Neutrophil-to-lymphocyte Ratio Is a Predictive Marker for Anti-MDA5 Positive Dermatomyositis

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Abstract

Objective: To correlate neutrophil-to-lymphocyte ratio (NLR) with fatality from dermatomyositis in anti-MDA5 positive patients.

Method: A retrospective study in which 195 patients were enrolled was conducted. Clinical and laboratory information was collated and ratios of neutrophil to lymphocyte counts (NLR) calculated. The primary end point was all-cause death.

Result: Of the 195 patients studied, all had interstitial lung disease, including 140 survivors and 55 non-survivors. An optimal NLR cut-off value of 4.86 for mortality prediction was identified. The NLR of non-survivors was significantly higher than that of survivors (p<0.001). Plasma levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) were significantly increased when NLR was greater than 4.86. Results of multivariate analysis established that NLR>4.86 was an independent predictor of mortality (HR: 2.52; 95%CI: 1.33-4.78; p=0.005). Abstinence from smoking (HR: 2.66; 95%CI: 1.33-4.78; p=0.003), emerge of rapidly progressive interstitial lung disease (RPILD; HR: 4.38; 95%CI: 2.37-8.08; p<0.001), low plasma LDH (HR: 3.82; 95%CI: 2.06-7.11; p<0.001) and appear with dyspnea (HR: 2.17; 95%CI: 1.22-3.86; p=0.009) were all protective factors predictive of survival.

Conclusion: NLR is a cost-effective and widely accessible biomarker with utility for risk stratification in patients with anti-MDA5+ dermatomyositis.

Introduction

Anti-MDA5 + dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) which commonly presents with skin manifestations and progresses to pulmonary involvement. The involvement of muscle tissue is relatively rare. Patients testing positive for anti-MDA5 account for 13–30% of all IIM [1]. During inflammatory activation, patients are prone to rapidly progressive pulmonary interstitial lesions which result in high mortality. Vascular inflammation is a dominant part of inflammatory activation and peripheral blood neutrophils and lymphocytes participate in the process [2]. The ratio of neutrophil to lymphocyte counts (NLR) is an indicator of systemic inflammation which is easier to obtain than other inflammatory indicators, such as plasma lactate dehydrogenase (LDH) or ferritin. Levels of LDH [3] and ferritin [4, 5] are well-established as good prognostic indicators, allowing correlations to be made between the severity of the disease and survival time. To date, little data regarding the diagnostic and predictive value of NLR in autoimmune diseases has been reported and any utility for anti-MDA5 + DM has not been evaluated. Therefore, the current study aimed to determine whether NLR has value for mortality prediction in cases of anti-MDA5 + DM.

Methods

Patient enrollment
Patients receiving treatment for anti-MDA5 + DM in West China Hospital, Sichuan, China between December 2015 and September 2021 were retrospectively recruited. The study was approved by the bioethics committee of West China Hospital (NO.246 in 2019). Anti-MDA5 + DM was diagnosed according to the guidelines published by the 239th European Neuro Muscular Center (ENMC)[6]. Interstitial lung disease (ILD) diagnosis relies on symptoms, signs and high-resolution CT (HRCT) [7]. Rapidly progressing ILD (RP-ILD) was defined according to the criteria proposed by Akira et al. [8] and HRCT score evaluated by 2 independent radiologists, according to the method of Ichikado et al. [9]. Neutrophil and lymphocyte counts were recorded on the patient’s first admission. NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Plasma levels of creatine kinase (CK), LDH and C-reactive peptide (CRP) were recorded, along with other clinical symptoms. Titers of anti-MDA5 antibodies were analyzed by ELISA or immunoblot.

**Statistical analysis**

All data analysis was performed using R statistical programming package, version 4.1.3 (R Programming). Overall survival (OS) was calculated from first treatment to death (event) or to last follow-up (census). Data is presented as numbers (percentages), mean ± standard deviation or median values and interquartile range (IQR). Univariate and multivariate COX regression analyses were performed to identify independent risk factors with an impact on OS. OS curves and comparisons were calculated by Kaplan-Meier survival curves and the log-rank test. The optimal truncation value of NLR affecting prognosis was determined by receiver operator characteristic (ROC) curve in R Programming. All statistical tests were two sided and a p < 0.05 considered statistically significant.

