Estimation of Overall Survival in Immunotherapy-Treated Bladder Cancer using Computer Vision

Brandon Ginley[1], Bolan Linghu[2], Chaitanya Parmar[1], Neil Beeharry[3], Shibu Thomas[3], Patricia Raciti[3], Joel Greshock[2], Kristopher Standish[1], Albert Juan Ramon[1]

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KEY TAKEAWAYS

We developed algorithms to generate a risk categorization from H&E tissues of bladder cancer which predict patient survival under anti-PD-1 immunotherapies. The algorithm, which incorporates inferred PDL-1 status, tissue and cell features, age, and sex, demonstrated that low-risk patients have significantly higher survival probabilities compared to high-risk patients.

H&E: Hematoxylin and eosin; **PD(L)-1:** Programmed death protein (ligand) 1

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CONCLUSIONS

- We developed algorithms to infer PDL-1 status and tumor microenvironment features from a digitized H&E slide typically used for disease diagnosis.
- An algorithm combining inferred PDL-1 status, demographics, and tumor microenvironment (lymphocyte, stroma, tumor, and necrosis morphology and texture) can estimate survival risk under anti-PD-1 therapies.
- This method offers a cheaper and faster alternative to immunohistochemistry, potentially aiding in the selection of patients who would benefit most from PD-(L)-1 therapy.

PD(L)-1: programmed death protein (ligand) 1, **H&E**: hematoxylin and eosin, **AUC**: area under the curve, **BC**: bladder cancer

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INTRODUCTION

Bladder cancer is a significant health challenge, ranking among the most common malignancies worldwide. The use of checkpoint inhibitors has shown to be effective, but patient response is variable. This underscores the need for advanced tools to better understand and optimize treatment outcomes. In this work, we aimed to develop an artificial intelligence (AI) algorithm to evaluate the overall survival of bladder cancer patients treated with anti-PD-1 therapies, to identify patients with high likelihood of durable outcomes and recognize patients that may require different or combination therapies to achieve better outcomes. Our research leverages patient treatment history, demographics, AI-based PDL-1 positivity, and digitally derived features of the tumor microenvironment, a method proved to be effective though exploration in larger sample sizes is warranted.

PD(L)-1: programmed death protein (ligand) 1, **AI/ML**: artificial intelligence/machine learning

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METHODS

A foundation model was trained on ~100k WSIs from various sources. H&E and PDL-1 IHC slides were used to fine-tune a model (MIA-PDL1[1]), which infers PDL-1 expression levels from H&E. Individualized IHC thresholds (TPS/CPS>=10% for 22C3, CPS>=1% on 28-8, etc) from pathologist reads created training labels. AI inferred probabilities >=0.5 were considered a positive result. We then trained MIA-Tissue to identify tissue regions of tumor, stroma, necrosis and lymphocytes. An open-source model (CellViT[2]) was used to identify neoplastic, inflammatory, connective, epithelial, and dead cells. 617 biologically inspired features were derived from the segmentations. A random survival forest (MIA-IO) was trained with outputs from each model along with patient age and sex to estimate overall survival from treatment start. This model was first developed with bladder cancer patients treated with any type of immunotherapy and further evaluated on a subset of anti-PD-1 treated patients (Pembrolizumab and Nivolumab). Log-rank test was used to determine statistical significance of inferred high-risk and low-risk event times for each model.

WSIs: Whole slide images; **H&E:** Hematoxylin and eosin; **IHC:** Immunohistochemistry; **MIA:** Microscopy image analysis; **TPS:** Tumor proportion score; **CPS:** Combined positive score; **PD(L)-1**: programmed death protein (ligand) 1, **AI**: artificial intelligence; **IO:** Immunotherapy outcome

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GUIDED REVIEW OF RESULTS

Table 1 shows datasets used for this study. MIA-PDL1 achieved 0.82/0.8 AUC on internal/independent test sets (**Table 2**). **Figure 1** outlines (via box-plot of testing ROIs) MIA-Tissue performance, with best results seen for stroma, tumor, and lymphocyte, and rarity leading to lower performance for necrosis. **Figure 2** shows an example overlay of both tissue segmentation and cell segmentation outputs. **Figures 3&4** demonstrate that *algorithm estimated* PDL-1 status, age, and sex do not reliably determine survival outcomes in anti-PD-1 treated internal test cohort. Ground truth IHC PDL-1 was not available for comparison. **Figure 5** shows that significant survival separation is achieved with added histologic features of the tumor microenvironment in internal test, confirmed in the independent testing cohort (**Figure 6).** Finally, **Table 3** outlines the most important features for determining survival risk, with lymphocyte features holding the most overall power, but necrosis, tumor, and stroma features also having significant play.

