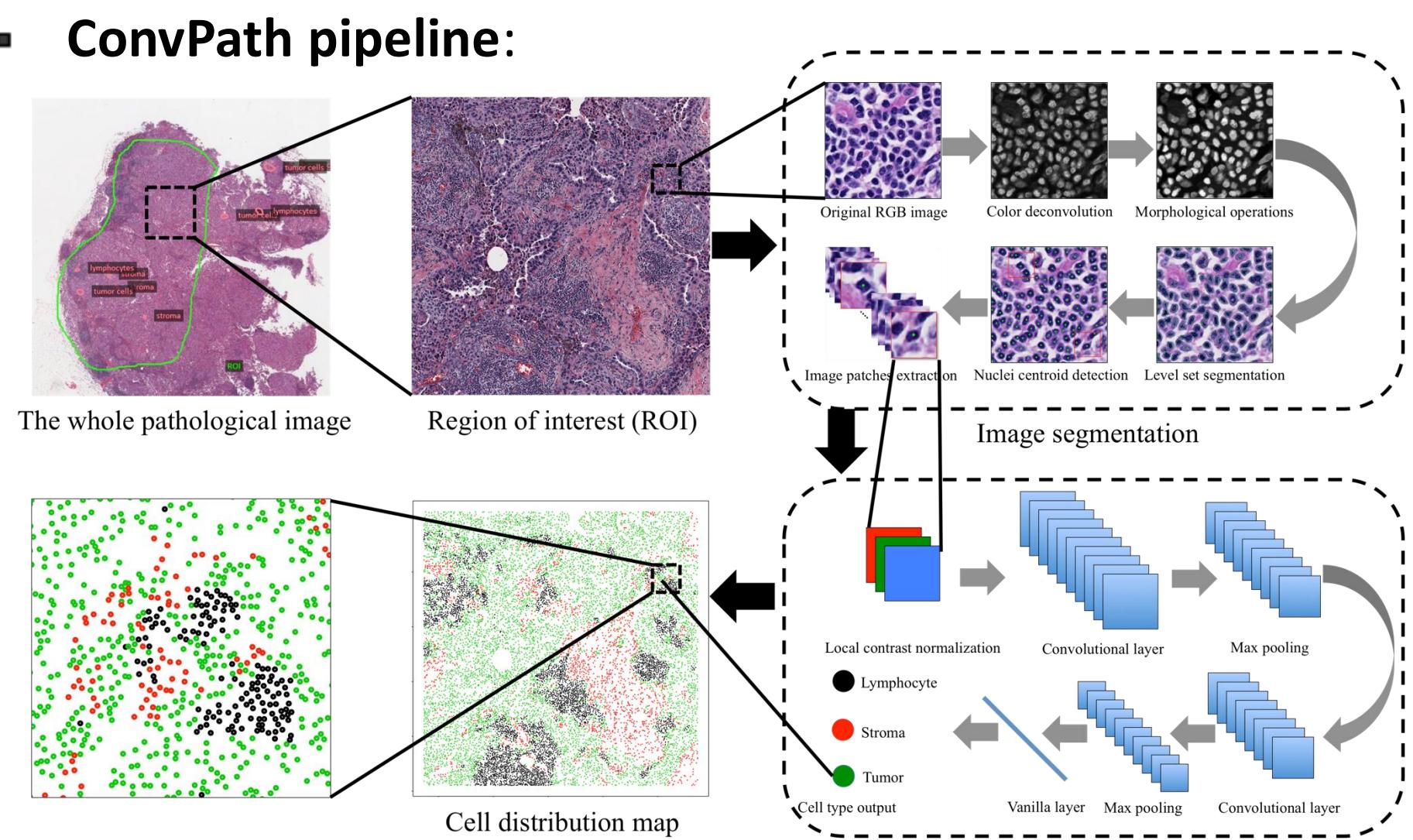


## INTRODUCTION

- Motivation**
  - To summarize spatial cell-cell interactions in cancer tissue images using various spatial summary statistics.
  - Studies have shown that cell-cell interactions in Tumor Microenvironment play key role in tumor progression.
- Goal:** Quantitatively summarize spatial features in the marked point pattern of Tumor Microenvironment(TME) and investigate their clinical meaning through survival analysis.
- Features: 13 spatial functional summary statistics and 2 Areal data indexes.**



