Editorial

The role of laboratory tests as a prognostic marker for immune-checkpoint therapy in non-small cell lung cancer

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Comment on: Sung M, Jang WS, Kim HR, *et al*. Prognostic value of baseline and early treatment response of neutrophil-lymphocyte ratio, C-reactive protein, and lactate dehydrogenase in non-small cell lung cancer patients undergoing immunotherapy. Transl Lung Cancer Res 2023;12:1506-16.

Keywords: Immune-checkpoint therapy; neutrophil-lymphocyte ratio (NLR); C-reactive protein (CRP); lactate dehydrogenase (LDH); non-small cell lung cancer (NSCLC)

Submitted Aug 31, 2023. Accepted for publication Sep 08, 2023. Published online Sep 14, 2023.
doi: 10.21037/tlcr-23-566
View this article at: https://dx.doi.org/10.21037/tlcr-23-566

Immune-checkpoint inhibitors (ICIs) like pembrolizumab, atezolizumab, ipilimumab, nivolumab, durvalumab, avelumab, and cemiplimab have been approved in non-small cell lung cancer (NSCLC) in various disease stages. Their use has exponentially increased in the past decade (1). Combination of ICI with platinum based chemotherapeutic agents is one of the standards of care in the metastatic setting regardless of the programmed death-ligand 1 (PD-L1) expression on the tumor (2). Pembrolizumab (Keytruda) is approved for use as a single-agent immunotherapy in NSCLC patients with PD-L1 expression of ≥1%, including those with ≥50% expression (3,4). Over the past decade, a concomitant endeavor has unfolded, aimed at integrating ICIs into clinical scenarios, such as the perioperative milieu and the post-concurrent chemoradiation therapy landscape, thus reflecting an evolving frontier in therapeutic exploration (4-6). This includes the landmark PACIFIC trial that showed a clear improvement in response rate (RR), duration of response (DOR), and overall survival (OS), with 1 year use of durvalumab post concurrent chemo-radiation therapy in unresectable stage III NSCLC (5). Routine practice also involves utilizing atezolizumab or pembrolizumab as adjuvant therapy post-resection and adjuvant chemotherapy, notably in patients with PD-L1 expression ≥1% (7,8). The CheckMate 816 trial then has paved the way for the utilization of nivolumab in the neoadjuvant context, specifically catering to patients with resectable stage IB–IIIA disease, marking a significant advancement in treatment strategies. Compared to chemotherapy alone, addition of nivolumab demonstrated longer event-free survival (EFS) and better pathological complete response (pCR) rate (6). With an explosion in the number of indications of ICIs use, it becomes important to carefully select patients who will benefit, as ICIs can cause life-threatening autoimmune adverse effects like pneumonitis, colitis, myocarditis, and encephalitis at any point of time during and after therapy (9).

Several attempts, hence are ongoing to conduct studies that are analyzing the prognostic and predictive use of various biomarkers including PD-L1 and tumor mutational burden (TMB) expressed on the tumor itself (10). Some of these include clinical and pathological characteristics like gender, body weight, type and location of metastasis, steroid and antibiotic use, blood-based laboratory tests like neutrophil-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), C-reactive protein (CRP), vascular endothelial growth factor (VEGF), and tumor specific factors like circulating DNA, soluble plasma PD-L1, TMB, and

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mutations like *TP53* and *STK11/KEAP1* (11).

With the above background, we review a recently published study in this journal. Sung *et al.* performed a single institutional retrospective analysis of NSCLC patients who received ICI like ipilimumab, nivolumab, pembrolizumab, and atezolizumab, to study the utility of NLR, LDH, and CRP (12). They utilized data from 597 patients between 2010 and 2021. Based on survival at 1 year, patients were divided into two groups. The study did have a relatively large number of patients who did not survive at 1 year (55.6%), which is slightly lower that than historical ICI clinical trials (60–70%) (1,2), indicating that the cohort may have had patients with aggressive disease and poor prognosis to begin with. Most of the patients in both groups were metastatic NSCLC (>95%). Baseline characteristics between the groups were well matched except for Eastern Cooperative Oncology Group (ECOG), which was higher for the non-survival group, which by itself could have contributed to the mortality. The parameters were recorded at baseline, which the authors define as 14 days before the first ICI initiation, and early ICI period which they define as 8 weeks from stating the medication. Abnormal values were clearly defined (NLR >4, CRP >8 mg/dL, and LDH >247 IU/L). As the disease course progressed from the baseline to early treatment phase, NLR, CRP, and LDH rose with statistical significance in the non-survival group, but not in the survival group. Median NLR and CRP were higher in the non-survival group, whereas LDH did not show any difference between the groups. Survival curve analysis showed that patients who had abnormal values in all three markers at both baseline and early treatment had the worse prognosis followed by those whose values increased from baseline to the early treatment period. Kaplan-Meier (KM) and univariate models showed differing results, with baseline NLR predictive of OS in the baseline only model and all three predictive of OS in the univariate analysis. But with the multivariate Cox regression model for survival at 1-year, early treatment CRP and LDH were predictive of OS. The authors also add that progressive lines of chemotherapy are associated with mortality as expected (12).

