



P2.078: Multi-omics Characterization of Genomic Instability Landscapes Predicts Response to Neoadjuvant Immunochemotherapy in Lung Squamous Cell Carcinoma

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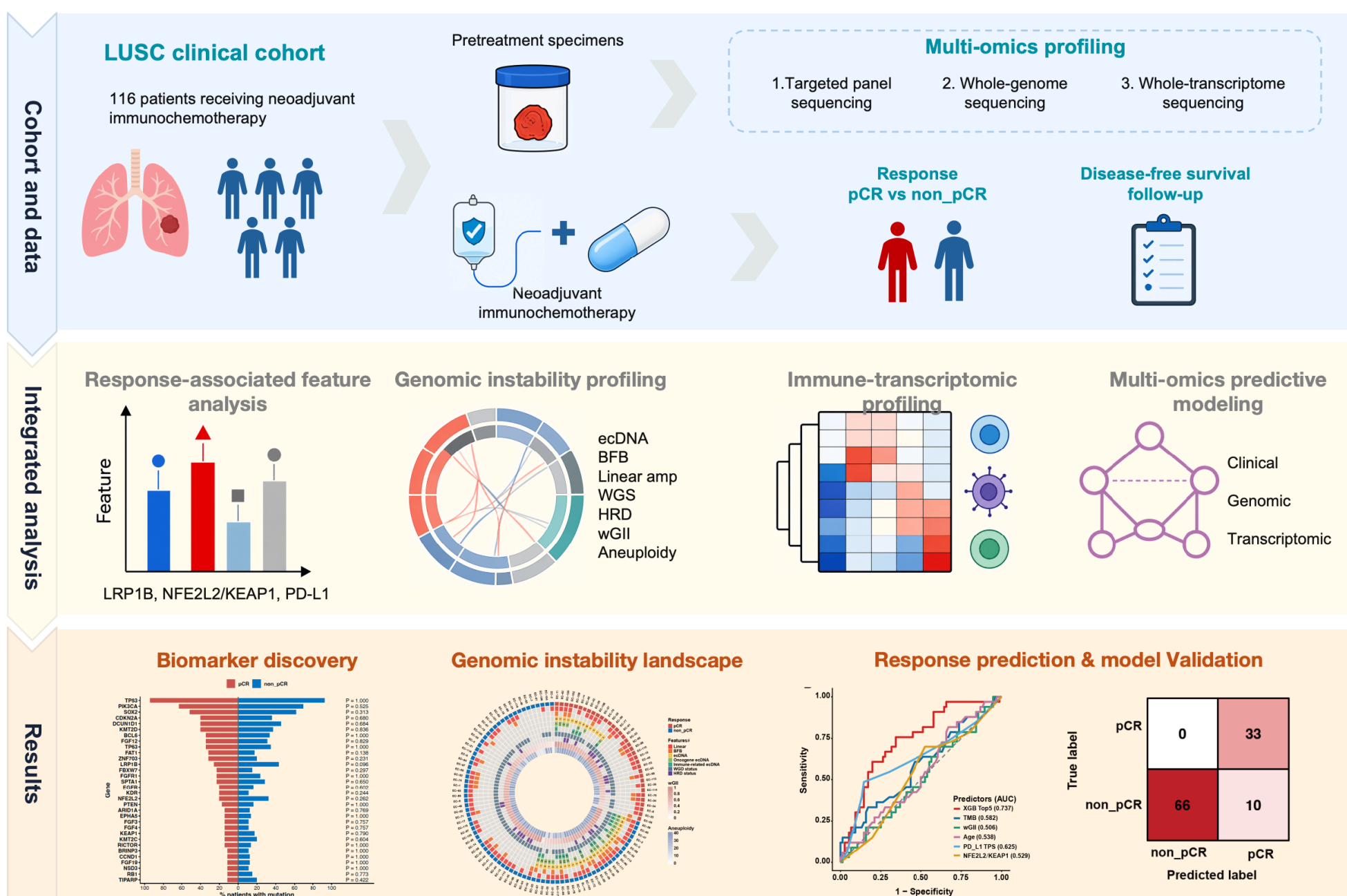
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INTRODUCTION

- Neoadjuvant immunochemotherapy (nICT) has been shown to improve pathological response and survival in resectable, locally advanced LUSC, yet response heterogeneity remains pronounced¹⁻².
- Currently used biomarkers, including PD-L1 TPS and TMB, exhibit limited predictive performance, highlighting the urgent need for more effective response stratification³⁻⁴.
- Herein, we integrated clinical, genomic, and transcriptomic features to identify key response determinants and develop multimodal predictive models.