## METHOD

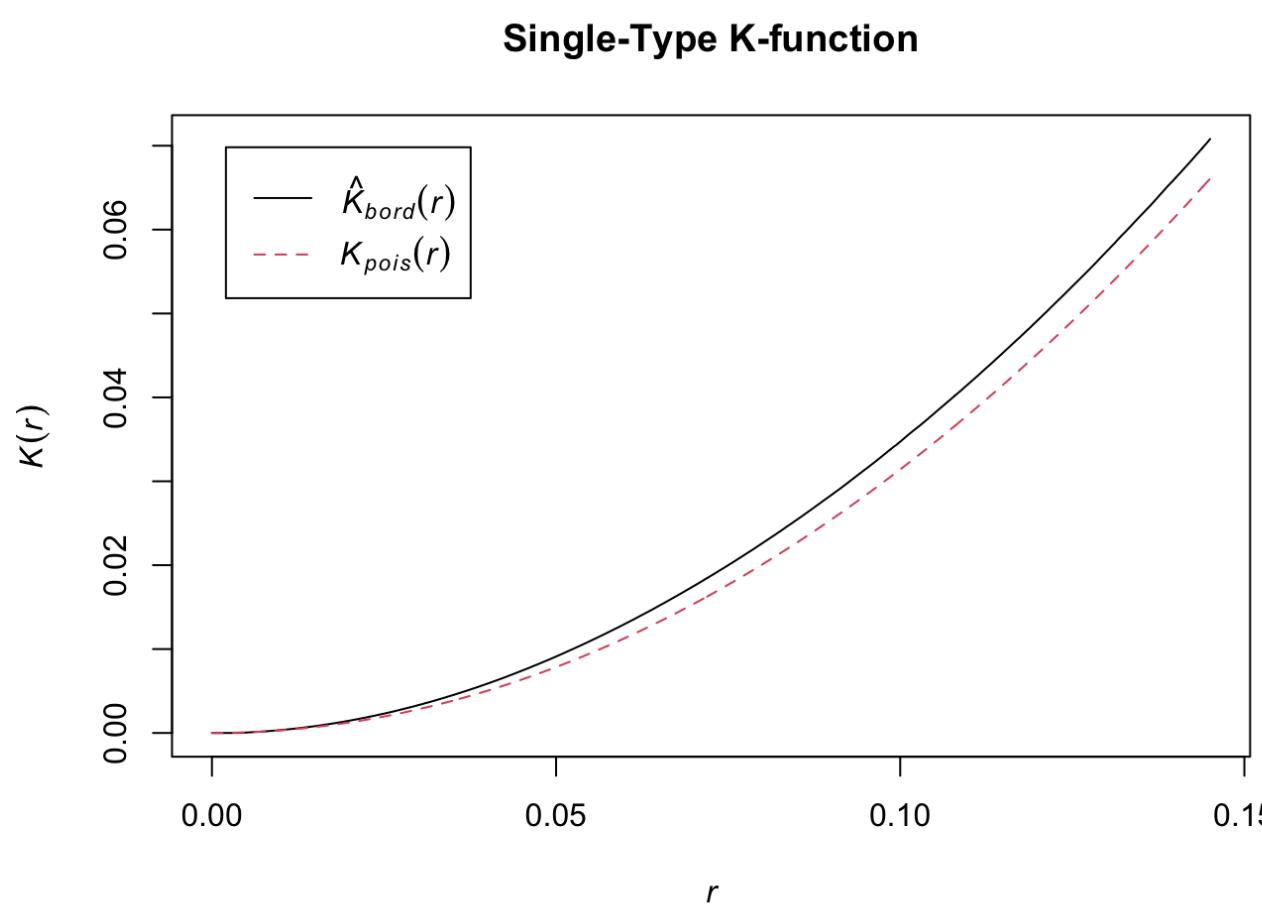
- Input data**
  - $(x_i, y_i)$ : coordinate of cell  $i$  in Euclidean space  $\mathbb{R}^2$
  - $x_i \in [0, 1]$ ,  $y_i \in [0, 1]$  in normalized image.
  - $i_T, j_I, k_S$ : different cell types of points, Tumor, Immune, Stromal
- An example of Spatial summary statistic**
  - K-function