IHC: Immunohistochemistry; **MIA:** Microscopy image analysis; **PD(L)-1**: programmed death protein (ligand) 1, **AUC:** area under receiver operator curve; **ROIs:** Regions of interest

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Table 1: Data breakdown for cohorts used in model development of presented analyses

Analysis category	*n*
MIA-PDL1 model (whole slides)	**1639**
Training	**1158**
Internal holdout	**388**
Independent holdout	**93**
MIA-Tissue model (patches)	**1919**
Training	**1520**
Validation	**321**
Testing	**78**
CellVIT cell segmentation model (patches)	**7904**
Training	**5248**
Testing	**2656**
MIA-IO model (whole slides)	**558**
All immunotherapies training – internal	**264**
All immunotherapies testing – internal	**67**
All immunotherapies testing – independent	**227**
PD1 therapies training – internal	**157**
PD1 therapies testing – internal	**39**
PD1 therapies testing – independent	**182**

MIA: Microscopy image analysis; **PD(L)-1**: programmed death protein (ligand) 1; **IO:** Immunotherapy outcome

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Table 2: Performance of AI-based PDL-1 estimation from H&E image[1]

Dataset	AUC
Internal test set	0.82
Independent test set	0.80

H&E: Hematoxylin and eosin; **PD(L)-1**: programmed death protein (ligand) 1, **AI**: artificial intelligence

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Figure 1: Performance of tissue segmentation

