BMJ Oncology

Potential of neutrophil-to-eosinophil ratio as a new prognostic tool for patients with advanced renal cell carcinoma receiving first-line immuno-oncology combinations

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To cite: Takemura K, Heng DYC. Potential of neutrophil-to-eosinophil ratio as a new prognostic tool for patients with advanced renal cell carcinoma receiving first-line immuno-oncology combinations. *BMJ Oncology* 2024;**3**:e000481. doi:10.1136/bmjonc-2024-000481

Linked

► http://dx.doi.org/10.1136/bmjonc-2023-000181

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Systemic therapies for advanced renal cell carcinoma (aRCC) have evolved dramatically since the approvals of immuno-oncology (IO) agents.[1] Thereafter, risk-based decision-making has become increasingly important to guide treatment selection. To date, there have been two widely-used nomograms for risk stratification of patients with aRCC: the Memorial Sloan Kettering Cancer Center (MSKCC) model[2] and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.[3] Both nomograms consist of similar clinical parameters such as short time from diagnosis to systemic therapy, poor performance status, low haemoglobin and high corrected calcium. In addition to these risk factors, the MSKCC model contains high lactate dehydrogenase (LDH), whereas the IMDC model contains neutrophils and platelets instead of LDH. In the era of IO combinations, several additional risk factors have been advocated including inflammatory markers such as neutrophil-to-lymphocyte ratio,[4] C-reactive protein[5] and absolute lymphocyte count,[6] given that these biomarkers are closely linked to how IO agents use host immunity during antitumour immune response against aRCC.

Tucker and colleagues performed exploratory analyses on the association between baseline neutrophil-to-eosinophil ratio (NER) and oncological outcomes of patients with aRCC in the JAVELIN Renal 101 trial, an ongoing multicentre, randomised, open-label, phase 3 study comparing avelumab plus axitinib with sunitinib in the first-line setting.[7] Their main findings of this study included that a lower level of baseline NER was associated with longer overall survival regardless of first-line therapy regimens as well as with longer progression-free survival among the programmed death ligand 1-positive subgroup in the avelumab plus axitinib arm suggesting the prognostic (and potentially predictive) significance of baseline NER in patients with aRCC. Even though the authors identified no individual gene expression profiles or previously reported gene expression signatures that differed between the baseline NER <median and ≥median subgroups, this study marked an important milestone for the development of new prognostic tools for patients with aRCC receiving contemporary first-line therapies, while future research should ideally correlate them with transcriptomic data.

The uniquity of NER is that this variable comprises two different parameters in the complete blood count, namely neutrophils and eosinophils. Compared with neutrophils, eosinophils are much less extensively investigated with regard to treatment response to IO combinations, although eosinophils have been shown to play an important role in the production of growth factors, cytokines and chemokines forming tumour microenvironment.[8] Even so, the evidence on the prognostic significance of baseline NER in patients with aRCC is limited apart from a bicentric, retrospective cohort study conducted by the same research group on patients with aRCC receiving nivolumab plus ipilimumab.[9] Taken together, it appears that the impact of NER on the prognostication and prediction of treatment response in patients with aRCC may be more prominent for IO combinations than for sunitinib potentially reflecting different mechanisms of action. However, it is imperative that new

prognostic markers are compared with existing criteria based on the C-index to see if the model performance improves.

We should acknowledge several limitations of this study. To begin with, the authors used the ratio rather than its constituent parameters despite the statement by Jasienski and Bazzaz: 'Empirical researchers love ratios - statisticians loathe them'.[10] Even if the authors intended hypothesis generation, more insights would have been gained from rigorous analyses including all relevant variables. Furthermore, it is crucial to capture the reasons for unavailable NER data in 107 of 886 (13%) patients because they may have introduced bias. We should also emphasise the strengths of this study. The authors conducted robust analyses of prospective clinical data paired with translational data. This study is the largest of its kind to date that has explored the relationship between baseline NER and oncological outcomes of contemporary patients with aRCC. We would sincerely urge future research to externally validate the findings of this study and hopefully improve our prognostic tools to allow oncologists to better personalise treatment strategies for patients with aRCC.

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Contributors KT: writing—original draft preparation. DYCH: supervision, writing—review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

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