

Neutrophil-to-lymphocyte ratio as a prognostic indicator in anti-MDA5 dermatomyositis with interstitial lung disease and its link to IFN- α and IL-6

Sirs,
 Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis with interstitial lung disease (DM-ILD) is a rapidly progressive disease with consequently high mortality. Identifying reliable prognostic markers at the diagnosis is essential for early intervention with multiple immunosuppressive treatments. Ferritin has been widely used for risk stratification (1), but the neutrophil-to-lymphocyte ratio (NLR) is also suggested to be a useful predictor of poor prognosis in these patients (2, 3). However, the association with its pathogenesis including cytokine profiles remain unclear.
 Our study included patients with PM/DM-ILD diagnosed between July 2009 and December 2023 at Nagasaki University Hospital and was approved by the Ethics Committee of Nagasaki University (approval no. 23082128), signed informed consent was provided by all patients. Patients were clinically observed for ≥ 12 months. PM/DM or CADM diagnosis in this study was previously described (4). The existence of ILD was evaluated at the diagnosis based on the

results from chest high-resolution CT scans. In the present study, we reviewed Japanese patients with anti-MDA5 antibody-positive DM-ILD. Cytokines/chemokines in serum were measured by a blinded multiplex cytokine bead assay in parallel using MILLI-PLEX[®] MAP Human Cytokine/Chemokine Magnetic Bead Panel 1-Premixed 38 Plex (Millipore, Billerica, MA, USA) kits, according to the manufacturers' instructions. The serum interferon- α (IFN- α) was also measured using the VeriKine Human Interferon Alpha Multi-Subtype Serum ELISA Kit (PBL Assay Science, Piscataway, NJ, USA), according to the manufacturers' instructions. We investigated the baseline parameters associated with poor prognosis, which is defined as one-year mortality. Overall, the outcomes of 31 patients with anti-MDA5 antibody-positive DM-ILD were analysed, and the patients were divided into the survival group and non-survival group according to one-year mortality (n=21 and 10, respectively). Both baseline NLR level (Fig. 1A) and ferritin level (Supplementary Fig. S1A) in the non-survival group was significantly higher than those in survival group. The area under the curve (AUC) for NLR level was 0.862 (Fig. 1B) and the optimal cut-off value of baseline NLR predicting one year mortality as 4.895. The Youden index was calculated to be 0.757, with a sensitivity of 0.900 and a specificity of 0.857. When the patients

were divided into the two groups according to the cut-off value of baseline NLR, one-year survival rates of patients in the low NLR and high NLR groups were 94.7% and 25.0%, respectively (Fig. 1C). In addition, the AUC for ferritin level was 0.795 (Suppl. Fig. S1B). The area under the curve for NLR in predicting one-year mortality was higher than that for ferritin, highlighting its potential as a superior biomarker to predict the poor prognosis at the diagnosis. Importantly, baseline NLR level significantly correlated with IFN- α and interleukin-6 (IL-6) (Fig. 1D-E) but not with the other cytokines and chemokines such as IFN- γ , IL-15, IL-17A, IL-18, IL-1 β , TNF- α (data not shown). These findings suggest that NLR not only predicts the poor prognosis but also be the mirror for the underlying cytokine-driven inflammatory process in anti-MDA5 antibody positive DM-ILD. IFN- α is central to anti-MDA5 antibody-related pathogenesis (5). Type I IFN induce reversible lymphopenia through directly regulating lymphocyte recirculation (6). IL-6 has been implicated in severe ILD of the patients with anti-MDA5 antibody positive DM (7). Exogenous IL-6 can increase in neutrophil numbers and a decrease in lymphocyte numbers (8). The positive correlation between NLR and these cytokines suggests that elevated NLR is indicative of a broader inflammatory response, potentially driven by an IFN- α -mediated cytokine cascade.