$$K(r) = \frac{1}{\lambda^2} \sum_j \sum_{i \neq j} I_r(d_{ij}) w_i, \quad \lambda = \frac{N}{A} \quad N : \text{number of points}$$

Where:

$$d_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2} \quad I_r(d_{ij}) = \begin{cases} 1, & \text{if } d_{ij} \leq r \\ 0, & \text{otherwise} \end{cases}$$

$w_i = \frac{1}{e_i}$ ,  $e_i$  represents the proportion of the circle within the window



$K(r) > \pi r^2$  indicates clustered point process

$K(r) < \pi r^2$  indicates inhibited point process

## DATA

- Dataset**
  - NLST dataset: 1585 image slides, 188 patients
  - OPMD dataset: 702 image slides, 128 patients
- Single-type: spatial correlation within T, I, or S
- Cross-type: spatial correlation between T2I, T2S, S2I
- Scalar predictors: Age, Stage

### Total of 54 predictors

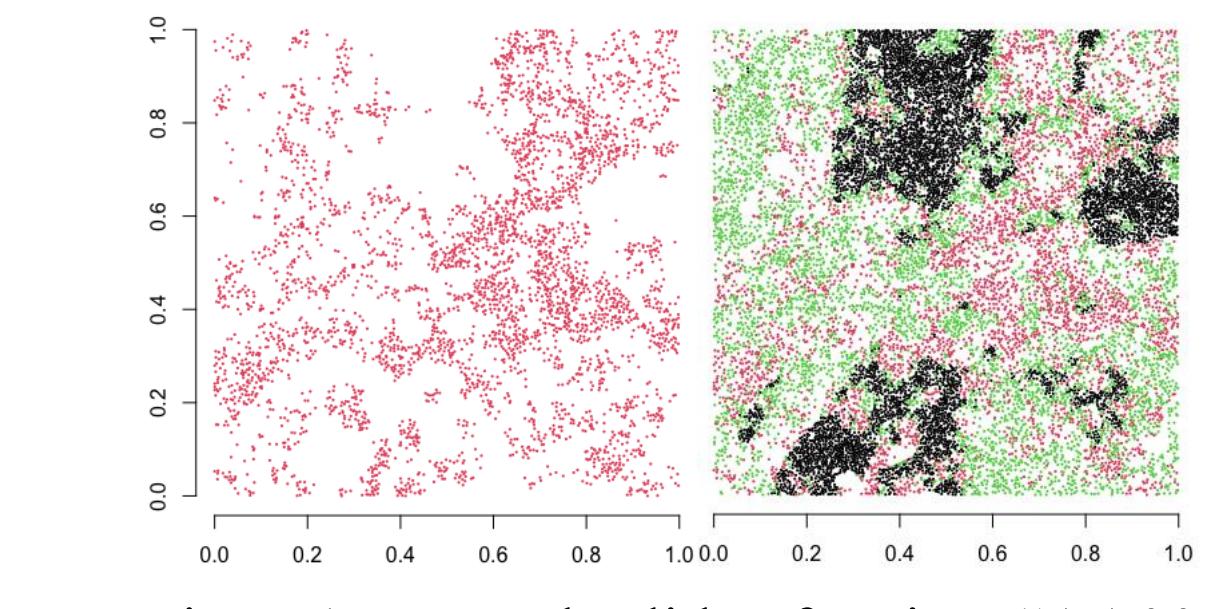
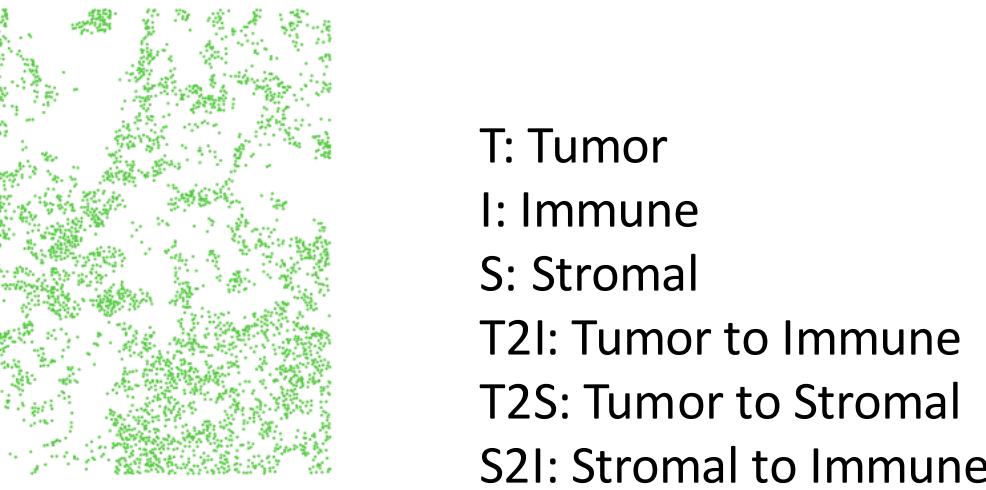