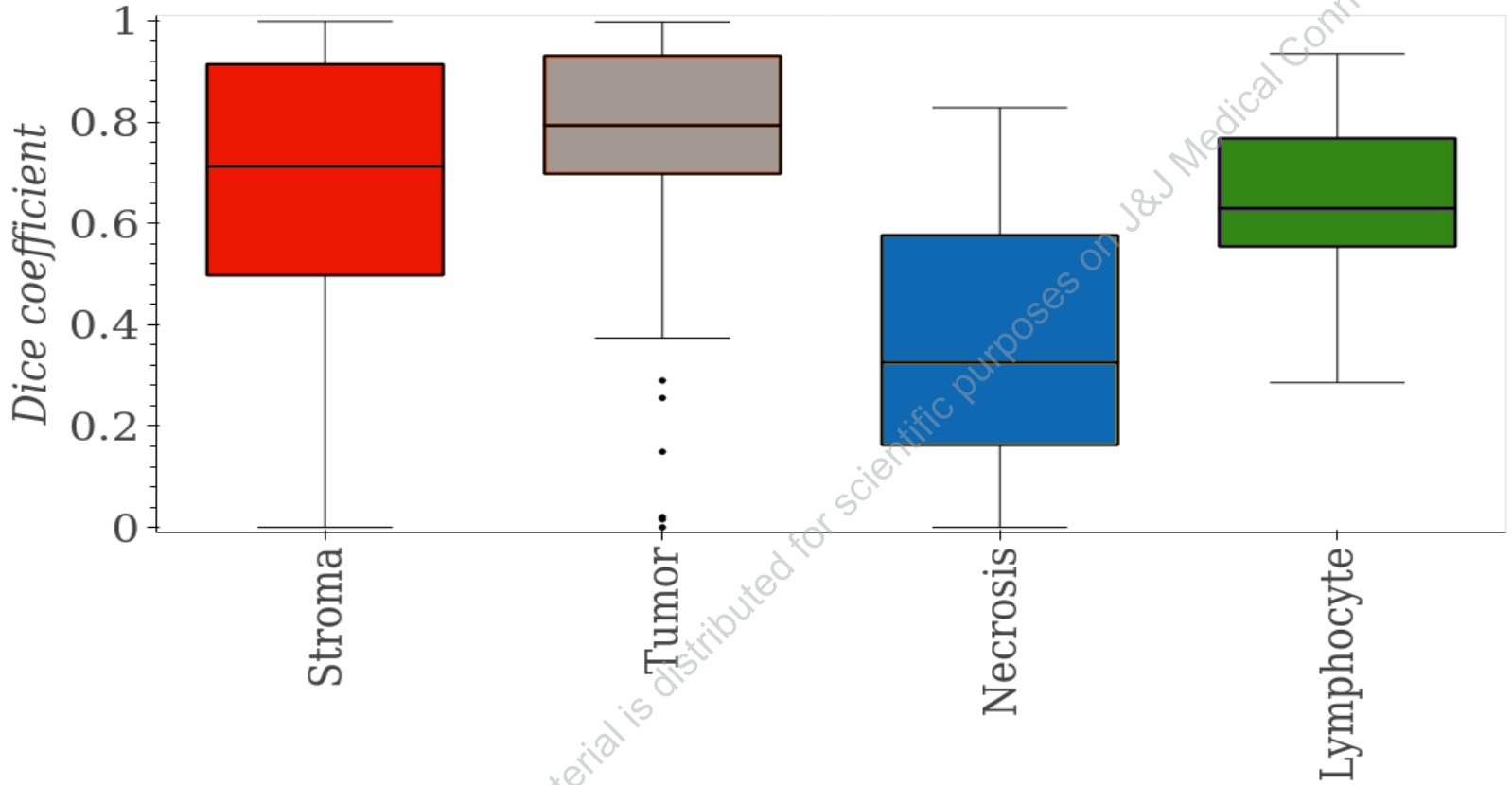

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Figure 2: Example segmentation outputs on whole slide image

