Abstract 4526: Machine learning-based transcriptomic signatures to predict treatment outcomes across targeted and immunotherapy regimens in renal cell carcinoma

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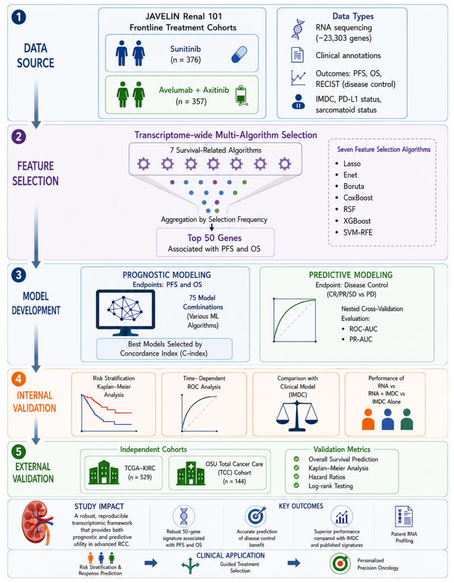
BACKGROUND

- Tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have improved outcomes in advanced renal cell carcinoma (RCC), but patient benefit remains highly variable[1,2].
- Durable responses occur only in a subset of patients, highlighting the need for individualized treatment selection[1-3].
- Current clinical risk models, including the International Metastatic RCC Database Consortium (IMDC) model, and published transcriptomic signatures have limited ability to guide regimen-specific therapy[3-5].
- We developed a machine learning (ML)–based transcriptomic framework to predict progression-free survival (PFS), overall survival (OS), and disease control across frontline RCC regimens.

STUDY DESIGN



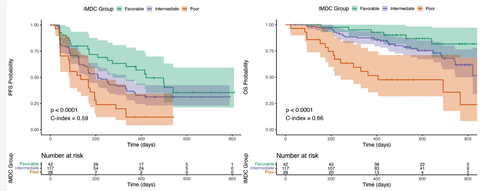
- JAVELIN Renal 101 RNA and clinical data were analyzed in two frontline cohorts.
- Transcriptome-wide screening identified PFS/OS-associated signatures.
- Models were evaluated for PFS/OS prediction, disease control, and external OS validation.

Results

IMDC risk groups show limited PFS/OS discrimination

Sunitinib cohort

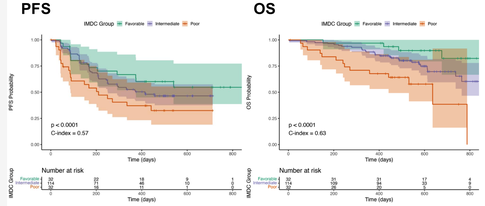
PFS



OS

Avelumab + Axitinib cohort

PFS



OS

Figure 1. IMDC based risk stratification in the sunitinib cohort (top) and avelumab plus axitinib cohort (bottom). KM curves show PFS (left) and OS (right) across IMDC risk groups.

IMDC risk groups by disease control status

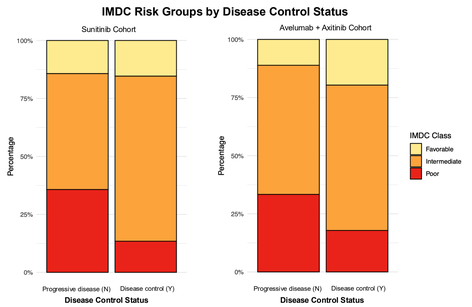
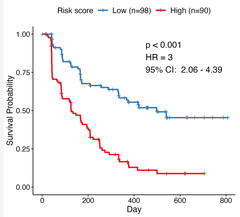


Figure 2. Distribution of IMDC risk groups by disease control status in the sunitinib and avelumab plus axitinib cohorts. N indicates progressive disease and Y indicates disease control.

Model-derived risk groups stratify PFS/OS

Sunitinib cohort

PFS



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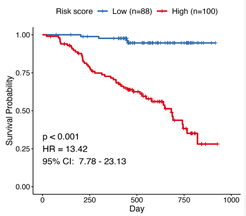
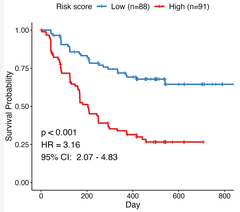


Avelumab + Axitinib cohort

PFS



OS

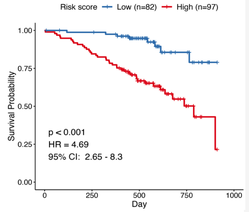


Figure 3. Transcriptomic model derived risk stratification in the sunitinib cohort (top) and avelumab plus axitinib cohort (bottom). Kaplan–Meier (KM) curves show PFS (left) and OS (right) for high- and low-risk groups defined by the best-performing models.

