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LETTER

Comment on: "The Predictive Value of NLR, PLR, LMR, NPAR and D-Dimer on the Efficacy and Prognosis of First-Line Immunotherapy for Extensive-Stage Small Cell Lung Cancer" [Letter]

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Dear editor

We read with interest the recent study assessing peripheral inflammatory indices, particularly the neutrophil-to-lymphocyte ratio after two treatment cycles (NLR2), as predictors of disease control and longer progression-free survival (PFS) in extensive-stage small-cell lung cancer (ES-SCLC) treated with first-line chemo-immunotherapy.[1] The pursuit of accessible, repeatable biomarkers is timely; nevertheless, several design-dependent interpretations warrant closer scrutiny because they may meaningfully influence how the reported associations should be understood.

A central interpretive challenge is that NLR measured around the second cycle is strongly shaped by treatment-related physiology and supportive-care exposures that are common in ES-SCLC. During this window, chemotherapy-induced myelosuppression and rebound leukocytosis, prophylactic or therapeutic granulocyte colony-stimulating factor, intercurrent infection, and short courses of corticosteroids for antiemesis or neurologic symptoms can substantially alter neutrophil and lymphocyte counts independent of antitumor immunity. Under these conditions, a low NLR2 may reflect a clinical trajectory characterized by fewer infectious complications, less steroid exposure, and better preservation of dose intensity, each of which is plausibly associated with improved PFS.[2,3] This raises the possibility that NLR2 functions partly as a composite marker of treatment tolerance and intercurrent events rather than a direct proxy of immunologic benefit. A more rigorous interpretation would be supported by aligning blood sampling to a standardized pharmacodynamic time point and incorporating key time-window covariates that plausibly drive leukocyte dynamics, such as dose delays or reductions and major infection- or steroid-related events.

In addition, the use of a post-baseline marker introduces a time-structured risk of bias that can inflate apparent prognostic performance. By definition, NLR2 is only observed among patients who remain on therapy long enough and stable enough to undergo cycle-2 assessment, and those early clinical events that preclude such assessment (rapid progression, hospitalization, or toxicity-related discontinuation) are themselves tightly coupled to short PFS. As a result, NLR2-based stratification can inadvertently embed information about early outcomes into the predictor, thereby exaggerating its "predictive" value. This concern is not merely statistical; it has direct clinical implications because it determines whether NLR2 adds information beyond what is already evident from early treatment course. A landmark framework anchored at the cycle-2 time point, with transparent accounting for patients who progress or discontinue before assessment, would help clarify whether NLR2 provides independent prognostic signal rather than reflecting survivorship to the measurement window.

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Finally, NLR2 may also partially repackage early antitumor response rather than anticipate it. By the time the second-cycle laboratory test is obtained, some patients will already have meaningful tumor shrinkage, potentially lowering inflammatory drive, whereas others may have early occult progression or escalating systemic inflammation, raising NLR.[4] In that setting, the observed association between NLR2 and longer PFS could be mediated by early response status, even if response is formally assessed shortly thereafter. Demonstrating incremental value beyond early response metrics, such as first radiographic assessment category or quantitative tumor change, would strengthen the inference that NLR2 independently stratifies prognosis rather than functioning as a surrogate for response already underway.

In summary, the study advances an important hypothesis, yet the cycle-2 NLR signal may capture a mixture of treatment tolerance, intercurrent clinical events, and early response dynamics. Clarifying these dependencies would improve the clinical interpretability of NLR2 and better define the circumstances under which it can be used to guide risk stratification in ES-SCLC.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this communication.

Author Contributions

Huazhen Wu and Jia Liao contributed equally and share joint first authorship. Methodology: HZW, JL, SWL; Writing—original draft: HZW, JL, LHH; Writing—review & editing: HZW, JL, LHH; Supervision: SWL. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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