Addressing Methodological and Interpretive Shortcomings in PSMA-PET Research

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Dear Editor,

I am writing to express my concerns and provide constructive criticism regarding the recently published article "Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study" (1). While the authors offer significant advancements in utilizing PSMA-PET for prostate cancer staging, I note several methodological and interpretive aspects warranting a closer examination.

Firstly, the retrospective design of this study inherently limits the control over confounding variables, which can introduce bias and affect the reliability of the findings. The authors acknowledge that cryptographic record linkage was used to update patient data, including mortality follow-up. However, they do not sufficiently discuss how potential inconsistencies or inaccuracies in historical data were addressed. For instance, variations in PSMA-PET imaging protocols across different centers might introduce measurement bias. This is particularly concerning given the multicentre nature of the study, where standardization of imaging and reporting is crucial (2). Future research should include rigorous methods to harmonize imaging protocols and consider prospective designs to mitigate these biases (3).

Secondly, the statistical methods employed, particularly the use of Cox regression

models with LASSO penalty, are robust for identifying predictors of overall survival. However, the study does not provide sufficient justification for the selection of variables included in the final model. The authors mention that 16 potential PSMA-PET-based PROMISE predictors were considered, but the criteria for inclusion or exclusion of these variables in the final model are not transparent. This lack of clarity raises concerns about potential overfitting, especially given the high dimensionality relative to the sample size. A more detailed explanation of the variable selection process, including any pre-specified criteria or thresholds, would enhance the reproducibility and credibility of the findings.

Lastly, the interpretation of the prognostic accuracy of the visual and quantitative PPP nomograms could benefit from a more nuanced discussion of their clinical applicability. While the study reports superior performance of the PPP nomograms compared to established clinical risk scores, it falls short in exploring the practical implications for clinical decision-making. For example, how would these nomograms influence treatment planning or follow-up strategies for patients at different stages of prostate cancer? The discussion should integrate real-world examples or case studies to illustrate the potential impact of these nomograms on patient management. Additionally, the study should consider the cost-effectiveness and accessibility of implementing PSMA-PET and PROMISE criteria in routine clinical practice, particularly in resource-limited settings (4).

Contributors

Dan Shan: Study design & Manuscript Writing and Revision.

Declaration of Interests

I declare no competing interests.

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