Liver International

WILEY

Liver INTERNATIONAL

LETTER TO THE EDITOR

Response to Letter to 'Serum CRP in Durvalumab–Tremelimumab-Treated HCC: Expanding the Inflammatory Narrative'

Takeshi Hatanaka[1] | Yutaka Yata[2,3] | Satoru Kakizaki[4] | Takashi Kumada[5]

[1]Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital, Maebashi, Japan | [2]Department of Gastroenterology, Hanwa Memorial Hospital, Osaka, Japan | [3]Department of Hepatology, Osaka Metropolitan University, Osaka, Japan | [4]Department of Clinical Research, NHO Takasaki General Medical Center, Takasaki, Japan | [5]Gifu Kyoritsu University, Ogaki, Japan

Correspondence: Yutaka Yata (yu-yata@maebashi.saiseikai.or.jp)

Received: 8 August 2025 | **Revised:** 8 August 2025 | **Accepted:** 19 August 2025

Dear Editor,
We sincerely thank Lei Y et al. [1] for their interest in and valuable critique of our study entitled 'Clinical Impact of Serum CRP Levels on Advanced HCC Treated With Durvalumab and Tremelimumab: A Multicentre Study' [2].

First, as pointed out by Lei Y et al., we fully agree that combining CRP with other inflammatory markers, such as interleukin-6 (IL-6) and the neutrophil-to-lymphocyte ratio (NLR), may enhance the predictive value for treatment outcomes. In this regard, our group has already demonstrated the clinical utility of NLR as a prognostic marker in patients with advanced HCC [3]. Future investigations should explore the utility of other inflammatory markers and their combinations to identify more robust predictive panels.

Second, we also recognise the importance of evaluating CRP levels during treatment (i.e., dynamic monitoring), as highlighted in their comments. However, as stated in our manuscript, on-treatment serum CRP values were not available in the current study. We acknowledge that assessing changes in inflammatory markers during treatment represents a critical area for future research.

Third, we agree that evaluating the predictive value of serum CRP according to treatment line (first-line vs. later-line therapy) is an important issue. Therefore, using our newly updated database—with the number of patients increased from 167 to 290 and the median observation period extended from 6.7 months to 8.5 months—we conducted additional analyses stratifying patients by treatment line to assess the prognostic significance of serum CRP (Figure 1). In this expanded cohort, while no significant difference in progression-free survival (PFS) was observed in the first-line and later line groups due to the small number of cases, serum CRP remained a useful marker for stratifying both PFS and overall survival (OS) in both the first-line and later line settings.

As Lei Y et al. emphasised, inflammatory markers play a pivotal role in the therapeutic strategy of immunotherapy. Continued efforts to validate more accurate predictive markers and evaluate their dynamic changes are warranted. Furthermore, external validation across independent cohorts will be essential to establish their generalisability.

We sincerely appreciate the thoughtful comments from Lei Y et al., which have helped clarify critical aspects of our study and

