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Reply to: Enhancing Predictive Biomarkers in Limited Cutaneous Systemic Sclerosis: The Role of Type I Interferon Score and Gender Considerations

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We appreciate the interest of Li et al. in our study on the role of the Type I Interferon (IFN) score in predicting disease progression in limited cutaneous systemic sclerosis (lcSSc). Their comments provide valuable feedback, and we take this opportunity to expand on the highlighted aspects of our work (ref: Li S. Enhancing Predictive Biomarkers in Limited Cutaneous Systemic Sclerosis: The Role of Type I Interferon Score and Gender Considerations, in press).

The first point raised is on the gender distribution in our cohort, being reportedly higher than the one observed in SSc. We recruited consecutive patients with lcSSc. The higher proportion of female patients consistent with the well-documented gender distribution in lcSSc. Multiple studies, including the largest analysis of lcSSc patients from the EUSTAR database [1], have reported a higher proportion of female patients within this subset, with women accounting for approximately 90% of cases, a significantly greater prevalence compared to diffuse cutaneous systemic sclerosis (dcSSc). Notably, male patients tend to present with more severe disease phenotypes, including a faster progression of skin involvement, with up to 60% developing dcSSc within the first year of symptom onset [2]. Therefore, our cohort reflects real-world data, and its generalizability should be considered in this context.

As second point raised by the readers, it is important to clarify that our study does not rely on a baseline IFN score measured at disease onset. Rather, we studied a prevalent cohort with a median (IQR) disease duration of 8 (10) years. This would rather underscore the notion that the predictive value of IFN score for future outcomes remains valid at any timepoint. Nonetheless, we fully acknowledge the importance of evaluating longitudinal changes in the IFN score in relation to both disease events and treatment. This aspect is currently under investigation, and our ongoing analysis will provide insights into the temporal dynamics of the

IFN score and the proportion and clinical features of patients that have a significant change in their IFN status over time. These data, once available, will contribute to a deeper understanding of the role of Type I IFN activation in disease progression and response to therapy.

The third point raised relates to an external validation of our data. We agree independent validation will be crucial to assess its generalizability, and we encourage further efforts in this direction, including testing across different ethnic backgrounds. Specifically, in our current dataset, the majority of are of white European background (93.3%), with only a small representation of East Asian and Middle Eastern participants. Given this imbalance, our sample size is not sufficient to draw meaningful comparisons across ethnic groups. Nonetheless, exploring potential racial differences remains an important avenue for future research in larger, more diverse populations.

References

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2. Carreira, P. E. *et al.* Gender differences in early systemic sclerosis patients: A report from the EULAR scleroderma trials and research group (EUSTAR) database. *Clin Exp Rheumatol* 36, S68–S75 (2018).