METHODS

- A retrospective cohort of 116 LUSC patients receiving nICT (SHChest cohort) was included, with pre-treatment biopsies subjected to multi-omics profiling.
- Targeted sequencing, WGS, and RNA-seq were performed to characterize somatic alterations, chromosomal instability, amplification events (linear/BFB/ecDNA), and transcriptomic features.
- Biomarker discovery and survival analysis were performed, and a machine-learning-based pCR prediction model was further built and externally validated in an independent cohort (n=26).



RESULTS

Result 1

- PD-L1 TPS $\geq 50\%$ and *NFE2L2/KEAP1* alterations were independently associated with pCR (Fig. 1A).
- ecDNA showed a potential interaction with PD-L1 TPS; the pCR association of PD-L1 TPS $\geq 50\%$ was stronger in ecDNA-positive patients, though not statistically significant (Fig. 1A-B)

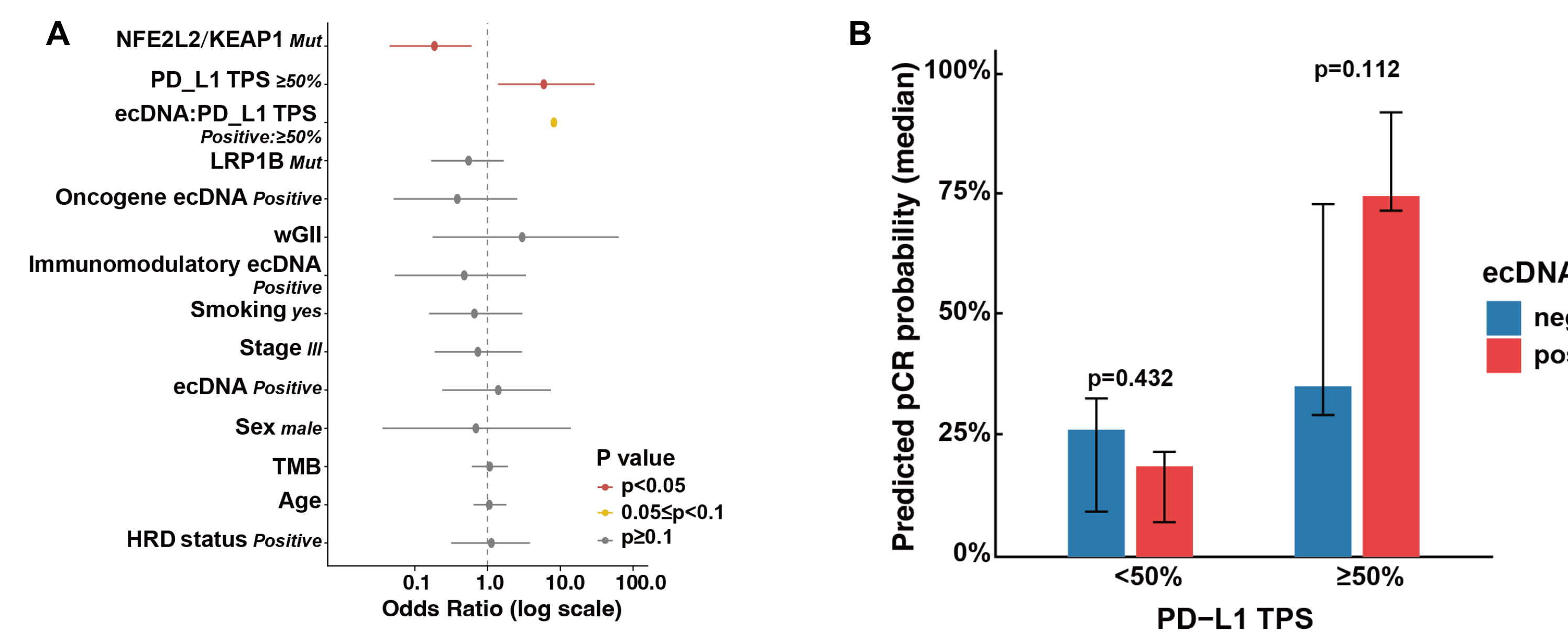


Fig 1. Associations of clinical and genomic features with pathological response.

