Reply to the comment on: Beyond diagnosis: exploring the significance of IgG4+ plasma cell count through immunostaining in IgG4-related disease

Sir,

We thank Chiang *et al*. for their interest in our recently published work "Beyond diagnosis: exploring the significance of IgG4+ plasma cell count through immunostaining in IgG4-related disease" (1). Their remarks are greatly appreciated, as they offer valuable perspectives for advancing our ongoing research efforts in IgG4-related disease (IgG4-RD).

Their observations regarding the potential progression from the proliferative phenotype to the fibrotic phenotype, as indicated by fibrosis and a changing cytokine environment, are particularly noteworthy. We agree that understanding and preventing this transition is critical for improving long-term outcomes in patients with IgG4-RD. Indeed, fibrosis is often a late-stage manifestation of the disease, and proactive medical intervention is essential to mitigate irreversible tissue damage.

Regarding the point on the discrepancy between our relapse rate findings and previous studies, we concur that further stratification of patient cohorts is essential (2). Their suggestion to construct a two-way table categorising patients by phenotype and IgG4+ plasma cell count is an excellent proposal. We conducted this subgroup analysis, and as you predicted, within the proliferative phenotype, relapses were more frequent in the subgroup with <100 IgG4+ plasma cells/HPF compared to the subgroup with ≥100 IgG4+ plasma cells/HPF (63.6% *vs*. 31.3%, p=0.04). The log-rank test also revealed a significant difference in relapse-free survival between these groups (p=0.04, HR 2.7 [95% CI 1.1–6.7]) (Fig. 1). These findings may suggest that patients within the proliferative phenotype with <100 IgG4+ plasma cells/HPF might represent a later stage of this phenotype.

Unfortunately, due to the low number of patients within the fibrotic phenotype with ≥100 IgG4+ plasma cells/HPF, subgroup analysis in this phenotype could not be performed. We agree that longitudinal follow-up studies could provide information to better define relapse risks and disease progression across different phenotypes.

We appreciate their reference to the article on the effectiveness of tofacitinib monotherapy for IgG4-RD or idiopathic retroperitoneal fibrosis (3). Indeed, inhibition of the JAK pathway is a promising therapeutic strategy in IgG4-RD, and we hope future trials using these treatments will be conducted, focusing in both the proliferative and fibrotic phenotypes (4-6).

In conclusion, we sincerely thank their comments and constructive feedback. Their suggestions provide directions for future research and highlight the complexity of IgG4-RD.

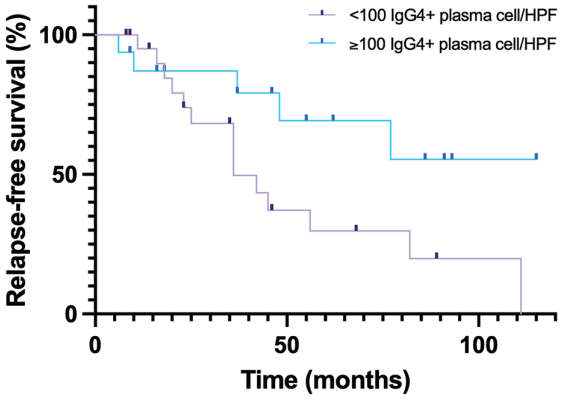

Fig. 1. The Kaplan-Meier survival analysis of relapse-free survival according to the IgG4+ plasma cell counts per high power field in the proliferative phenotype.

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