Transcriptomic models provide prognostic value beyond IMDC

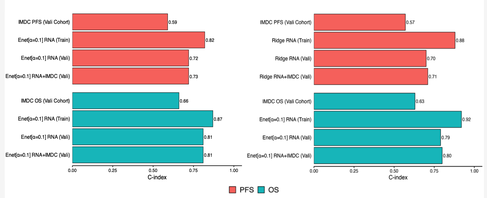
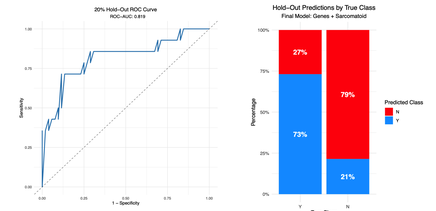


Figure 4. Concordance index (C-index) comparison of RNA only, RNA plus IMDC, and IMDC only models across both treatment cohorts.

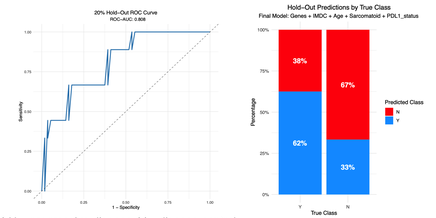
Key interpretation: Transcriptomic risk scores showed stronger PFS/OS separation than IMDC, and adding IMDC provided minimal additional improvement.

PFS-derived signatures predict disease control

Sunitinib cohort



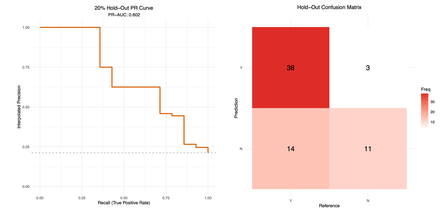
Avelumab + Axitinib cohort



* N = progressive disease, Y = disease control

Figure 5. PFS-derived transcriptomic classifiers predict disease control in the sunitinib cohort (top) and avelumab plus axitinib cohort (bottom). ROC curves show holdout performance, and bar plots show predicted disease control by true class.

Sunitinib cohort



Avelumab + Axitinib cohort

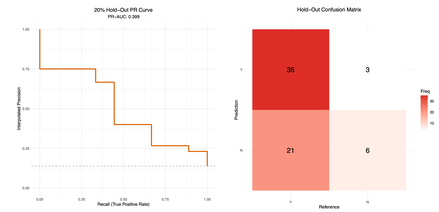


Figure 6. Additional disease control classifier performance in the 20% holdout cohorts. Precision recall (PR) curves are shown on the left and confusion matrices are shown on the right for the sunitinib cohort (top) and avelumab plus axitinib cohort (bottom).

Signature benchmarking

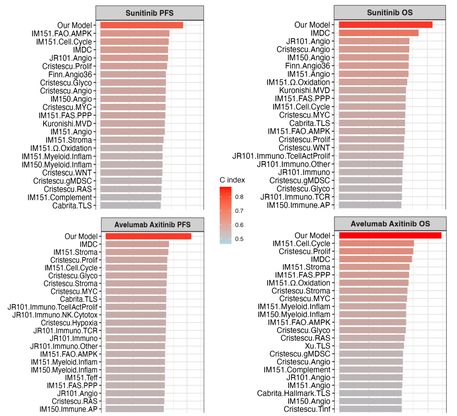


Figure 7. ML-derived transcriptomic signatures achieved the highest C-index across PFS and OS in both treatment cohorts compared with IMDC and published RCC transcriptomic signatures.

Conclusions

- Regimen-specific transcriptomic signatures stratified PFS and OS across sunitinib and avelumab plus axitinib cohorts.
- RNA-based models provided independent prognostic value beyond IMDC, with minimal incremental benefit from adding IMDC.
- PFS-derived transcriptomic classifiers predicted disease control in both treatment cohorts.
- External validation and benchmarking support further prospective evaluation.

References

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