Result 2

- pCR tumors displayed enhanced immune activation signatures, whereas non-pCR tumors were enriched for squamous epithelial differentiation programs, particularly those related to keratinization (Fig. 2).

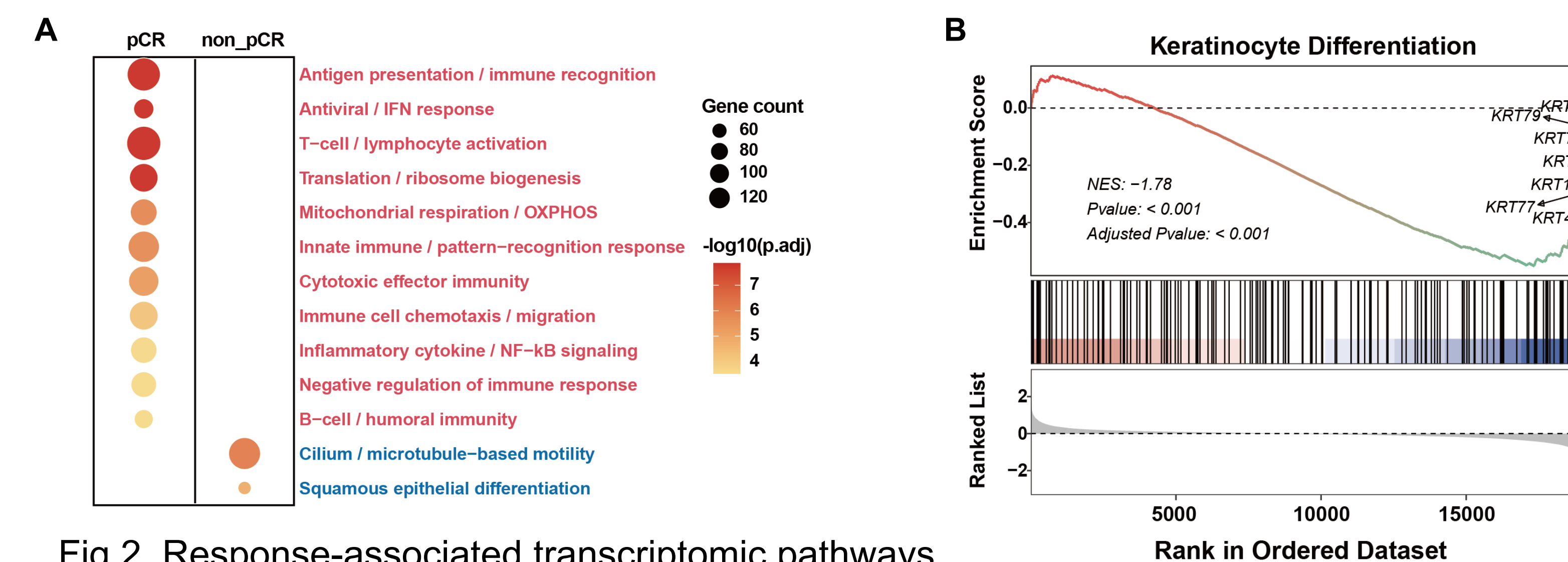


Fig 2. Response-associated transcriptomic pathways.

CONCLUSION

- An integrated clinical-genomic model accurately predicts pCR and identifies non-responders to nICT, offering a practical tool for response stratification.
- Immune-related transcriptomic features further elucidate the biological underpinnings of response heterogeneity.
- These findings highlight the potential of multi-omic integration to inform clinical decision-making in LUSC receiving nICT.

Abbreviations: LUSC, lung squamous cell carcinoma; TPS, tumor proportion score; TMB, tumor mutation burden; WGS, whole-genome sequencing; BFB, breakage-fusion-bridge; ecDNA, extrachromosomal DNA; pCR, pathological complete response; wGII, weighted genome instability index; NPV, negative predictive value; DFS, disease-free survival.

Result 3

- An XGBoost model integrating five clinical-genomic features (TMB, wGII, age, PD-L1 TPS, and *NFE2L2/KEAP1* alterations) achieved an AUC of 0.737, with 100% sensitivity for identifying pCR cases and 100% NPV for excluding patients unlikely to attain pCR, in both the SHChest cohort and the PD-L1 TPS $< 50\%$ subgroup (Fig. 3A-C).
- The model remained robust in the independent validation cohort, with 88.5% accuracy and maintaining 100% NPV for non-pCR prediction (Fig. 3D).
- Model-based response stratification provided superior DFS discrimination compared with pathological response (Fig. 3E).