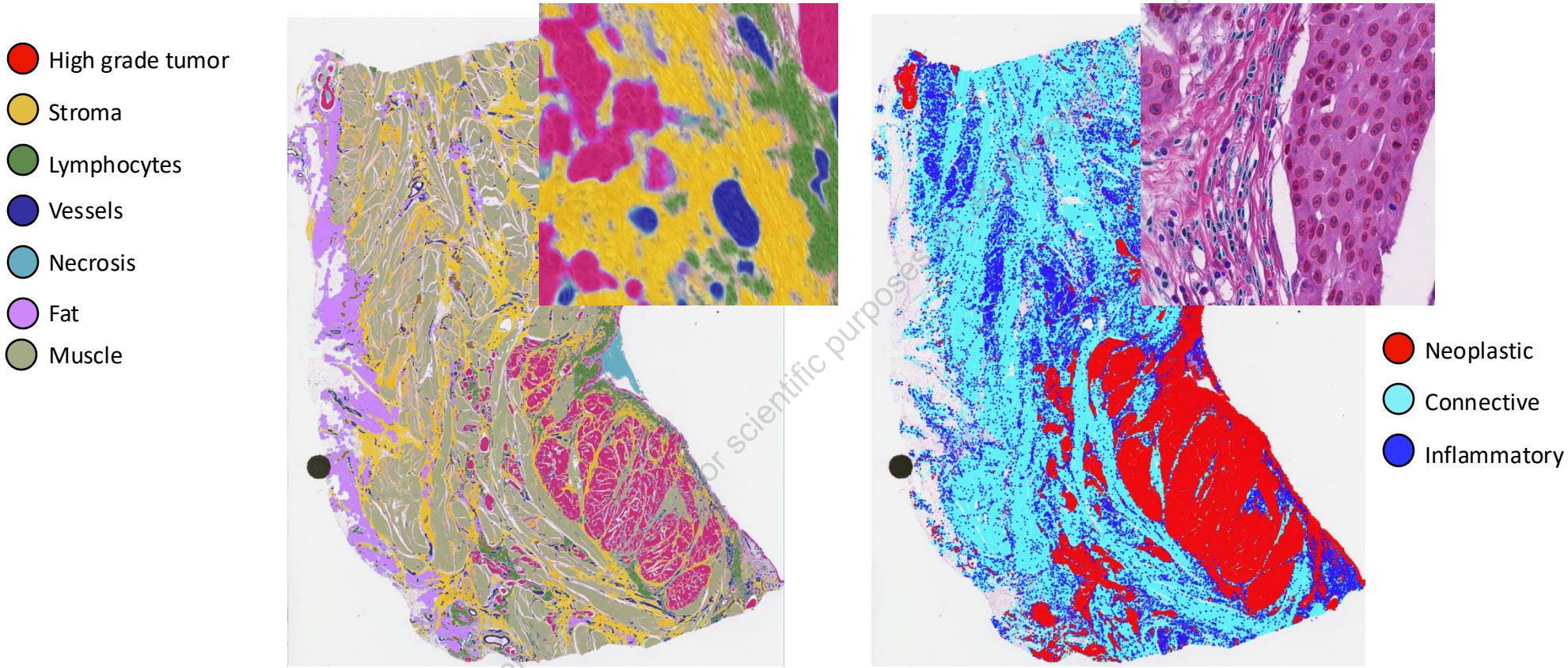

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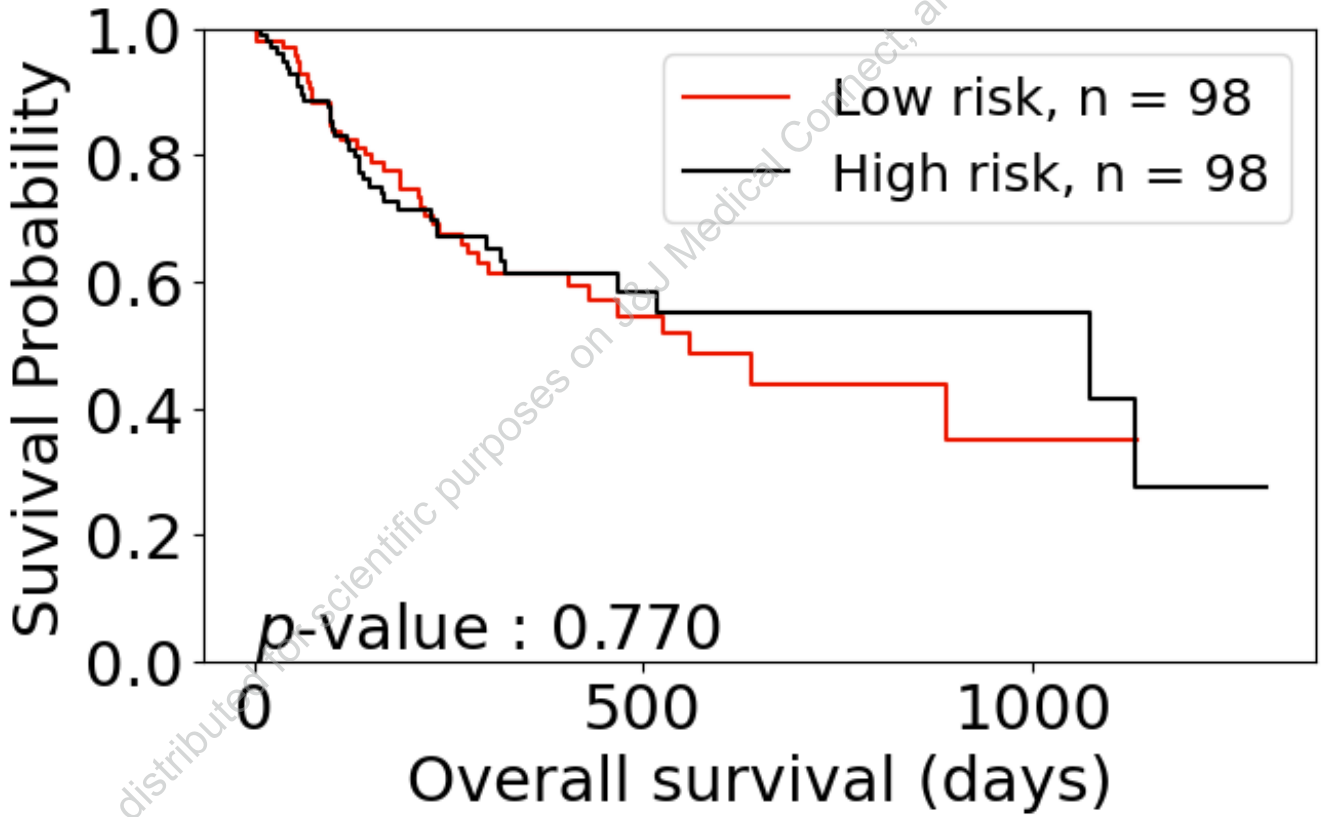
Figure 3: Overall survival curves for anti-PD-1 treated patients using inferred PDL-1 status as risk score



