Estimating tumour microenvironment cellular states from bulk RNAseq produces biomarkers of clinical outcome across stages

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Background: We still lack predictive biomarkers of response for lung cancer, a complex and heterogeneous disease for which there is a need for better predictive biomarkers for personalized therapies. A better understanding of the tumor microenvironment (TME) is needed to improve patient outcomes. Here, we propose a novel computational approach that leverages bulk RNA-seq to infer clinically relevant patient-specific cell groups and states, which are normally detectable only with more costly and complex single-cell assays.

Methods: We developed an integrated computational approach based on cell type deconvolution and transcription factor activity estimation combined with an advanced machine learning framework to extract clinically relevant features from bulk RNAseq data. We analyzed a cohort of 62 primary lung adenocarcinoma (LUAD) samples from IUCT patients across disease stages (Hurtado et al. 2024). As validation, we use an independent RNA-seq cohort of early-stage LUAD with 77 RNAseq and 15 scRNA-seq samples collected at Vanderbilt University (Senosain et al. 2023). To assess the potential for this approach in late stage samples, we applied it to a multicenter French cohort with 130 advanced NSCLC patients treated with immunotherapy (IT) (N=90) or chemotherapy (N=40) in first-line setting (E. Gobbini, GFPC and UNICANCER).

Results: Our results identified cell populations associated with immune response and evasion (Hurtado et al. 2024). In early-stage samples, we observed a dual role of natural killer cells, suggesting their involvement in both immune activation and suppression. This dual behavior was linked to patient survival, highlighting natural killer cells as important players (Figure 1AB). In the late stage cohort we identified cell type groups significantly associated with immunotherapy response (p-value = 0.025, F-statistic = 5.188, effect size = 0.051) which predicted response with better performance than several existing approaches (Figure 1C).

Conclusion: Our approach characterizes RNA-seq based TME profiles through immune cell states and interactions, which enhances patient stratification. It identifies immune cell phenotype and interaction biomarkers linked to survival and progression that are validated across independent cohorts.

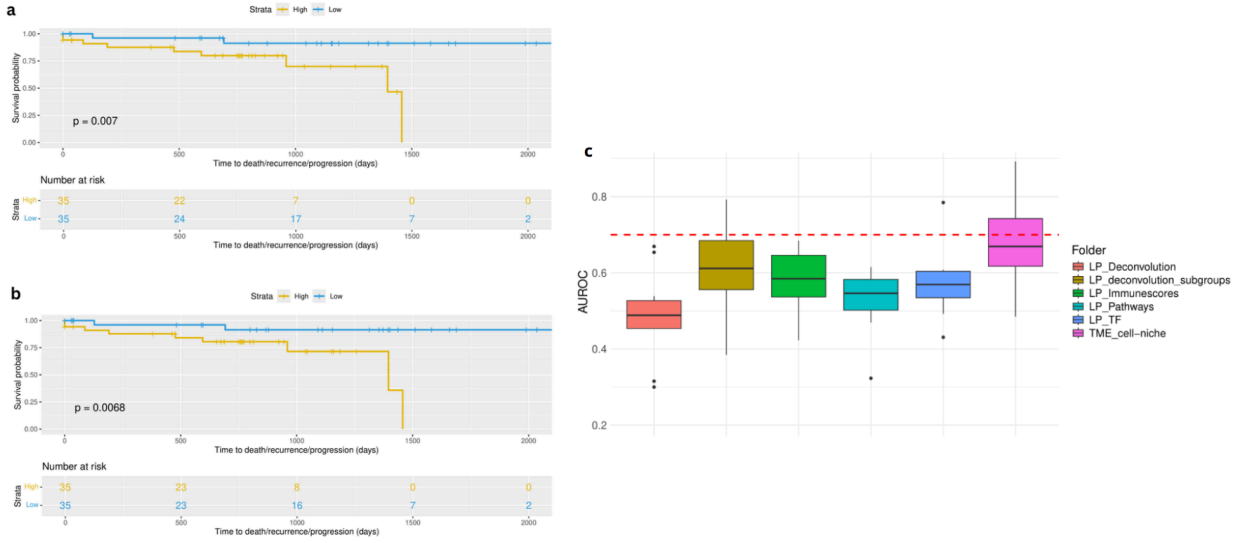

Figure 1. (AB). Multivariate cox proportional hazards models were developed across all selected 10 TME patient profiles in the early-stage Vanderbilt cohort to evaluate recurrence-free-survival. Survival curves based on high and low risk groups using linear predictors after fitting Cox PH model using cell type groups as covariates (p-value = 0.007, p-value = 0.0068). C. Machine learning models performance (AUC-ROC) to predict immunotherapy response in the late-stage cohort using different approaches to estimate TME features (our approach is named TME_cell-niche, line red corresponds to AUC = 0.7).

References

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