Molecular Dissection of Renal Cell Carcinoma with Inferior Vena Cava Thrombus Highlights Prognostic Significance of Epithelial—Mesenchymal Transition and Cellular Proliferation Signatures

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Intro:

5-year survival in clear cell renal cell carcinoma (ccRCC) varies based on stage and grade at diagnosis. However, some patients with similar disease stages have different survival outcomes, highlighting the importance of identifying molecular aberrations that lead to progression or recurrence. Our study aims to identify gene expression pathways enriched in patients with advanced disease and evaluate their prognostic significance.

Methods:

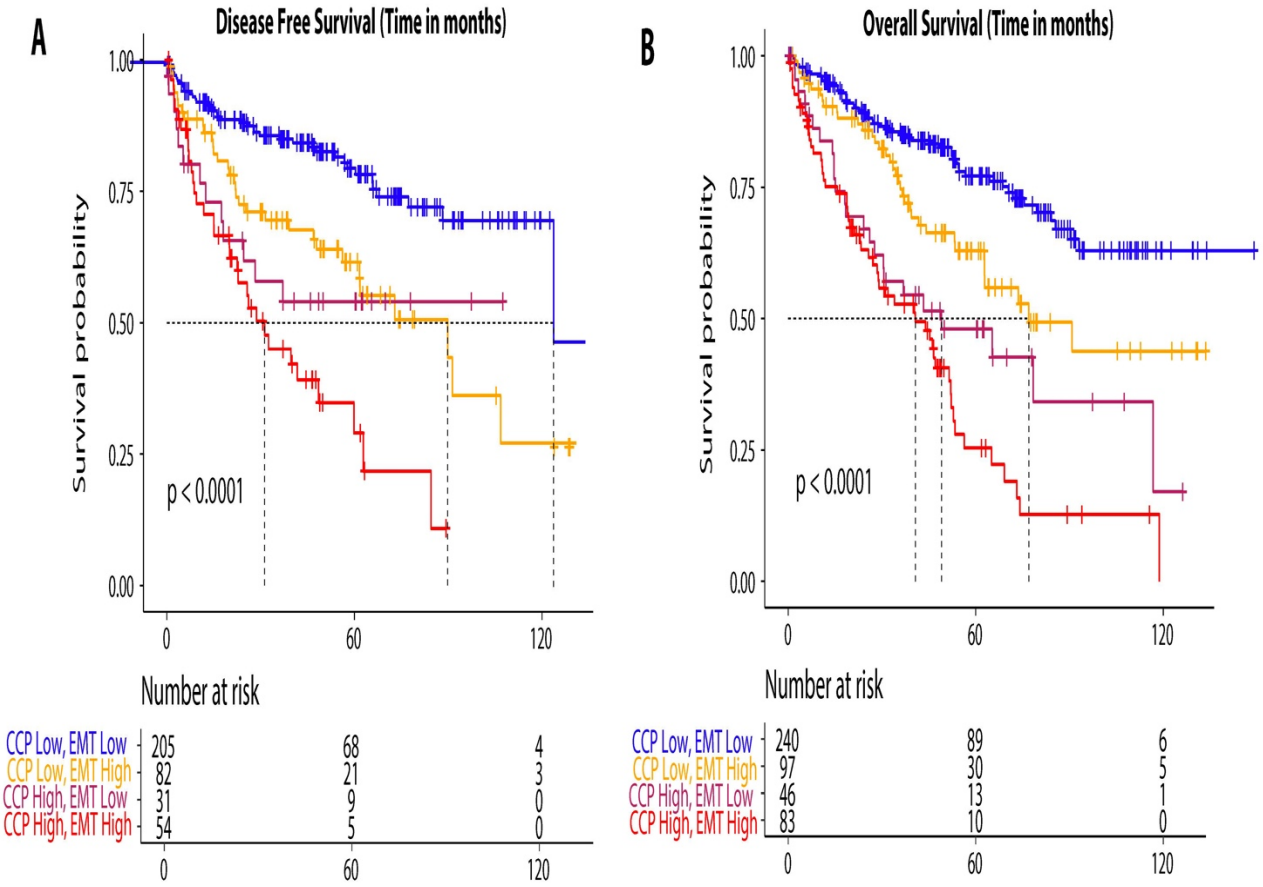
After IRB approval, we retrospectively identified 5 patients with ccRCC and IVC thrombus who underwent surgery(discovery cohort). Pathologists identified 3 areas of FFPE specimen from the primary and tumor thrombus for targeted RNA next-generation sequencing. Differential expression analysis was performed to identify gene expression. Using The Cancer Genome Atlas (TCGA) ccRCC gene expression data (n=466), we evaluated the potential prognostic significance of differentially expressed genes in the discovery cohort. We stratified patients on the enrichment of epithelial-mesenchymal transition (EMT) and cell cycle proliferation (CCP) pathways. Kaplan-Meier (KM) survival analysis and multivariable cox-proportional hazard testing to investigate the independent prognostic impact of the interaction between EMT and CCP on disease-free survival (DFS) and overall survival (OS).

