Comment on: Triple-combination therapy did not improve prognosis in anti-MDA5 positive dermatomyositis: a multicentre longitudinal cohort study by You *et al.*

Sirs,

I read with interest the paper published by You *et al*. (1) evaluating the effectiveness and safety of triple therapy MDA5+ DM patients with ILD. I commend the authors for addressing an important clinical issue; however, I would like to raise several methodological concerns that may limit the validity of their conclusions.

It is important to recall that the theoretical foundation of propensity score methods, as established by Rosenbaum and Rubin (2), relies on the assumption of strong ignorability, that is, treatment assignment is independent of potential outcomes conditional on the observed covariates. This assumption is untestable and requires that all relevant confounders be measured and included in the propensity score model. In the present study, the covariate set used to construct the propensity score, limited to distance, lymphocyte count, ferritin, periungual erythema, and mechanic's hands, is insufficiently justified and others key clinical predictors of prognosis, such as age, lung function, baseline pulmonary involvement, fever, and C-reactive protein (CRP), appear to have been omitted. In the absence of these variables, the ignorability assumption is unlikely to hold, increasing the risk of substantial bias in the estimated treatment effect.

Additionally, the authors provide no assessment of the model's robustness, such as sensitivity analyses or checks for model misspecification. The region of common support is not described, nor is it reported whether any observations fell outside this region and were excluded. Failure to evaluate and report overlap in propensity scores between treatment groups may lead to extrapolation beyond the data and threatens the internal validity of the analysis.

Furthermore, the authors applied inverse probability of treatment weighting (IPTW) to reduce confounding by indication. However, achieving covariate balance is essential for valid causal inference using this method. Standardised mean differences (SMDs) greater than 0.1 after weighting indicate residual imbalance and potential bias (3, 4). In Figure 1, SMDs for variables such as "Distance" and "Ferritin" remain above this threshold after adjustment, undermining the assumption of conditional exchangeability between groups. It is well established that serum ferritin is a prognostic biomarker associated with increased mortality in MDA5-positive dermatomyositis (5). Elevated baseline ferritin levels in the triple therapy group may reflect indication bias in treatment allocation.

Although the authors report using stabilised IPTWs for survival analysis, no diagnostics are presented regarding the distribution of weights or potential violations of the positivity assumption. Extreme weights can inflate variance and lead to unstable estimates, particularly in small samples or when treatment assignment is highly predictable.

Finally, there appears to be a discrepancy between the increased incidence and mortality of RP-ILD in cluster 2 and 3 after IPTW adjustment (Table VI) and the absence of significant differences in the adjusted survival curves (Fig. 2C-D). This inconsistency warrants further clarification and additional sensitivity analysis to assess the robustness of the findings.

In conclusion, while the analytical approach is conceptually appropriate, the limited covariate adjustment, persistent post-weighting imbalance, and lack of robustness evaluation raise concerns about the validity of the reported treatment effect. I respectfully invite the authors to elaborate on their methodological approach and to clarify how potential limitations in covariate adjustment were addressed in their analysis.

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