Letter to the Editor

Is neutrophil-to-lymphocyte ratio and C-reactive protein the prognostic role in metastatic colorectal cancer using regorafenib?

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Comment on: Zhao N, Xu H, Zhou D, *et al.* The prognostic role of neutrophil-to-lymphocyte ratio and C-reactive protein in metastatic colorectal cancer using regorafenib: a systematic review and meta-analysis. J Gastrointest Oncol 2022;13:1772-81.

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We read with interest the recent paper by Zhao *et al.* entitled "The prognostic role of neutrophil-to-lymphocyte ratio and C-reactive protein in metastatic colorectal cancer using regorafenib: a systematic review and meta-analysis" (1), which was published in the latest issue of *Journal of Gastrointestinal Oncology*.

The author made an important conclusion that potential prognostic factors for evaluating the efficacy of regorafenib in patients with metastatic colorectal cancer (mCRC) may include neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP), suggesting that the effect of regorafenib on overall survival (OS) may change depending on the baseline NLR. However, after carefully reviewing this study, we would like to draw attention to a few important issues that may need to be resolved to increase the validity of the conclusions.

First, we noticed that this review did not have a PROSPERO registration or a central registration depository (CRD) number. In addition, the investigators didn't give us a thorough report on their search strategy or a manual search process for this paper. We were unsure if their search strategy will uncover all the articles on this topic. Therefore, we suggested that authors provide a detailed search procedure to make this meta-analysis unassailable.

Secondly, the definitions of patients in the study of Zhao *et al.* and some included studies were significantly different. Yang *et al.* enrolled patients with chemotherapy-refractory Microsatellite Stable (MSS) colorectal cancer (2), while Del Prete *et al.*'s study included patients with pretreated colorectal cancer (3). However, Zhao *et al.* included patients with pathologically confirmed colorectal cancer and diagnosed metastatic disease by the tumor/lymph node/metastasis (TNM) staging method (1). Thus, we recommend the authors choose the same criteria for a more precise and trustworthy result.

Third, the author seems to have made an obvious mistake of expression when describing the heterogeneity of subgroup 1 in *Fig. 3*. The review mentioned that there was significant heterogeneity in the included studies (I^2=0%, P=0.72), and the fixed-effects model was used. However, I^2=0% indicated low or no heterogeneity, which is why the fixed-effects model was used. Also, the data analyzed here should be the overall heterogeneity (I^2=93.4%, P=0.0001) suggesting significant heterogeneity, hence the random effect model should be adopted (1).

Fourth, treatment details were inconsistent in the studies the authors included. The studies did not all use regorafenib monotherapy, but some used combination therapy and one study used Later-line chemotherapy with regorafenib (4). The authors included three papers in the results analysis of CRP and survival. Moriwaki *et al.* were treated with regorafenib, Chida *et al.* were treated with Regorafenib and trifluridine/tipiracil, and the study of Watanabe *et al.* adopted Later-line chemotherapy with regorafenib (4-6). These three methods are clearly different. Trifluridine/tipiracil itself may also have some therapeutic effect on mCRC (6), and the timing of medication may influence the prognosis (4). But the authors did not conduct subgroup

analysis, which may have influenced the authors' results.

Finally, no publication bias, according to the authors, existed in the research shown in *Fig. 4*. However, more than 10 articles used the funnel plot to assess publication bias (1). Furthermore, as sensitivity analysis is crucial for meta-analysis, we found that the author neglected to conduct it to strengthen the results.

In conclusion, Wang *et al.* performed an excellent meta-analysis to investigate the prognostic significance of NLR and CRP in mCRC treated with regorafenib. In our opinion, to fully comprehend the connection between them, the literature needs to examine large samples and conduct future research on the subject.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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