**Results**

A total of 234 anti-MDA5+ DM patients were identified during the period between December 2015 and September 2021. Of the total, 4 patients were excluded due to missing core data and 35 patients presented without ILD on first admission. After these exclusions, 195 patients remained and were enrolled. Baseline patient characteristics are shown in Table 1. The median age of the cohort was 50 years (44.00-57.00 years). Two thirds (68.21%) were female, and the majority (83.59%) had never smoked. Some patients had comorbidities, such as heart failure (8.72%), diabetes (8.72), fatty liver (20.00%) and hypertension (7.18%), although these comorbidities appeared to have little impact on prognosis. More than half of the patients had arthralgia (61.54%), Gottron sign (61.54%) or heliotrope sign (51.79%). Almost half had developed dyspnea by the first admission (42.05%). Skin ulcers were relatively rare (11.79%). The median survival time was 13.50 months (1.64-32.56 months). Levels of inflammatory biomarkers, such as LDH (p<0.001), CRP (p<0.001) and red blood cell distribution width (RDW) (p=0.025), showed significant differences between survivors and non-survivors. Non-survivors had higher CK levels than survivors (80.00IU/L [45.50-220.50] vs 51.00IU/L [30.00-99.00]; p=0.002). Median values for white blood cell and platelet counts were 5.59×10^9/L (4.06-7.44×10^9/L) and 187×10^9/L (146.50-234.50×10^9/L), respectively. The median NLR value was 4.85 (3.41-7.07) with lower values in
anti-MDA5+ survivors than in non-survivors (4.34 vs 6.19; p<0.001). Changes in NLR were synchronized with those of other inflammatory markers, such as LDH (Fig. 3A) and CRP (Fig. 3B).

**Univariate and multivariate analysis**

Results of univariate analysis showed that NLR (p<0.001), plasma LDH (p<0.001), smoking (p<0.009), RPILD (p<0.001), dyspnea (p<0.001) and HRCT score were associated with OS of MDA5+ DM patients (Table 2).

Factors identified by univariate analysis as being related to survival were subjected to multivariate COX regression analysis. The optical truncation value of NLR affecting the prognosis was found to be 4.86 by R statistical software. Kaplan-Meier curves showed that patients with a lower NLR (<4.86) at baseline showed significantly higher OS compared with those with a higher NLR (≥4.86) at baseline (p<0.001; Fig. 1).

Patients with a history of smoking had a higher risk of death than non-smokers (HR: 2.66; 95%CI: 1.33-4.78; p=0.003). The prognosis of patients with RPILD was poorer than patients without RPILD (HR: 4.38; 95%CI: 2.37-8.08; p<0.001). Levels of plasma LDH (HR: 3.82; 95%CI: 2.06-7.11; p<0.001) and dyspnea (HR: 2.17; 95%CI: 1.22-3.86; p=0.009) were predictive of survival. However, HRCT score was not a prognostic indicator for anti-MDA5+ DM patients (Table 3). A forest plot for subgroup analyses of overall survival is presented in Figure 2.

**Discussion**

DM is a heterogeneous autoimmune disease with the anti-MDA5+ form exhibiting a characteristic rash and interstitial lung disease (ILD). The involvement of muscle tissue is rare, so that serum CK levels are usually normal. However, many patients develop rapidly progressive acute pulmonary failure, accounting for high mortality rates [10].

