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Letter to the Editor

Re: Jurczok N, Dernbach G, Ebner B, et al. Multiregional immune profiling reveals prognostic patterns in bladder cancer. Eur Urol Oncol. In press. http://dx.doi.org/10.1016/j.euo.2025.12.006

Jurczok et al present a multiregional immune profiling analysis in 251 cystectomy patients with muscle-invasive bladder cancer (MIBC), digitally quantifying six checkpoint proteins (IDO, LAG-3, PD-1, PD-L1, TIM-3, VISTA) from invasive-front and tumor-center cores and relating these metrics to survival via multivariable Cox models [1]. Clustering intratumoral densities yields three immune descriptors (CID1–3) that separate outcomes beyond Union for International Cancer Control (UICC); median OS spans 100.5 mo in CID1 versus 18.5 mo in CID3, and they advise sampling at least four spatially distinct areas to recover maximal expression for most markers. These clinically instructive findings raise two points—refining the temporal structure within the Cox specification and, building on their normalization and sensitivity work, considering a compact optional layer of input-stability checks for cross-center integration or external validation—which warrant further discussion.

Analytically, the semiparametric Cox approach—adjusted for core clinicopathologic covariates and treating checkpoint densities or the ordered CID1→CID3 descriptor as time-invariant—constitutes an appropriate primary inferential strategy. Nevertheless, aggregate proportional hazards diagnostics may miss transient yet clinically meaningful departures in heterogeneous settings [2]. Within the same framework, it would be prudent to explore time-varying coefficients for selected immune features (eg, PD-1/PD-L1 on immune cells, TIM-3–positive immune-cell densities) or for the CID ordinal, and to pre-specify a small set of clinically motivated interactions (eg, descriptor by stage or spatial-contrast-by-marker). These extensions accord with spatial signals—IDO-positive immune cells enriched at the invasive front, a bimodal PD-L1 pattern in tumor cells, and notable front–center correlations—suggesting that clinical context may modulate effect sizes over follow-up. In addition, landmark analyses at prespecified times would preserve interpretability for decision-making while stress-testing early-event sensitivity, without altering endpoints or the multiregional design [3].

In parallel, building on their preprocessing and sensitivity steps—log2 transformation, z-standardization, clinically motivated cut-offs, and attention to distance/linkage in clustering—we propose, as an optional extension, a compact, model-agnostic suite of input stability checks to support survival inference and descriptor construction when batch heterogeneity or data harmonization is anticipated. Specifically, applying Feature Agglomeration to consolidate collinear inputs into interpretable composites can mitigate multicollinearity and preserve clustering geometry, while Highly Variable Gene Selection down-weights near-constant features so low-information variables do not dominate distances or attenuate hazard contrasts [4]. In addition, rank-based association screens—Spearman's rho and Kendall's tau—can guide transformations and inform interaction prespecification without committing the analysis to a single parametric assumption [5]. These measures are not intended to supplant the current pipeline; rather, they are lightweight adjuncts where external validation constraints or multi-institutional integration warrant added stability.

Overall, embracing time-variation and prespecified interactions within the existing Cox framework, while retaining a minimal input stability layer for future datasets, would—without disrupting their multiregional logic—enhance stability, interpretability, and portability of survival inference and immune descriptor stratification. Practically, this hybrid path respects their inferential core—hazard ratios tied to clinically legible covariates—yet allows gains to extend to unsupervised layers and validation, including heeding their recommendation to sample $\geq$4 distinct cores for maximal expression detection. As immune profiling workflows scale across institutions, such pragmatic add-ons can secure the reproducibility already indicated and facilitate broader clinical uptake.

Conflict of interest: The authors have nothing to disclose.

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