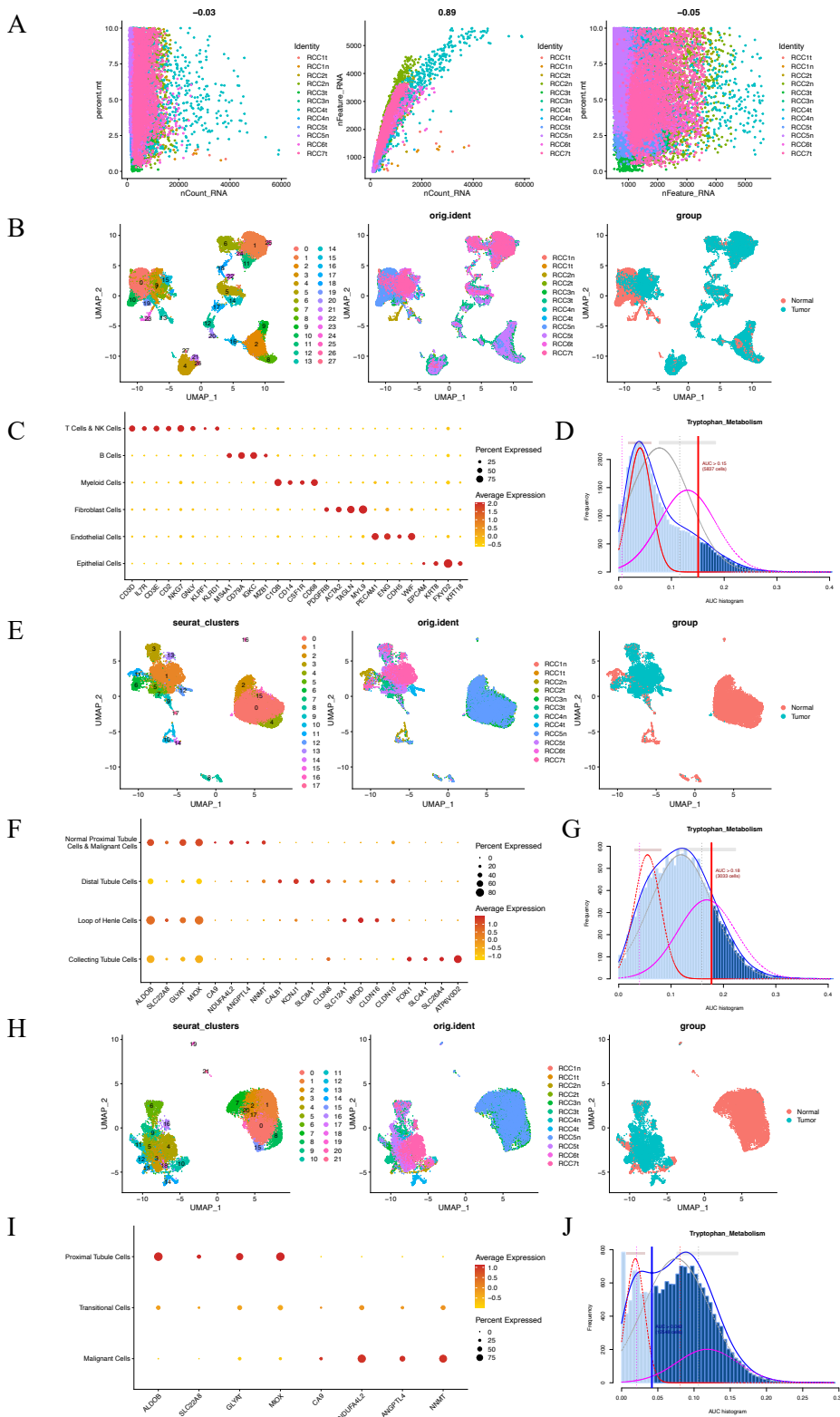
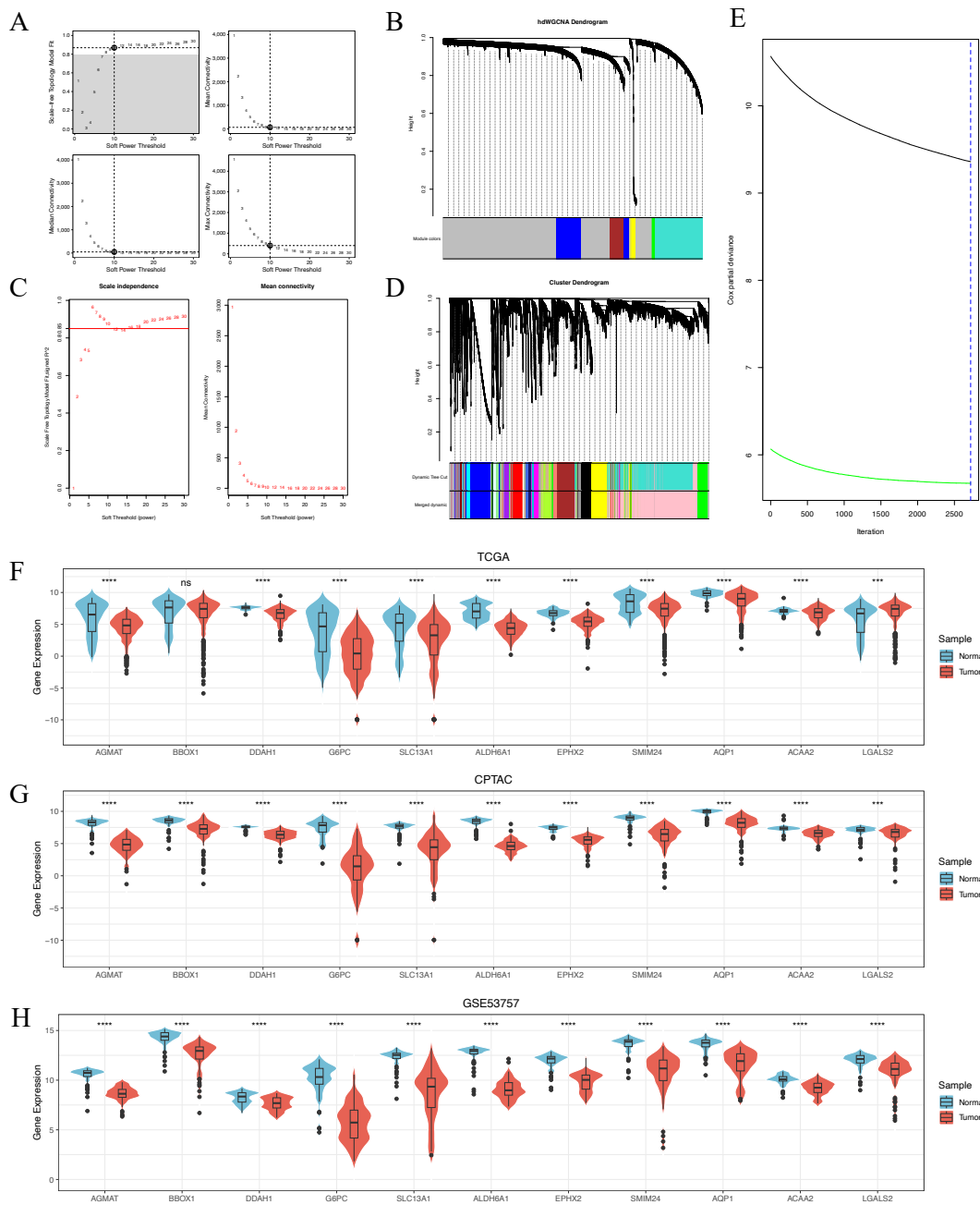


## Supplementary Figures



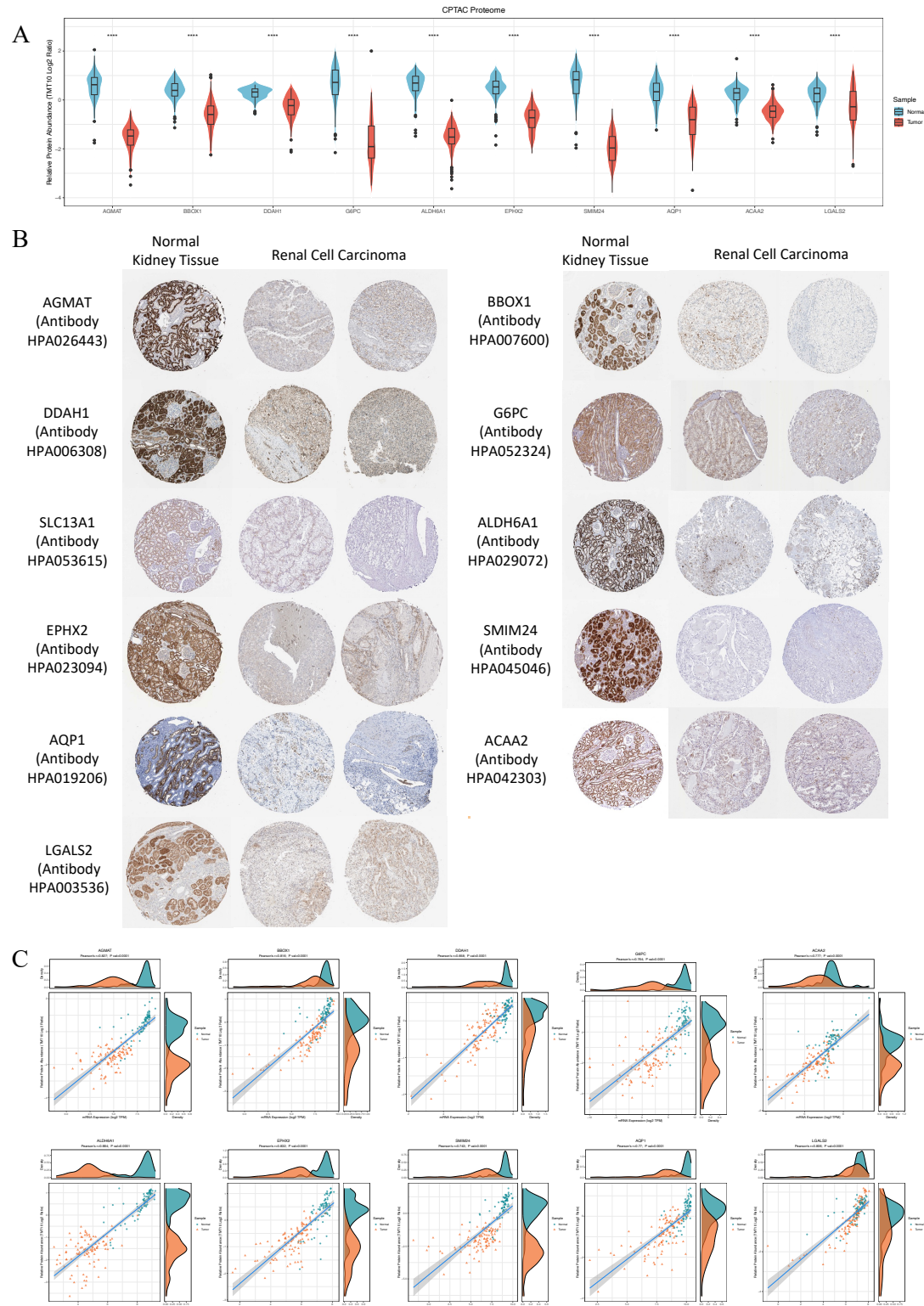
**Supplementary Figure 1 | The processing of scRNA-seq data from GSE156632.** **A.** Quality control process for single cell sequencing data. **B.** UMAP plot displaying cells categorized by diverse cell clusters and sample sources after batch effect removal. **C.** Marker genes employed to

classify cells into six major cell types. **D.** The AUC scoring threshold applied to differentiate the activity of tryptophan metabolism in cells using the AUCCell algorithm. **E.** UMAP plot displaying epithelial cells categorized by diverse cell clusters and sample sources. **F.** Marker genes employed to classify epithelial cells into four minor cell types. **G.** The AUC scoring threshold applied to differentiate the activity of tryptophan metabolism in epithelial cells using the AUCCell algorithm. **H.** UMAP plot displaying proximal tubule cells categorized by diverse cell clusters and sample sources. **I.** Marker genes employed to classify proximal tubule cells into normal, transitional, and malignant cells. **J.** The AUC scoring threshold applied to differentiate the activity of tryptophan metabolism in proximal tubule cells using the AUCCell algorithm.