Neutrophils and lymphocytes play important roles in systemic autoimmune diseases with numbers and functions changing during disease progression. A component of the routine blood cell examination (RBC), NLR values have attracted increased attention in recent years for their utility in inflammatory and autoimmune disease. Previous work has indicated that NLR reflects disease activity in rheumatoid arthritis (RA) [11] and Bechet disease (BD) [12, 13], is a predictive marker for psoriatic arthritis (PsA) [14] and relates to the occurrence of lupus nephritis in systemic lupus erythematosus (SLE) [15, 16]. However, to the best of our knowledge, the relationship between NLR and MDA5+ DM has not been previously studied. Multiple indicators have been correlated with the prognosis of anti-MDA5+ DM, such as anti-MDA5 tilter [17], ferritin [4, 5, 17, 18], KL-6 [19] and the proportion of CD4+CXCR4+T cells [20]. The current study revealed elevated NLR to be an independent predictor for poor survival in anti-MDA5+ DM patients, in addition to LDH, CRP and other inflammatory indicators.
Knowledge regarding the pathogenic mechanisms of DM remains limited but it seems to disproportionately affect genetically susceptible populations and is triggered by infectious agents (viruses, picornaviruses, flaviviruses) [2]. Neutrophils and lymphocytes produce a variety of cytokines and participate in DM pathogenesis. Vasculopathy is a well-established feature of MDA 5 + DM [21, 22]. Oxidative stress is involved in the pathophysiology of vascular inflammation in DM [23, 24]. Oxidative stress is associated with excessive inflammatory activity and NLR is a non-specific indicator of oxidative stress, reflecting the state of the body’s immune system [25, 26]. Antigen-stimulated responses in autoimmune diseases include production of reactive oxygen species and the resulting oxidative stress has an impact on disease progression, response to therapy and prognosis. NLR correlates with inflammatory factors, such as CRP, LDH and ferritin, and interplay of multiple factors, including pro- and anti-inflammatory factors, may be responsible for measured NLRs. NLR is also related to other pathological conditions, such as cancer [27–29], osteoarthritis [30, 31] and myocardial infarctions [32, 33].

NLR measurements are relatively inexpensive and easily incorporated into routine clinical practice. The predictive properties of NLR allow it to serve as a prognostic marker to aid clinical decision-making at an early stage of anti-MDA5 + DM disease. Anti-MDA5 + DM has a high mortality rate due to the common development of rapidly progressive interstitial lung disease (RP-ILD) which is difficult to treat, especially in combination with infection [34–36]. Seasonal and geographical variations in anti-MDA5 + DM suggest that infections, especially viruses, may be a predisposing factor, perhaps due to the induction of a cytokine storm [37, 38]. Viral RNA activates MDA5 in infected cells, leading to the production of type I interferon (IFN-I) and cytokines [38]. Increased neutrophils during bacterial infection and decreased lymphocytes during viral infection contribute to high NLRs and dismal prognoses. Intervention at the early stage of anti-MDA5 + DM, when elevated NLRs may first be detected, may prevent or delay the development of cytokine storms and tissue damage.

Plasma LDH levels have previously been reported to be increased in RPILD and associated with high titers of anti-MDA5 antibody. A recent study has suggested that LDH > 335/L was an independent risk factor for poor prognosis in anti-MDA5 + DM [3]. The current study found that serum LDH in patients with NLR > 4.86 was significantly higher than that in patients with NLR < 4.86 (Fig. 3A). This suggests that NLR measurements have a related function to those of LDH. However, LDH is released by many tissues, such as liver and kidney, and is greatly affected by CK levels. Therefore, NLR may prove to be a more appropriate indicator of inflammatory state in anti-MDA5 + DM.

Previous studies have identified HRCT score as an independent risk factor for poor prognosis in anti-MDA5 + DM [5] but the current studies do not replicate those results. This inconsistency may have arisen due to selection of first admission HRCT images from patients who have been hospitalized and scanned on several occasions.

Some DM patients deteriorate rapidly, often within the time-scale of 1 month. Therefore, early HRCT scores may not reliably indicate abnormality and vigilance is required to ensure repeated scans on follow-
We acknowledge several limitations to the current study. All data were derived from patients presenting at a single center. Moreover, NLR measured at initial presentation was included but not that after treatment, so that NLR changes could not be assessed. In addition, many factors, including treatment program and inflammatory severity, contribute to poor prognosis in anti-MDA5 + DM. Prognosis must be evaluated in combination with other indicators.

**Conclusion**

In conclusion, NLR less than 4.86 was found to be an independent predictor of longer survival for patients with MDA5 + DM. NLR may prove to be a marker with clinical utility due to its low cost, accessibility and reproducibility.

**Declarations**

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**Authors contributions**

Concept and design-Tao Liu, Qibing Xie, acquisition of subjects and/or data- Wen Li, Zehao Zhang, Ting Jiang, Yu Fei, Jing Huang, analysis and interpretation of data- Tao Liu, and the preparation of manuscript- Tao Liu. All the authors read and approve the final manuscript.