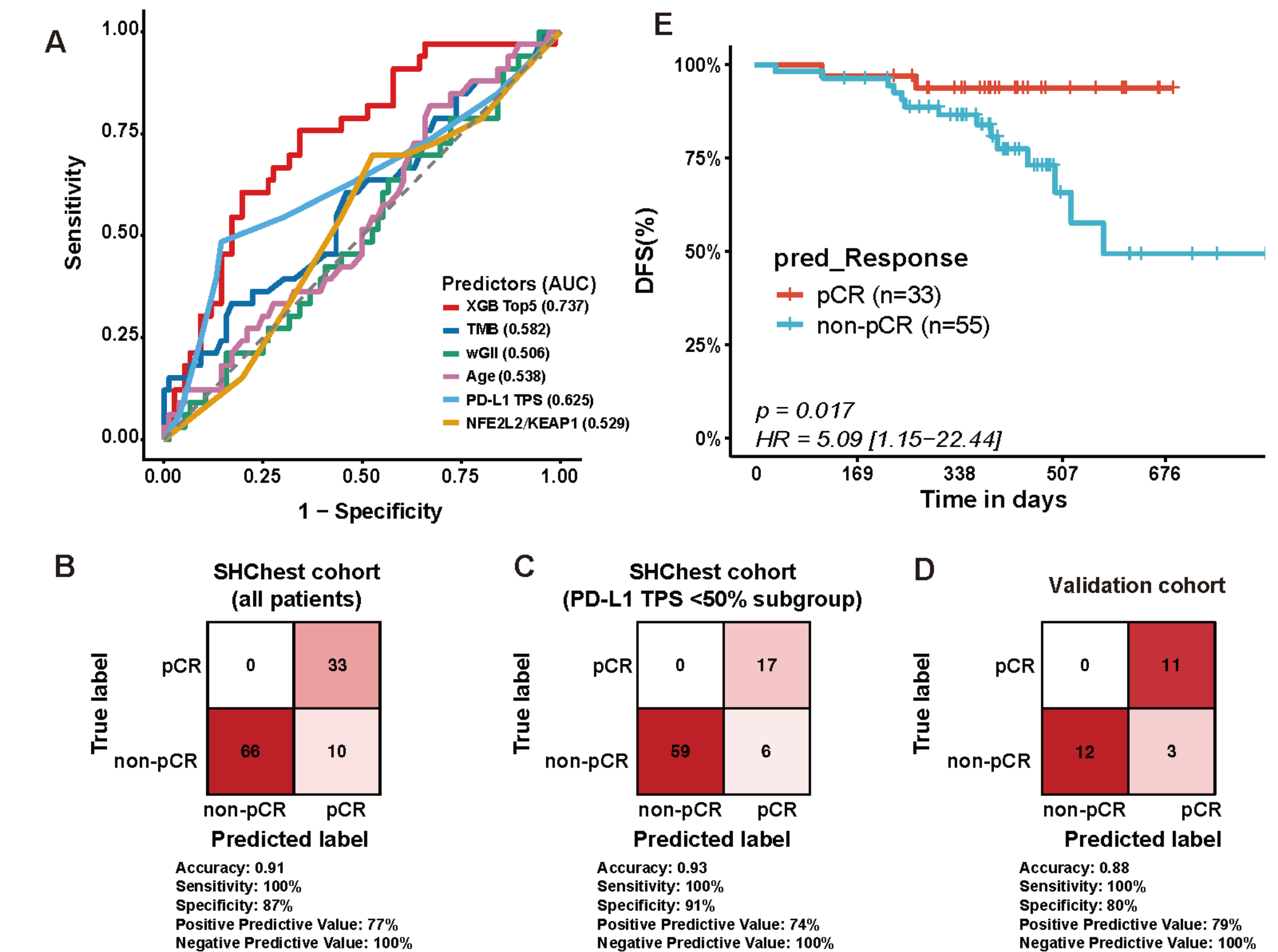


Fig 3. Construction and validation of the multi-omic therapeutic efficacy prediction model.

REFERENCES & DISCLOSURE

References

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Disclosure

The authors declare no potential conflicts of interest.