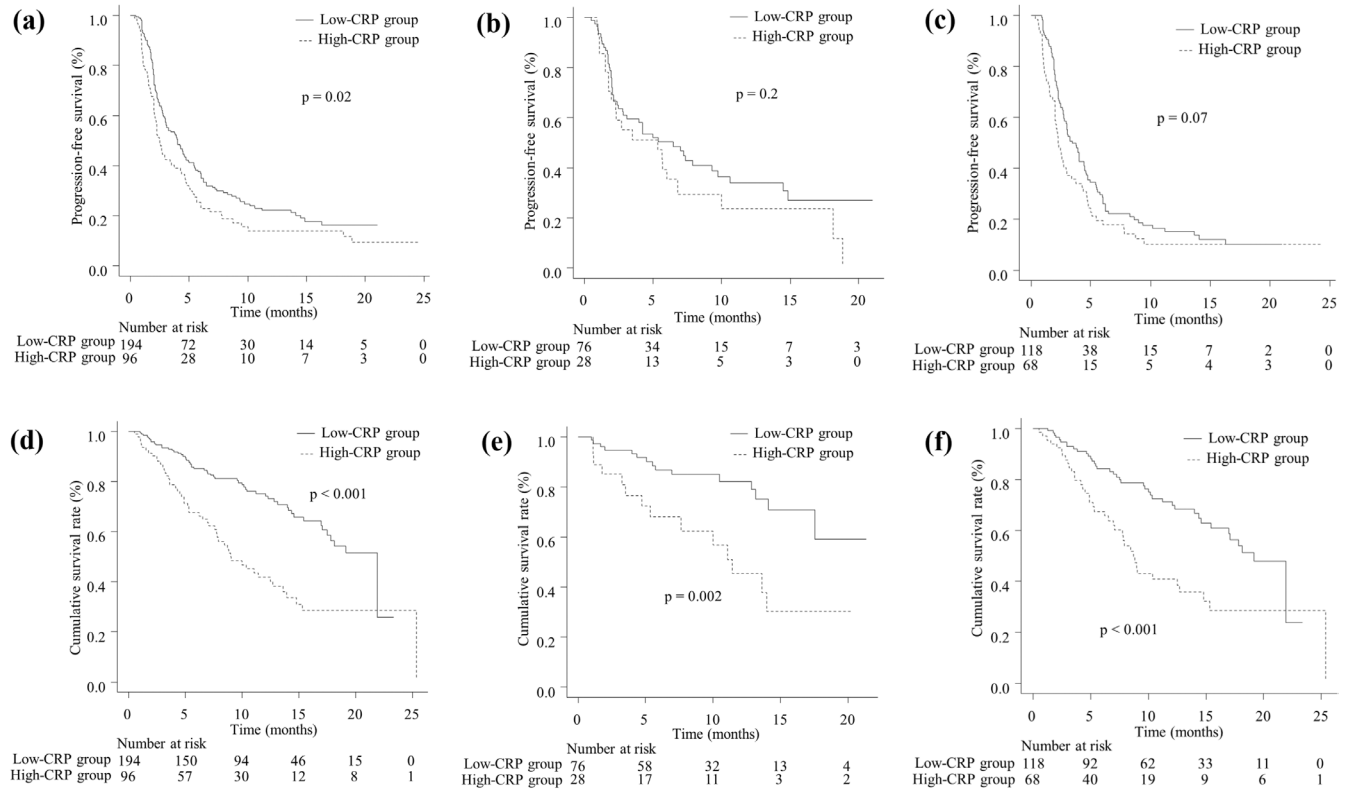

FIGURE 1 | (a) PFS in the entire cohort. The median PFS was 4.0 months (95% CI, 3.0–4.8) in the low CRP group and 2.5 months (95% CI, 2.1–3.5) in the high CRP group, with a statistically significant difference ($p = 0.02$). (b) PFS in the first-line setting. The median PFS was 6.5 months (95% CI, 2.0–9.7) in the low CRP group and 5.3 months (95% CI, 1.8–6.8) in the high CRP group. No significant difference was observed between the two groups ($p = 0.2$). (c) PFS in the later line setting. The median PFS was 3.5 months (95% CI, 2.8–4.4) in the low CRP group and 2.3 months (95% CI, 2.0–3.0) in the high CRP group. The difference between the groups was not statistically significant ($p = 0.07$). (d) OS in the entire cohort. The median OS was 21.9 months (95% CI, 17.5 to NA) in the low CRP group and 9.0 months (95% CI, 7.6–12.8) in the high CRP group, indicating better survival in the low CRP group. (e) OS in the first-line setting. The median OS was not reached in the low CRP group, with a 1-year survival rate of 82.2% (95% CI, 69.5–90.0), while the median OS was 11.4 months (95% CI, 5.4 to NA) in the high-CRP group. The difference was statistically significant ($p < 0.001$). (f) OS in the later line setting. The median OS was 19.2 months (95% CI, 15.4 to NA) in the low CRP group and 8.8 months (95% CI, 7.0–12.8) in the high-CRP group, with a statistically significant difference ($p < 0.001$). CI, confidence interval; CRP, C-reactive protein; NA, not applicable; PFS, progression-free survival; OS, overall survival.

highlighted important directions for future research in this rapidly evolving field.

Satoru Kakizaki
Takashi Kumada

Acknowledgements

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analysed during this study are included in this published article.

Linked Articles

Serum CRP in Durvalumab-Tremelimumab Treated HCC: Expanding the Inflammatory Narrative, https://doi.org/10.1111/liv.70250.

Takeshi Hatanaka
Yutaka Yata

References

1. Y. Lei, H. Xie, and M. Chen, "Serum CRP in Durvalumab-Tremelimumab Treated HCC: Expanding the Inflammatory Narrative," *Liver International* 45 (2025): e70250.

2. T. Hatanaka, Y. Yata, A. Hiraoka, et al., "Clinical Impact of Serum CRP Levels on Advanced HCC Treated With Durvalumab and Tremelimumab: A Multicentre Study," *Liver International* 45, no. 7 (2025): e70192, https://doi.org/10.1111/liv.70192.

3. T. Matono, T. Tada, T. Kumada, et al., "Neutrophil-Lymphocyte Ratio Predicts Overall Survival in Patients With HCC Treated With Durvalumab Plus Tremelimumab," *Hepatology Research* (2025), https://doi.org/10.1111/hepr.14224.