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CORRESPONDENCE

Reply to 'Comment on 'Circulating Neutrophils in patients with hepatocellular carcinoma"

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We thank Liu and Meng for their interest[1] in our paper entitled 'Neutrophils: driving progression and poor prognosis in patients with hepatocellular carcinoma?'.[2] We would like to respond to their comments.

The authors point out that there were significant differences between the two cohorts that we have studied and suggest that our analytical approach was not consistent with 'statistical rules' and that these may have resulted in 'incorrect conclusions'. The authors go on to suggest that unmatched conditions should have been eliminated in our combined cohort analyses and reference two methods, namely Propensity Score Matching or Decision Tree and Random Forest.

We have considered these suggestions carefully and on these statistical matters we have to respectfully disagree. We entirely accept that there were differences between our UK and Hong Kong cohorts. Having demonstrated the key associations with neutrophils in our own large UK cohort with hepatocellular carcinoma, we deliberately chose a validation cohort where other factors that could impact peripheral blood counts—such as race, aetiology, age, testing laboratory—were different. While the combination analyses enhanced statistical significance, all of the reported associations were present in each independent cohort despite the differences between them—which we see as a major strength of our study rather than a limitation. In the larger combined group, in which 'cohort' was included as a variable, a key added value was that it provided sufficient numbers of cases to perform sub-analyses where numbers were smaller in individual cohorts. For example, the presence of cirrhosis may have been a confounder as it can also affect cell number. By combining UK and Hong Kong cohorts, we were able to study associations in just over 400 patients and confirm that the reported cancer associations persisted in the absence of cirrhosis.

We could reiterate in more depth additional details of our study, but feel it is sufficient in addition to our explanation above, to state that we believe that our approaches to the statistical analyses were biologically relevant and robust. Furthermore, suggesting some sort of matching would have improved the integrity of our study is simply not true. As described in the papers referenced by Liu and Meng,[1] matching methods are typically used when comparing a treatment arm of a clinical trial with a non-treatment arm—with the need to ensure that reported outcomes are independent of differences —such as race, age, sex, severity of underlying disease—that may impact outcome. It is not appropriate to try and apply this kind of matching to an observational study of a large heterogenous population in which many variables may influence outcome and the opportunity to assess their independent contributions is related to the size of the cohort—and diminished by elimination of cases. In our combined analysis of factors influencing survival, the UK versus Hong Kong cohort was included as a variable in the multivariate analyses and it was not significantly different—with a hazard ratio of 0.93 (0.82–1.05)—which indicates that cohort differences had little relevance. This was in contrast to a number of other factors which had demonstrable importance. At a more practical level, any kind of matching has to be done in an inclusive and comprehensive fashion addressing all potential confounders—not just one or two. Matching on race or aetiology alone would diminish our combined cohort to <100 patients, without even considering sex, age, cirrhosis, treatment etc.

The overall concern of Liu and Meng[1] stems from an assumption that we propose neutrophils alone are central to disease progression and outcome for patients with HCC. Actually, this is not our belief. Roles for lymphocytes in determining disease progression in the immunosuppressed tumour microenvironment (TME) are undoubtedly of paramount importance. In the Hong Kong cohort rather than the UK cohort, peripheral lymphocyte was associated significantly with survival. Roles for platelets are also increasingly realized. It is the role of neutrophils that has received far less attention and our study—in which circulating neutrophils were the only immune cell type independently associated with poorer prognosis in both of the cohorts despite their differences—provides a compelling argument for turning our attention to them. In our study, we also demonstrated significant correlations between neutrophils and lymphocytes (negative) and neutrophils and platelets (positive), and proposed that studying their interactions in more depth, as well as how levels in the circulation reflect the TME, would be very worthwhile. We agree—as suggested by Liu and Meng—that studying relationships between cell counts in a longitudinal fashion may aid our understanding of their roles in disease progression and responses to treatment. Not having done this as yet does not, however, invalidate the findings reported in our study of data generated from cell counts at the time of diagnosis. In short, we firmly stand by our conclusions and discussion points.

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ADDITIONAL INFORMATION

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