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**Availability of data and materials**

The datasets generated and/or analysed during the current study are not publicly available due to ethical/legal/commercial reasons but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participants**

The study is complied with the Declaration of Helsinki and is approved by the ethics committee of West China Hospital (No. 246 in 2019). All methods were carried out in accordance with relevant guidelines and regulations. There is no informed consent from participants because of retrospective study. Ethics committee of West China Hospital approved informed consent waiver.
Consent for publication

Not applicable. The manuscript does not include any information or image that could lead to identification of a study participant.

Competing interests

All the authors declare that they have no competing interests.

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Tables

Table 1. Demographic and clinical characteristics of different groups in anti-MDA5+ patients with ILD.
|                         | Overall          | Survival        | Un-survival      | p     |
|-------------------------|------------------|-----------------|------------------|-------|
| n                       | 195              | 140             | 55               |       |
| Age (median [IQR])      | 50.00 [44.00, 57.00] | 49.00 [43.75, 56.00] | 53.00 [46.50, 58.00] | 0.038 |
| Gender (%)              | 62 (31.79)       | 41 (29.29)      | 21 (38.18)       | 0.303 |
| Smoking (%)             | 32 (16.41)       | 18 (12.86)      | 14 (25.45)       | 0.055 |
| Heart failure (%)       | 17 (8.72)        | 9 (6.43)        | 8 (14.55)        | 0.127 |
| Diabetes (%)            | 17 (8.72)        | 13 (9.29)       | 4 (7.27)         | 0.868 |
| Fatty liver (%)         | 39 (20.00)       | 30 (21.43)      | 9 (16.36)        | 0.551 |
| Hypertension (%)        | 14 (7.18)        | 7 (5.00)        | 7 (12.73)        | 0.116 |
| Arthralgia (%)          | 120 (61.54)      | 91 (65.00)      | 29 (52.73)       | 0.155 |
| Dyspnea (%)             | 82 (42.05)       | 49 (35.00)      | 33 (60.00)       | 0.003 |
| Skin ulcer (%)          | 23 (11.79)       | 19 (13.57)      | 4 (7.27)         | 0.327 |
| Gottron sign (%)        | 120 (61.54)      | 87 (62.14)      | 33 (60.00)       | 0.910 |
| Heliotrope sign (%)     | 101 (51.79)      | 79 (56.43)      | 22 (40.00)       | 0.057 |
| RDW (median [IQR])      | 47.60 [44.80, 52.30] | 47.00 [44.20, 51.80] | 49.20 [46.15, 54.20] | 0.025 |
| CK (median [IQR])       | 56.00 [31.50, 120.00] | 51.00 [30.00, 99.00] | 80.00 [45.50, 220.50] | 0.002 |
| CRP (median [IQR])      | 5.87 [2.54, 16.75] | 4.27 [2.40, 10.48] | 15.30 [4.75, 34.40] | <0.001 |
| LDH (median [IQR])      | 321.00 [261.50, 441.50] | 301.00 [232.50, 365.25] | 443.00 [327.00, 658.00] | <0.001 |
| RPILD (%)               | 63 (32.31)       | 28 (20.00)      | 35 (63.64)       | <0.001 |
| HRCT score (mean (SD))  | 88.82 (40.27)    | 82.89 (38.65)   | 103.89 (40.70)   | 0.001 |
| Death (%)               | 55 (28.21)       | 0 (0.00)        | 55 (100.00)      | <0.001 |
| Survival time (median [IQR]) | 13.50 [1.64, 32.56] | 24.13 [8.29, 40.02] | 0.77 [0.33, 2.50] | <0.001 |
| WBC (median [IQR])      | 5.59 [4.06, 7.44] | 5.42 [3.86, 7.06] | 6.47 [4.33, 8.63] | 0.066 |
| PLT (median [IQR])      | 187.00 [146.50, 234.50] | 191.50 [152.50, 234.25] | 184.00 [126.50, 234.00] | 0.174 |
| NLR (median [IQR])      | 4.85 [3.41, 7.07] | 4.34 [3.15, 6.63] | 6.19 [4.70, 9.84] | <0.001 |
Data are presented as numbers (percentages), mean±standard deviation (SD), or median values and interquartile range (IQR).