Figure 1: Example slide of patient "AA0001"

### Workflow

- Extracted spatial features per image
- Applied FPCA for functional dimension reduction
- Top 2 FPC scores used as covariates in FCoxPH

## RESULTS

### Survival Analysis

#### Multivariate FCoxPH model

- Adjusted for other scalar variables such as age, tumor stage.

#### Single-type J-function

- J-function captures the balance between how likely a random location is near a point and how likely points are near each other.

Predictor	Coef (NLST)	Coef (OPMD)	P-value (NLST)	P-value (OPMD)
J.REP.PC1	-5.337e-18	-3.785e-16	0.384	0.398
J.REP.PC2	3.404e-17	-2.870e-15	<b>0.158</b>	<b>0.067</b>
J.REP.I.PC1	1.370e-17	-1.176e-17	0.104	0.997
J.REP.I.PC2	3.634e-17	-9.803e-15	0.299	0.153
J.REP.T.PC1	1.949e-18	2.405e-16	0.370	0.542
J.REP.T.PC2	2.343e-17	-3.785e-15	0.557	<b>0.020</b>
J.REP.S.PC1	-1.532e-21	5.209e-16	0.993	0.420
J.REP.S.PC2	-1.967e-19	-2.637e-15	0.248	<b>0.083</b>