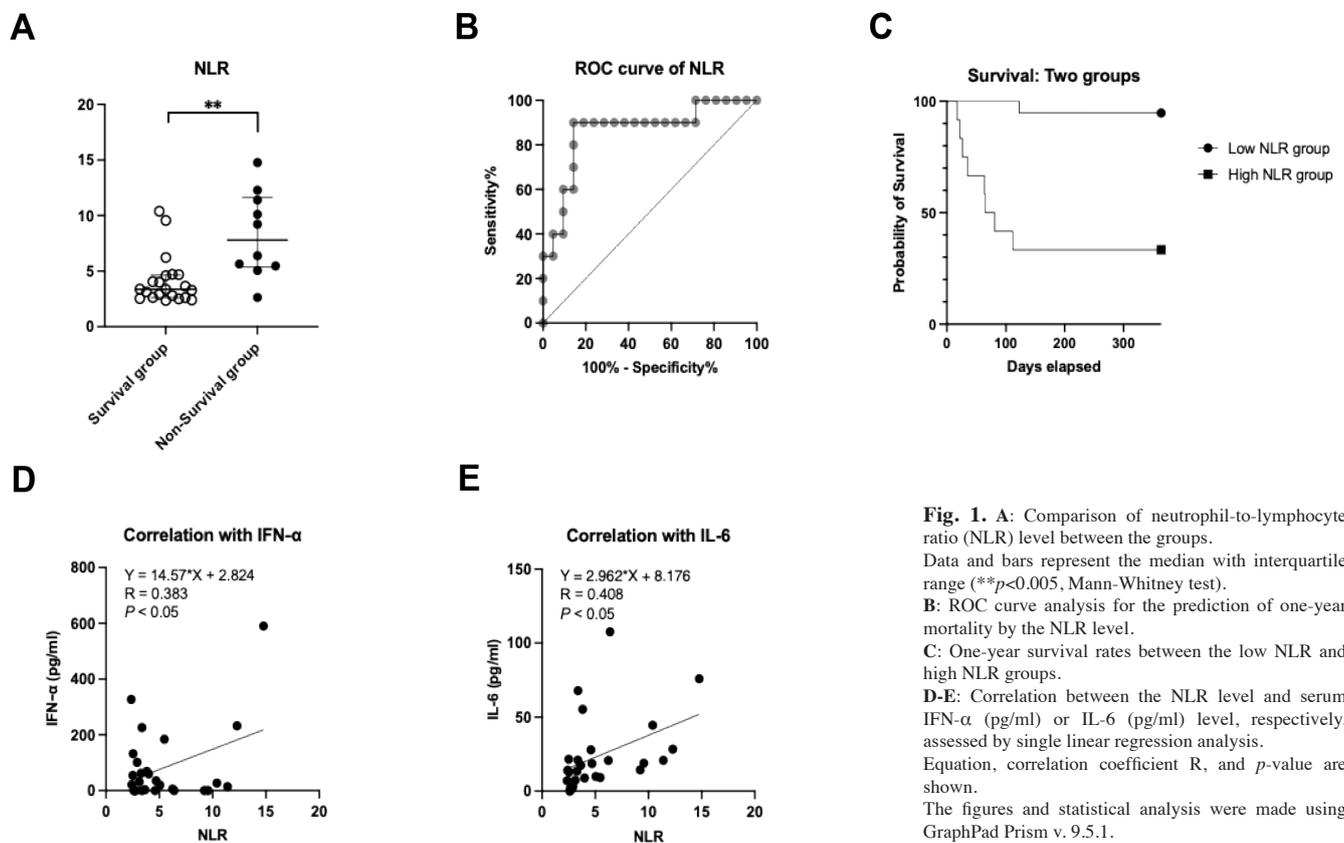


Fig. 1. A: Comparison of neutrophil-to-lymphocyte ratio (NLR) level between the groups. Data and bars represent the median with interquartile range (** $p < 0.005$, Mann-Whitney test). B: ROC curve analysis for the prediction of one-year mortality by the NLR level. C: One-year survival rates between the low NLR and high NLR groups. D-E: Correlation between the NLR level and serum IFN- α (pg/ml) or IL-6 (pg/ml) level, respectively, assessed by single linear regression analysis. Equation, correlation coefficient R, and p -value are shown. The figures and statistical analysis were made using GraphPad Prism v. 9.5.1.

Letters to the Editors

Our findings highlight the importance of NLR as a simple, cost-effective, and clinically relevant prognostic tool in anti-MDA5 antibody-positive DM-ILD, reflecting the cytokine network. Further studies are warranted to validate its role in guiding treatment decisions and improving patient outcomes.

Acknowledgements

The authors wish to thank the patients and medical staff for their contribution to the study.

Y. ENDO¹, MD, PhD
T. KOGA¹, MD, PhD
Y. MIZUNOO¹
T. SHIMIZU¹, MD, PhD
N. SAKAMOTO², MD, PhD
A. KAWAKAMI¹, MD, PhD

¹Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Medical Sciences;

²Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Please address correspondence to:

Tomohiro Koga
Department of Immunology and Rheumatology,
Division of Advanced Preventive Medical
Sciences,
Nagasaki University Graduate School of
Medical Sciences,
1-7-1 Sakamoto,
Nagasaki 852-8501, Japan.
E-mail: tkoga@nagasaki-u.ac.jp

Competing interests: none declared.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2026.

References

1. GONO T, KAWAGUCHI Y, SATOH T *et al.*: Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. *Rheumatology* (Oxford) 2010; 49: 1713-19. <https://doi.org/10.1093/rheumatology/keq149>
2. LIU T, LI W, ZHANG Z *et al.*: Neutrophil-to-lymphocyte ratio is a predictive marker for anti-MDA5 positive dermatomyositis. *BMC Pulm Med* 2022; 22: 316. <https://doi.org/10.1186/s12890-022-02106-8>
3. XIN H, HE P, XI B *et al.*: Neutrophil-to-lymphocyte ratio and short-term mortality in patients having

anti-MDA5-positive dermatomyositis with interstitial lung disease: a retrospective study. *BMC Pulm Med* 2025; 25: 40.

<https://doi.org/10.1186/s12890-025-03512-4>

4. SHIMIZU T, KOGA T, FURUKAWA K *et al.*: IL-15 is a biomarker involved in the development of rapidly progressive interstitial lung disease complicated with polymyositis/dermatomyositis. *J Intern Med* 2021; 289: 206-20. <https://doi.org/10.1111/joim.13154>
5. ZHANG SH, ZHAO Y, XIE QB, JIANG Y, WU YK, YAN B: Aberrant activation of the type I interferon system may contribute to the pathogenesis of anti-melanoma differentiation-associated gene 5 dermatomyositis. *Br J Dermatol* 2019; 180: 1090-98. <https://doi.org/10.1111/bjd.16917>
6. KAMPHUIS E, JUNT T, WAIBLER Z, FORSTER R, KALINKE U: Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. *Blood* 2006; 108: 3253-61. <https://doi.org/10.1182/blood-2006-06-027599>
7. CHEN M, QUAN C, DIAO L *et al.*: Measurement of cytokines and chemokines and association with clinical severity of dermatomyositis and clinically amyopathic dermatomyositis. *Br J Dermatol* 2018; 179: 1334-41. <https://doi.org/10.1111/bjd.17079>
8. POJDA Z, TSUBOI A: *In vivo* effects of human recombinant interleukin 6 on hemopoietic stem and progenitor cells and circulating blood cells in normal mice. *Exp Hematol* 1990; 18: 1034-37.