, ZHANG Miaojia, and TAN Wenfeng wrote the manuscript. All authors read, revised, and approved the final version of the manuscript.

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