Table1: Summary of J-function predictors

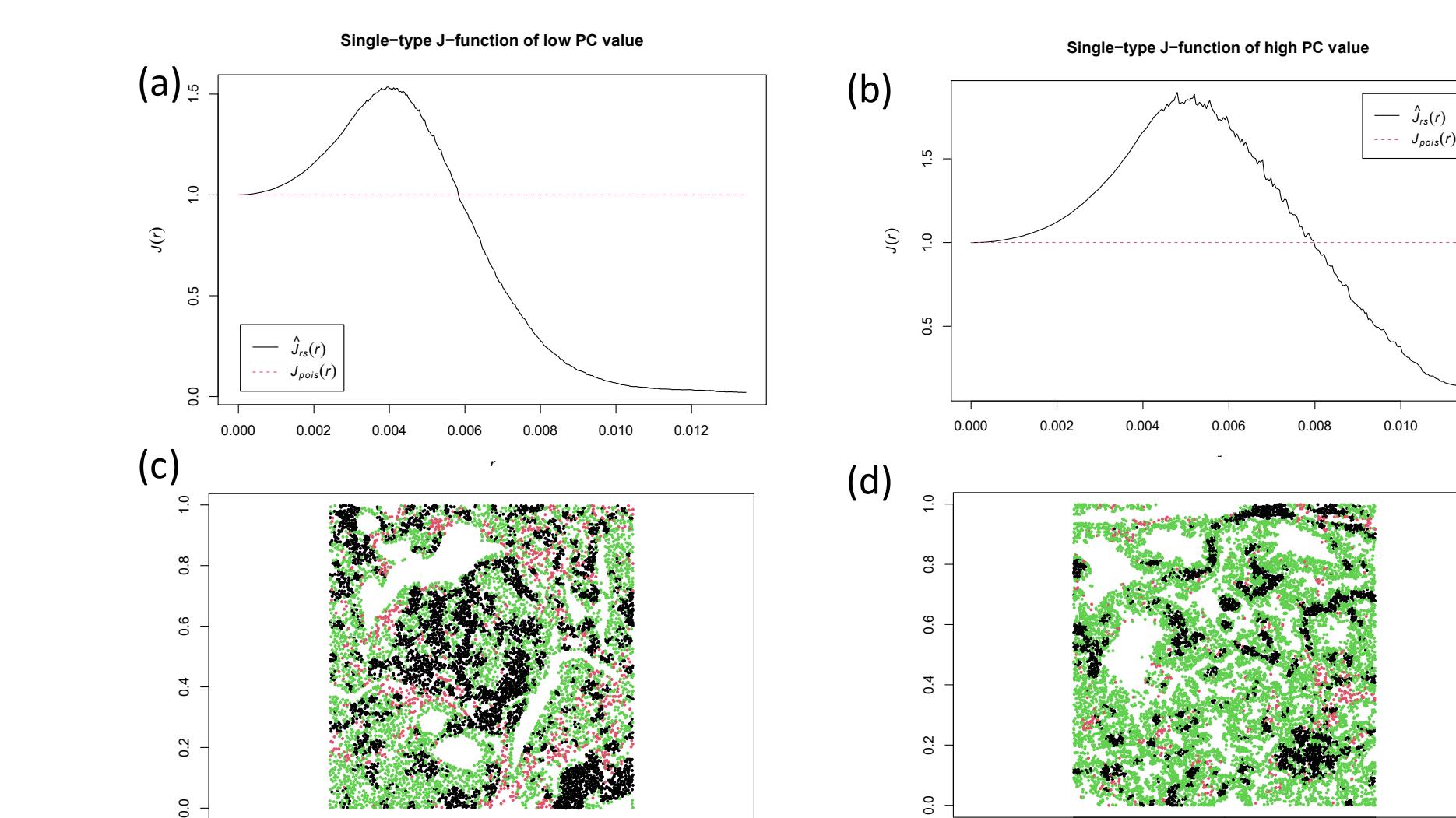


Figure2: (a) J-function of low-risk group image, (b) J-function of high-risk group image, (c) low-risk group image, (d) high-risk group image

## RESULTS

#### Cross-type G-function

- G-function captures the cumulative distribution of nearest-neighbor distances between points.

Predictor	Coef (NLST)	Coef (OPMD)	P-value (NLST)	P-value (OPMD)
G.CROSS.T2I.PC1	-2.292e-17	-4.081e-18	<b>0.109</b>	0.274
G.CROSS.T2I.PC2	-5.330e-17	-3.174e-16	0.587	<b>0.117</b>