PD(L)-1: programmed death protein (ligand) 1

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Figure 4: Overall survival curves for anti-PD-1 treated patients using median age or sex as risk scores

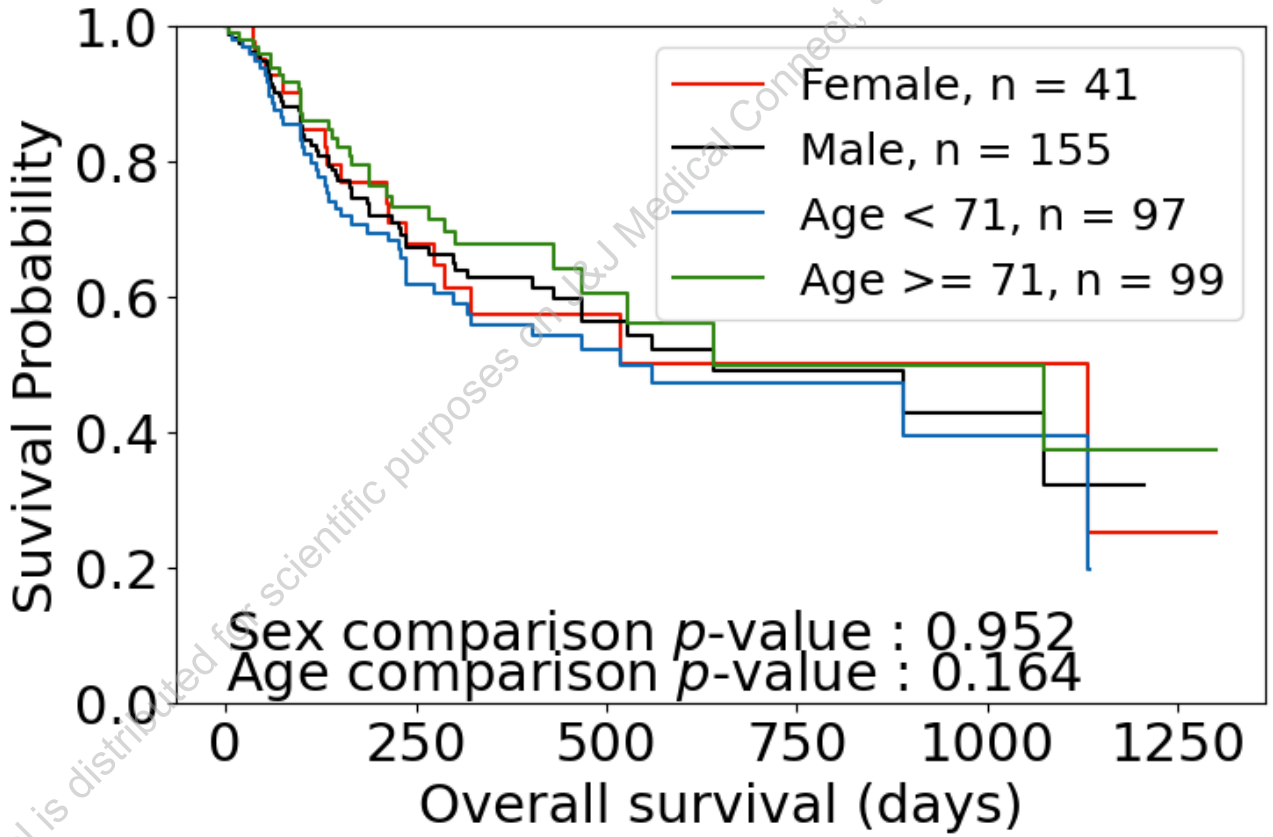

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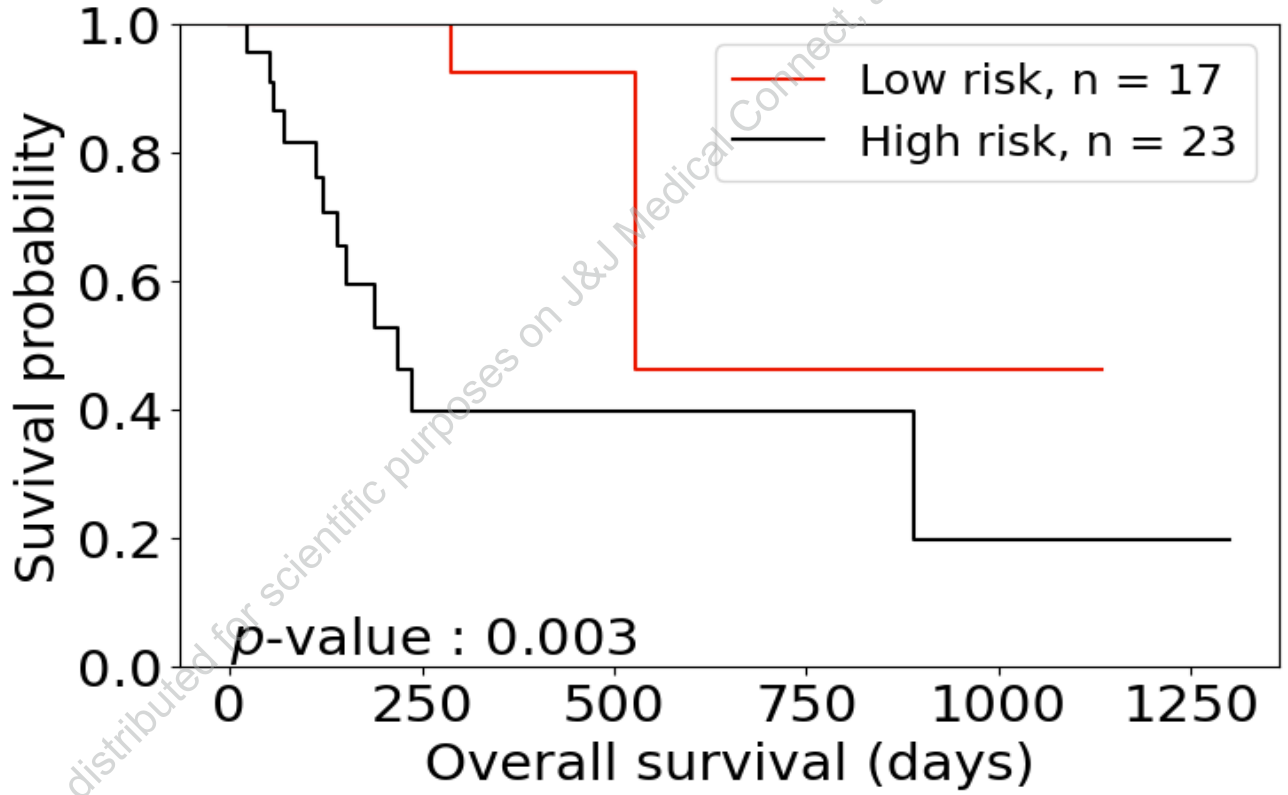
Figure 5: Survival curves based on combined demographics, AI-based PDL-1 and tumor microenvironment risk score in internal anti-PD-1 treated test set, segregated by median survival forest (MIA-IO) score.



MIA: Microscopy image analysis; **PD(L)-1**: programmed death protein (ligand) 1, **AI**: artificial intelligence; **IO:** Immunotherapy outcome

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Figure 6: Survival curves based on combined demographics, AI-based PDL-1 and tumor microenvironment risk score in independent anti-PD-1 treated test set, segregated by median survival forest (MIA-IO) score.