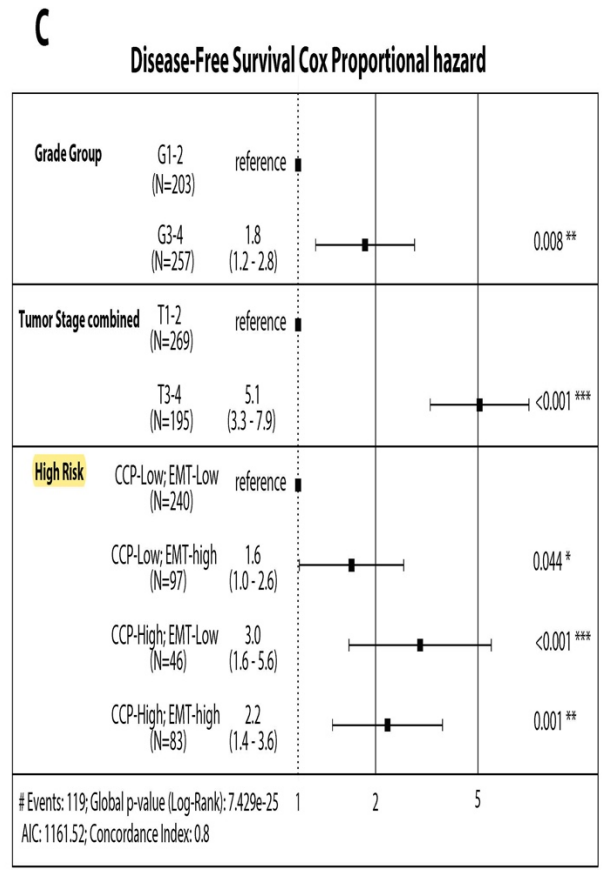
Results:

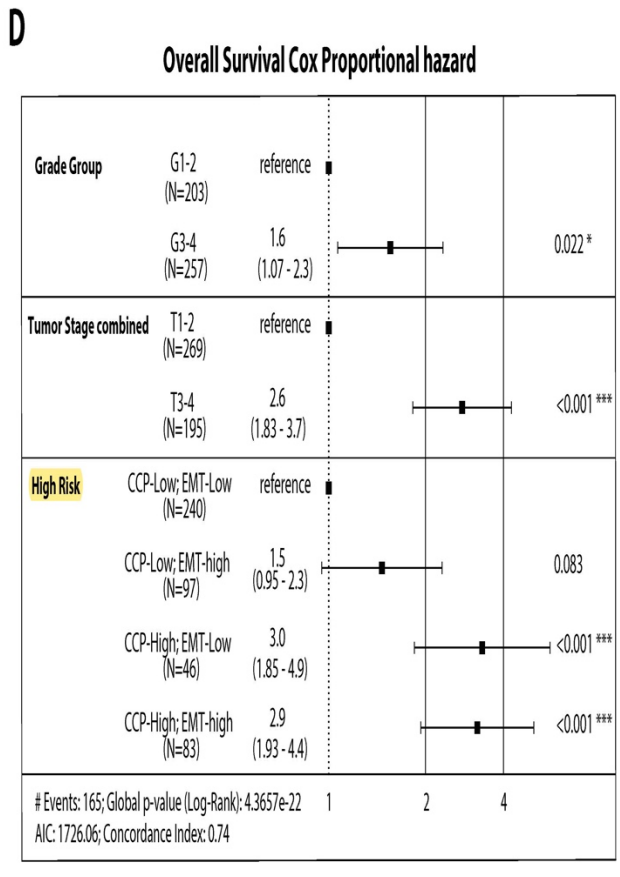
In our discovery cohort, *WT1* and CCP genes were overexpressed in tumor thrombi. In the TCGA cohort, tumors with *WT1* overexpression also overexpressed EMT and CCP genes. Using expression data of 200 EMT genes, we calculated EMT scores and derived CCP scores for all TCGA tumors. KM analysis demonstrates patients with CCP^{low} and EMT^{low} tumors have the lowest risk of recurrence and death. Interestingly, EMT enrichment allows stratification of patients with CCP^{low} tumors, showing patients CCP^{low} and EMT^{high} have shorter DFS and worse OS (Fig. 2A-B). Multivariable analysis confirms patients with CCP^{low} tumors and EMT enrichment have a shorter DFS (Fig. 2C-D).

Conclusion:

Our study reveals the independent prognostic significance of the interaction between EMT and CCP genes on disease-free and overall survival. While further validation in prospective clinical cohorts is warranted, these findings could potentially impact treatment recommendations in patients undergoing biopsy for small renal masses.


A
Disease Free Survival (Time in months)
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
60
120
Number at risk
CCP Low, EMT Low 205 68 4
CCP Low, EMT High 82 21 3
CCP High, EMT Low 31 9 0
CCP High, EMT High 54 5 0
0
60
120
B
Overall Survival (Time in months)
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
60
120
Number at risk
CCP Low, EMT Low 240 89 6
CCP Low, EMT High 97 30 5
CCP High, EMT Low 46 13 1
CCP High, EMT High 83 10 0
0
60
120


C
Disease-Free Survival Cox Proportional hazard
Grade Group
G1-2 (N=203) reference
G3-4 (N=257) 1.8 (1.2 - 2.8) 0.008 **
Tumor Stage combined
T1-2 (N=269) reference
T3-4 (N=195) 5.1 (3.3 - 7.9) <0.001 ***
High Risk
CCP-Low; EMT-Low (N=240) reference
CCP-Low; EMT-high (N=97) 1.6 (1.0 - 2.6) 0.044 *
CCP-High; EMT-Low (N=46) 3.0 (1.6 - 5.6) <0.001 ***
CCP-High; EMT-high (N=83) 2.2 (1.4 - 3.6) 0.001 **
Events: 119; Global p-value (Log-Rank): 7.429e-25
AIC: 1161.52; Concordance Index: 0.8
1
2
5


D
Overall Survival Cox Proportional hazard
Grade Group
G1-2 (N=203) reference
G3-4 (N=257) 1.6 (1.07 - 2.3) 0.022 *
Tumor Stage combined
T1-2 (N=269) reference
T3-4 (N=195) 2.6 (1.83 - 3.7) <0.001 ***
High Risk
CCP-Low; EMT-Low (N=240) reference
CCP-Low; EMT-high (N=97) 1.5 (0.95 - 2.3) 0.083
CCP-High; EMT-Low (N=46) 3.0 (1.85 - 4.9) <0.001 ***
CCP-High; EMT-high (N=83) 2.9 (1.93 - 4.4) <0.001 ***
Events: 165; Global p-value (Log-Rank): 4.3657e-22
AIC: 1726.06; Concordance Index: 0.74
1
2
4