Table3: Summary of G-function predictors

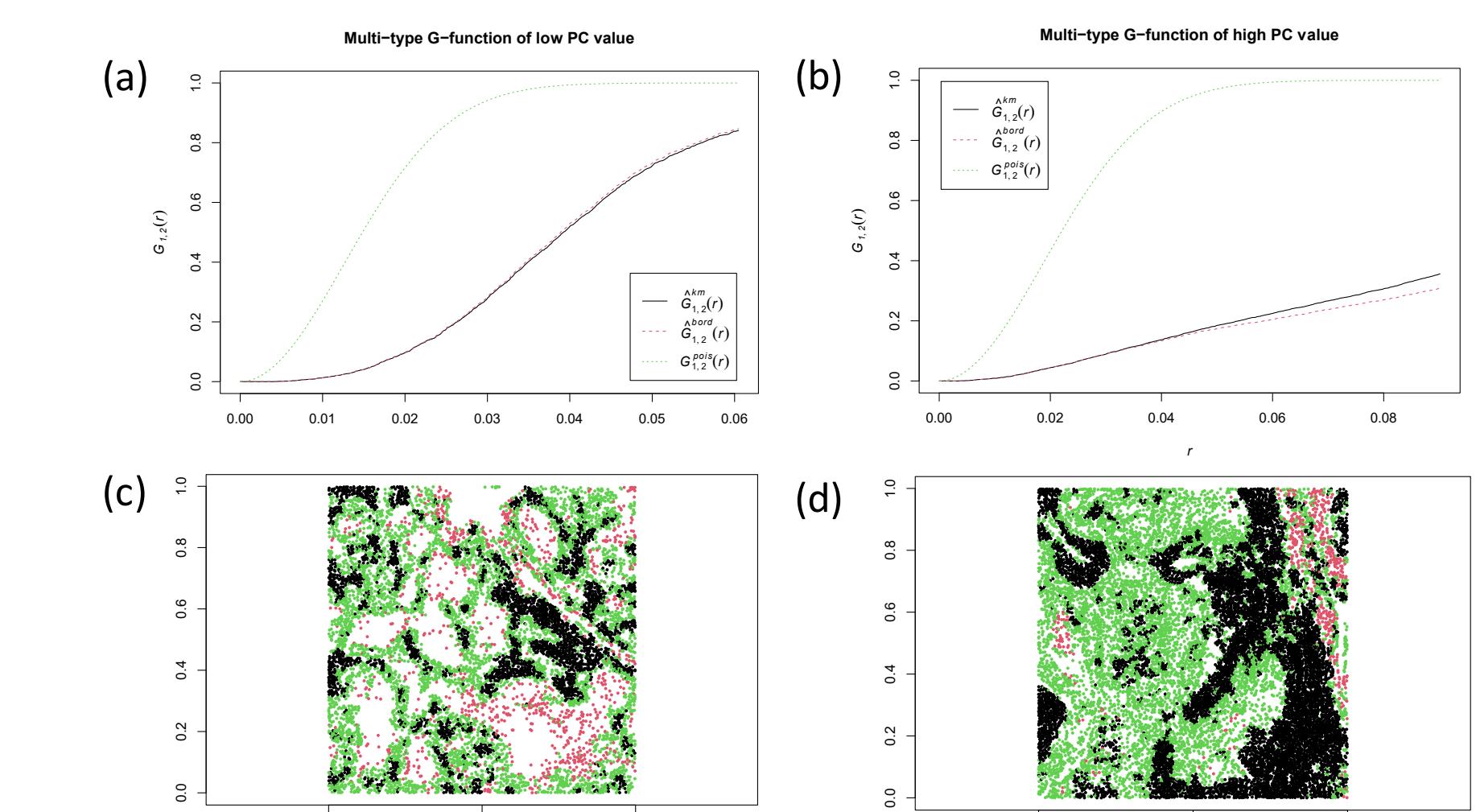


Figure4: (a) G-function of low-risk group image, (b) G-function of high-risk group image, (c) low-risk group image, (d) high-risk group image

## Downstream Analysis

#### LOOCV(Leave One Out Cross Validation)

- Trained (N-1) images to predict the risk score of each image
- Averaged risk score of each patient from all associated images.

#### Kaplan-Meier Survival curves

- Grouped patient into High-risk and Low-risk groups
- Log-rank test showed significance difference between groups.