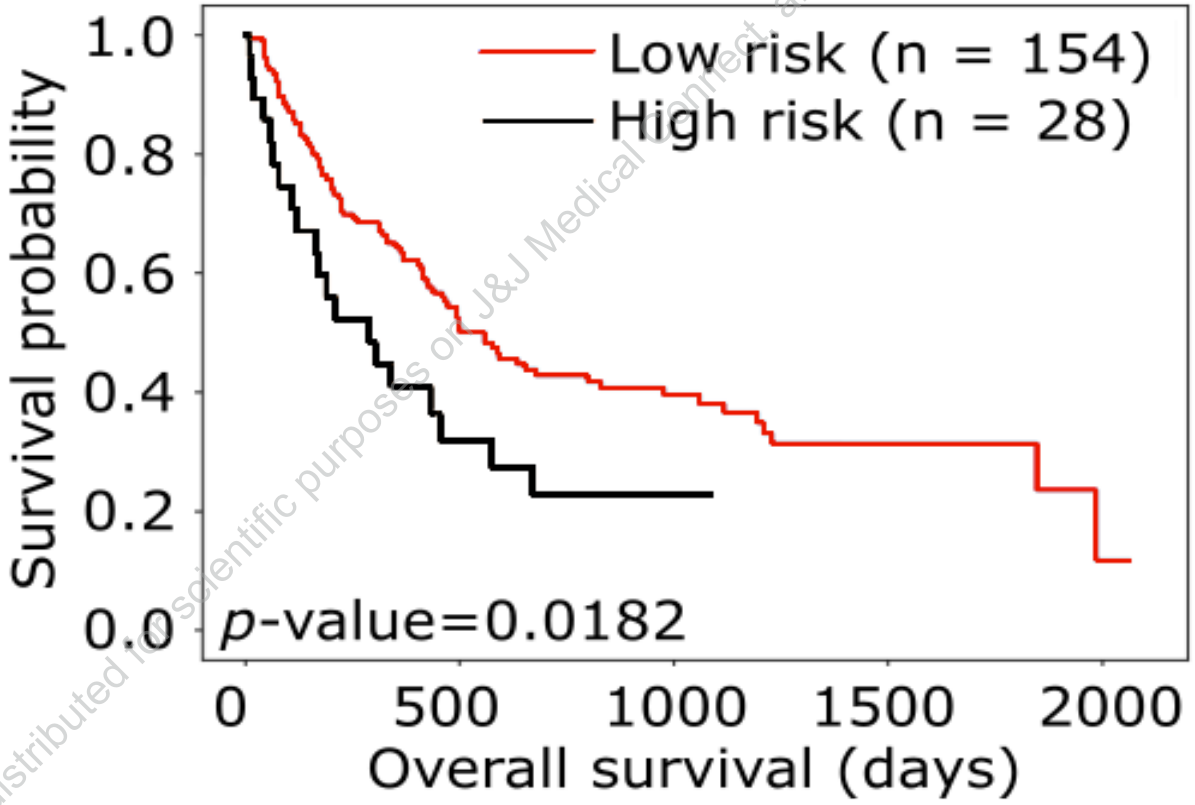

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Table 3: Top 5 important feature groups for overall survival estimation as a function of performance loss when features are dropped out

Category	C-index drop
Lymphocyte shape factors	0.083
Necrosis textures	0.067
Lymphocyte textures	0.057
Tumor shape factors	0.033
Stroma textures	0.025

C-index: Concordance index

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[1]Albert Juan Ramon et al., Inferring PDL-1 status from H&E images using digital pathology to identify patients responsive to anti-PD(L)-1 immuno-oncology therapy for bladder cancer trials.. *JCO* 42, 4579-4579(2024). DOI:10.1200/JCO.2024.42.16_suppl.4579

[2]Fabian Hörst, Moritz Rempe, Lukas Heine, Constantin Seibold, Julius Keyl, Giulia Baldini, Selma Ugurel, Jens Siveke, Barbara Grünwald, Jan Egger, Jens Kleesiek,, CellViT: Vision Transformers for precise cell segmentation and classification, Medical Image Analysis, Volume 94, 2024, 103143, ISSN 1361-8415, https://doi.org/10.1016/j.media.2024.103143. (https://www.sciencedirect.com/science/article/pii/S1361841524000689)

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