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Authors' reply

We thank Changjing Cai and colleagues for their interest and appreciation of our work.[1] Although microsatellite instability-low (MSI-L) colorectal cancers have been described as a separate subgroup from microsatellite stable (MSS) tumours, studies included in our network meta-analysis combined MSI-L and MSS tumours for several reasons. First, MSI-L and MSS tumours exhibit similar clinical, pathological, and molecular characteristics, reducing the usefulness of separate classification.[2] Second, the criteria to define MSI-L have varied between studies, leading to inconsistencies and complicating the interpretation of findings.[3] In addition, although Cai and colleagues suggest different survival associations for MSI-L and MSS tumours, the reported hazard ratio for MSI-L compared with MSS (2·105, 95% CI 0·584–7·580) indicates substantial imprecision and suggests that the prognosis of these two subtypes might not significantly differ.[4] Lastly, simplifying the classification to microsatellite instability-high (MSI-H) versus MSI-L or MSS assists in clinical decision making, which is reflected in most clinical guidelines.[5]

We agree that defined cutoff values, instead of classifications based on percentiles, would be desirable to develop clinical applications, as discussed in our Article. However, despite variable evaluation criteria, tumour infiltrating lymphocytes (TIL) maintained their associations with colorectal cancer survival.[1] Composite scores, such as Immunoscore and immune cell score, have standardised TIL assessment and have been validated as promising prognostic and predictive markers in colorectal cancer.[1] We also reported the influence of TIL subtypes (CD3+ and CD8+ T cells) on colorectal cancer survival.[1]

We further agree that tumour mutational burden and TILs are closely correlated. So far, the clinical translation of tumour mutational burden in colorectal cancer, especially for patients with early-stage colorectal cancer, has remained limited due to spatiotemporal heterogeneity, technical complexity, and high cost.[6] By contrast, TILs might provide a more direct, accessible, and consistent measure of immune response within the tumour microenvironment.

We declare no competing interests.

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