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*Opinion*

# Extended Insights Into Advancing Multi-Omics and Prognostic Methods for Cancer Prognosis Forecasting

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**Abstract**

Zhang *et al.*'s recent article utilizes comprehensive single-cell data to identify differences in tumor cell populations, highlighting the *CKS1B*+ malignant cell subcluster as a potential target for immunotherapy. It develops a prognostic and immunotherapeutic signature (PIS) based on this subcluster, demonstrating good performance in predicting lung adenocarcinoma (LUAD) prognosis. The study also validates the role of *PSMB7* in LUAD progression. However, there are areas for improvement. There is a lack of clarity regarding the relationship between the *CKS1B*+ malignant cell subcluster and the PIS, particularly in terms of why *PSMB7* was selected for functional studies. The sequencing data are retrospectively obtained from public databases and lack prospective clinical validation. It is suggested to collect LUAD patient tissues for RT-qPCR and RNA-seq analysis and seek external multi-center validations. Additionally, integrating emerging multi-omics methods is recommended to further validate the findings. Despite these limitations, the study represents progress in understanding LUAD and treatment strategies, and continuous evaluation and refinement of multi-omics and machine learning methods are expected for future research and clinical practice.

**Keywords:** multi-omics; cancer; prognosis; machine learning

Lung adenocarcinoma (LUAD) is characterized by considerable heterogeneity, which presents substantial challenges for precise prognosis prediction [1]. Immunotherapy has revolutionized treatment for LUAD patients, with immune checkpoint inhibitors enhancing outcomes and providing a neoadjuvant option for early-stage resectable disease [2]. Nevertheless, a subset of patients does not demonstrate positive responses to immunotherapy, presenting a critical challenge in identifying specific cohorts that are likely to benefit from such treatments [3].

The recently published article by Zhang *et al.* [4] has captured our attention. The authors have leveraged comprehensive single-cell data to uncover notable differences in tumor cell populations, with a particular emphasis on *CKS1B*+ malignant cell subcluster which is linked to treatment response and stemness potential, indicating that it might serve as potential targets for immunotherapy efficacy. Additionally, the authors have developed a prognostic and immunotherapeutic signature (PIS) using machine learning algorithms based on *CKS1B*+ malignant cell subcluster, which demonstrated superior performance in predicting LUAD prognosis across multiple cohorts compared to numerous previously published prognostic signatures. Moreover, they validated the potential role of the key gene, *PSMB7*, in LUAD progression. This study highlights the crucial role of advancing multi-omics and prognostic methods for cancer prognosis forecasting. Nevertheless, further insights warrant consideration, as they hold the potential to enhance research protocols and yield greater benefits for cancer patients in the future.

Firstly, there seems to be a notable disconnect between *CKS1B*+ malignant cell subcluster and the established PIS. Although the *CKS1B*+ malignant cell subcluster is identified as significant in the single-cell analysis, the functional validation predominantly centers on *PSMB7*, lacking a clear elucidation of its relevance to this specific sub-population. It might be better if the authors could clarify the relationship between *CKS1B*+ malignant cell subcluster and the markers selected for PIS, explaining the rationale for choosing *PSMB7* for functional studies rather than *CKS1B* or other markers. Therefore, it is prudent to conduct further analyses, including investigations into co-expression patterns within single-cell and spatial transcriptome datasets, regulatory network analyses, as well as knockdown and rescue experiments.

Secondly, despite significant efforts to combine data from various databases to enhance the sample size, the prognostic model clearly lacked validation in a real-world clinical setting. It is recommended to collect a minimum of 50 paraffin-embedded tissue samples from advanced

LUAD patients who have received immunotherapy treatment, and conduct RT-qPCR as well as RNA-seq analyses to assess the expression levels of incorporated PIS genes to validate the reliability of the established model. Furthermore, the authors could collaborate with research institutions and hospitals for external multi-center validations. For example, Dai *et al*. [5] performed a meta-analysis of cohort studies to develop a predictive model for seizure recurrence following the discontinuation of antiseizure medications, and they subsequently validated it in a prospective cohort.

Thirdly, it is recommended for the authors to integrate emerging multi-omics methodologies (such as spatial transcriptome analysis, proteomics, metabolomics, genomics, pathomics, radiomics, etc.) to further validate their findings, since multi-omics integration is necessary for revealing tumor heterogeneity and immune dynamics [6–8]. Spatial transcriptome analysis could reveal cell types and PIS-related patterns in various regions of the tumor, both interior and peripheral, offering insights into the interaction network between stromal cells, immune cells, and tumor cells, as well as uncovering mechanisms that contribute to immune escape [9,10]. For example, a seminal study conducted by De Zuani *et al*. employs single-cell and spatial transcriptomics analysis to provide a high-resolution molecular map of tumor-associated macrophages, thereby advancing our understanding of their role within the tumor microenvironment [11]. For proteomics and metabolomics, although the data are limited, they offer a more precise reflection of the dynamic characteristics of disease progression [12–14]. For instance, through the integration of proteomics and metabolomics, Qian *et al*. [15] identified several differential metabolites in patients with lung cancer, indicating that the pathogenesis of lung cancer may involve significant metabolic disturbances and dysregulated protein expression. Besides, the cooptation of pathomics and radiomics presents significant potential for elucidating complex biological mechanisms and enhancing clinical decision-making processes. Artificial intelligence, especially deep learning and multimodal fusion algorithms, facilitates the extraction of latent patterns from these heterogeneous datasets, which are typically beyond the reach of conventional analytical methods [16,17].

## Conclusion

Overall, this study marks significant advancements in understanding LUAD and developing effective treatment strategies based on multi-omics and prognostic methods. We look forward to the continuous evaluation, refinement of multi-omics analyses, as well as more optimized machine learning methods for future research and clinical practice.

## Author Contributions

Research design: HLT and JL; literature collection, literature analysis: JDX, JJX, and ZT; manuscript preparation: JDX, JJX, and ZT; manuscript editing: HLT and JL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflict of Interest

The authors declare no conflict of interest.

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