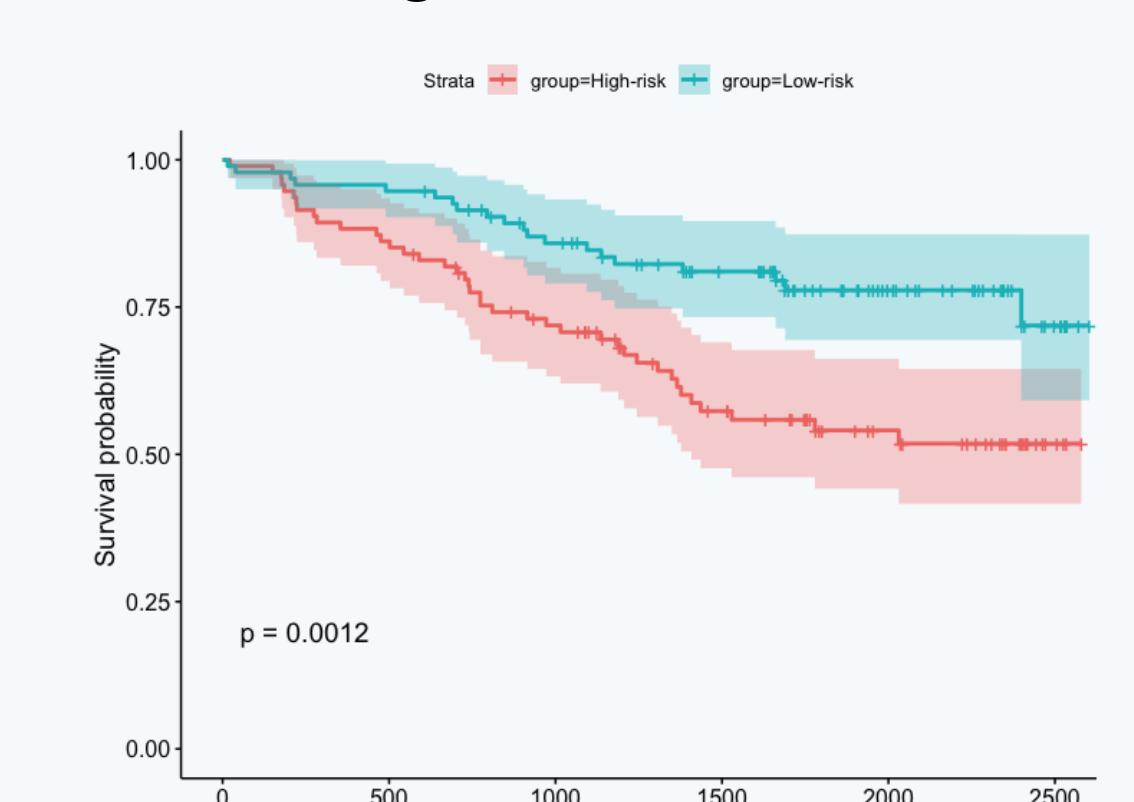


Figure5: Kaplan-Meier plot between high-risk, low-risk groups

Group	N	Observed	Expected	$(O - E)^2/V$
High-Risk	94	40	27.5	10.5
Low-Risk	94	20	32.5	10.5

Table4: Log-rank test

## SUMMARY

#### Spatial correlation in Tumor Microenvironment

- Statistically significant spatial features were extracted from pathology slides. Among 54 candidate predictors, **12 (NLST)** and **9 (OPMD)** variables showed statistically significant spatial associations.

## REFERENCE

- LIX\_Deciphering cell to cell spatial relationship for pathology images using SpatialQPFs. Sci Rep. 2024 Nov 28;14(1):29585. doi:10.1038/s41598-024-1383-1. PMID: 39609530; PMCID: PMC11605059.  
Chul Moon, Qiwei Li, Guanghua Xiao. "Using persistent homology topological features to characterize medical images: Case studies on lung and brain cancers." The Annals of Applied Statistics, Ann. Appl. Stat. 17(3), 2192-2211, (September 2023)

\*Bolding signifies features with p-value  $\leq 0.20$