The authors have performed an analysis that is both straightforward and replicable within clinical settings, using a substantial dataset from a single institution. This study contributes to the expanding body of evidence endorsing the utilization of readily accessible and cost-effective laboratory parameters for prognosticating responses to ICIs in cancer care (13). Comparatively, genomic testing using commercially available sequencing panels are relatively expensive and adds significantly to healthcare costs (14). The result of the study is in line with the data already available in literature. While not introducing novelty, this study strengthens the argument for heightened research into these biomarkers. All three parameters have been examined both individually and collectively in multiple retrospective studies to understand their relevance in assessing responses to ICIs (10). Patients with baseline and during treatment NLR $\geq$5 have had lower OS (15) and lower progression-free survival (PFS) (16,17). Regarding predicting ICI adverse effects, NLR has had a debatable utility with one study showing high NLR association with lower occurrence of ICI adverse effects yet with adverse clinical outcomes (18). Elevated LDH level correlates with higher tumor burden in diseases like melanoma and colorectal cancer. This has been noted in post-hoc analysis of trials like KEYNOTE-001. Higher tumor burden has been predictive of response to ICI activity but may also lead to higher adverse effects. Since LDH corelates with tumor burden, it may be hypothesized that it could be predictive of ICI adverse effects (19). RR to ICI like ipilimumab and nivolumab has been lower in patients with high LDH in cancers like melanoma (20). A meta-analysis of patients with NSCLC treated with ICI, showed that elevated baseline LDH was associated with shorter PFS and OS (21). Baseline CRP levels mirror the trend observed in LDH, where elevated levels align with adverse treatment outcomes. One study used a cut off >1 mg/dL, compared to >8 mg/dL used by Sung *et al.* (12,22). CRP can exhibit a flare response characterized by swift elevation post-ICI initiation, followed by a decline, potentially predictive of ICI monotherapy response. Patients with elevated biomarkers may thus elicit a higher immune response. However, this pattern might not necessarily indicate response to "chemoimmunotherapy" in NSCLC (13). The velocity of CRP rise during ICI treatment, is another parameter, studied and may predict disease progression (23).

Despite the ample evidence available, the incorporation of these parameters into clinical practice still lacks widespread acceptance. This is largely due to the inherent limitations of these studies, including that of Sung *et al.*, due to its retrospective design and the inherent flaws of such studies (12). Laboratory tests like NLR, CRP, and LDH are markers of infection and inflammation, and can be altered by several coexisting conditions a patient may have (24), leading to the inability to control for these factors in retrospective studies. The authors themselves have acknowledged and mentioned it as a part of the limitations (12). Another hurdle

is the lack of a universally established threshold that denotes the commencement of predictive usefulness. Discrepancies can arise across different laboratories conducting the tests. Conducting a prospective randomized trial remains the sole approach to address this matter comprehensively and mitigate confounding factors such as infection and inflammation. Clinical trials studying ICIs can incorporate analyzing these parameters as a secondary or tertiary objective, which can help answer these questions. Enlisting patients in ongoing prospective clinical trials like Alliance A151804 will guide our path forward. These trials involve the systematic collection of bio samples, enabling us to address this question in a methodical manner (25).

Nevertheless, the study in question rekindles the topic on whether simple and cost-efficient laboratory tests could predict and prognosticate ICIs use.

Acknowledgments

We would like to sincerely thank the editorial board of *Translational Lung Cancer Research* for inviting us to write this editorial.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-566/coif). The authors have no conflicts of interest to declare.

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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Cite this article as: Ashok Kumar P, Basnet A. The role of laboratory tests as a prognostic marker for immune-checkpoint therapy in non-small cell lung cancer. Transl Lung Cancer Res 2023;12(9):1838-1841. doi: 10.21037/tlcr-23-566