Abbreviation: RDW, red cell volume distribution width; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell count; PLT, platelet count; NLR, neutrophils/lymphocyte ratio; DM, dermatomyositis; RPILD, rapidly progressive interstitial lung disease; HRCT, high-resolution CT; LDH, lactate dehydrogenase.

Table 2. Variables associated with death among people with anti-MDA5+DM on Univariable Cox Regression Analysis.

| Characteristics | HR (95%CI)  | P Value |
|-----------------|-------------|---------|
| Gender          | 1.48(0.86-2.55) | 0.16    |
| Age             | 1.13(0.57-2.25) | 0.717   |
| Smoking         | 2.25(1.22-4.12) | 0.009   |
| Arthralgia      | 0.65(0.38-1.1)  | 0.106   |
| Dyspnea         | 2.62(1.52-4.5)  | 0       |
| Fatty liver     | 0.78(0.38-1.58) | 0.486   |
| Dysphagia       | 0.52(0.13-2.12) | 0.36    |
| Diabetes        | 0.76(0.28-2.11) | 0.602   |
| Hypertension    | 1.84(0.83-4.07) | 0.132   |
| Infection       | 3.01(1.52-5.98) | 0.002   |
| Skin ulcer      | 0.51(0.18-1.41) | 0.192   |
| Gottron sign    | 0.88(0.52-1.52) | 0.656   |
| Heliotrope sign | 0.57(0.33-0.97) | 0.039   |
| RPILD           | 6.46(3.69-11.3) | 0       |
| HRCT score      | 3.62(1.99-6.6)  | 0       |
| LDH             | 5.28(2.94-9.48) | 0       |
| CRP             | 1.01(1.01-1.02) | 0       |
| NLR             | 3.93(2.14-7.22) | 0       |

Abbreviation: HR, hazards ratio; CI, confidence interval.
Table 3. Variables associated with death among people with anti-MDA5+ DM on Multivariable Cox Regression Analysis.

| Characteristics | HR (95%CI)     | P Value |
|-----------------|----------------|---------|
| LDH             | 3.82(2.06-7.11)| 0       |
| Smoking         | 2.66(1.39-5.06)| 0.003   |
| RPILD           | 4.38(2.37-8.08)| 0       |
| Dyspnea         | 2.17(1.22-3.86)| 0.009   |
| HRCT score      | 1.46(0.76-2.79)| 0.252   |
| NLR≥ 4.86       | 2.52(1.33-4.78)| 0.005   |

Abbreviation: HR, hazards ratio; CI, confidence interval.

Figures

![Figure 1](image-url)
Survival curve of anti-MDA5+ DM patients with ILD based on initial NLR. The survival rate was calculated by the Kaplan-Meier test and compared using the log-rank test. P<0.05.

| Variable | N  | Hazard ratio | p         |
|----------|----|--------------|-----------|
| LDH      | 0  | 1            | Reference |
|          | 1  | 3.82 (2.06, 7.11) | <0.001   |
| smoking  | 0  | 1            | Reference |
|          | 1  | 2.66 (1.39, 5.06) | 0.003    |
| RPILD    | 0  | 1            | Reference |
|          | 1  | 4.38 (2.37, 8.08) | <0.001   |
| Dyspnea  | 0  | 1            | Reference |
|          | 1  | 2.17 (1.22, 3.86) | 0.009    |
| HRCTscore| 0  | 1            | Reference |
|          | 1  | 1.46 (0.76, 2.79) | 0.252    |
| NLR      | <4.86 | 1         | Reference |
|          | ≥4.86 | 2.52 (1.33, 4.78) | 0.005    |

Figure 2. Forest plot of the multivariable cox analysis of the prognostic factors for patients with ILD in anti-MDA5+DM in the discovery cohort. The ■ indicates the weight of the variable in the multivariable cox analysis; higher numbers indicate greater weight; variables with P<0.05 in the univariate analysis were included in the multivariable analysis.

Figure 2

See image above for figure legend.
Figure 3

Median and interquartile range of LDH(a) and CRP(b) related to NLR.