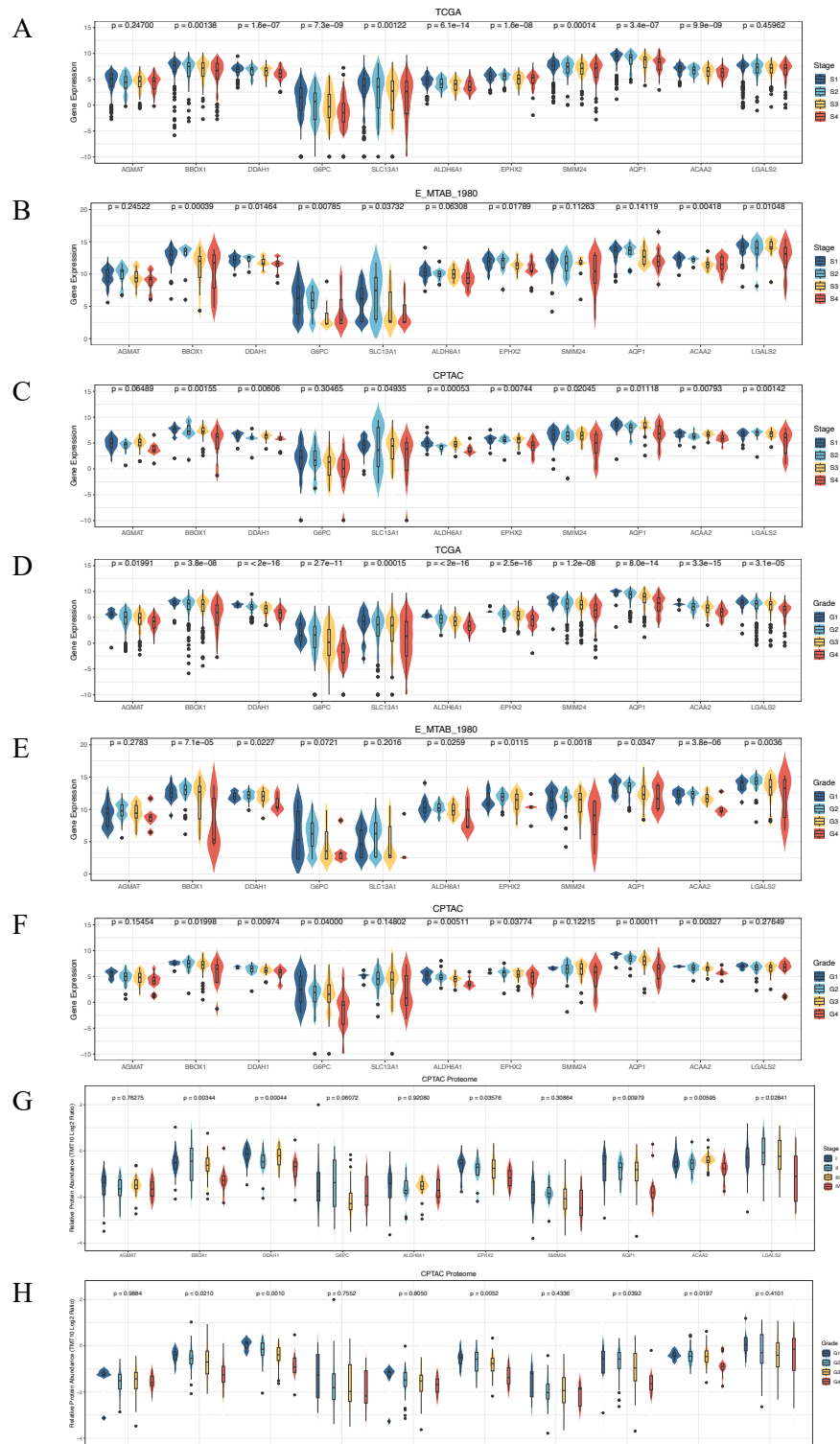




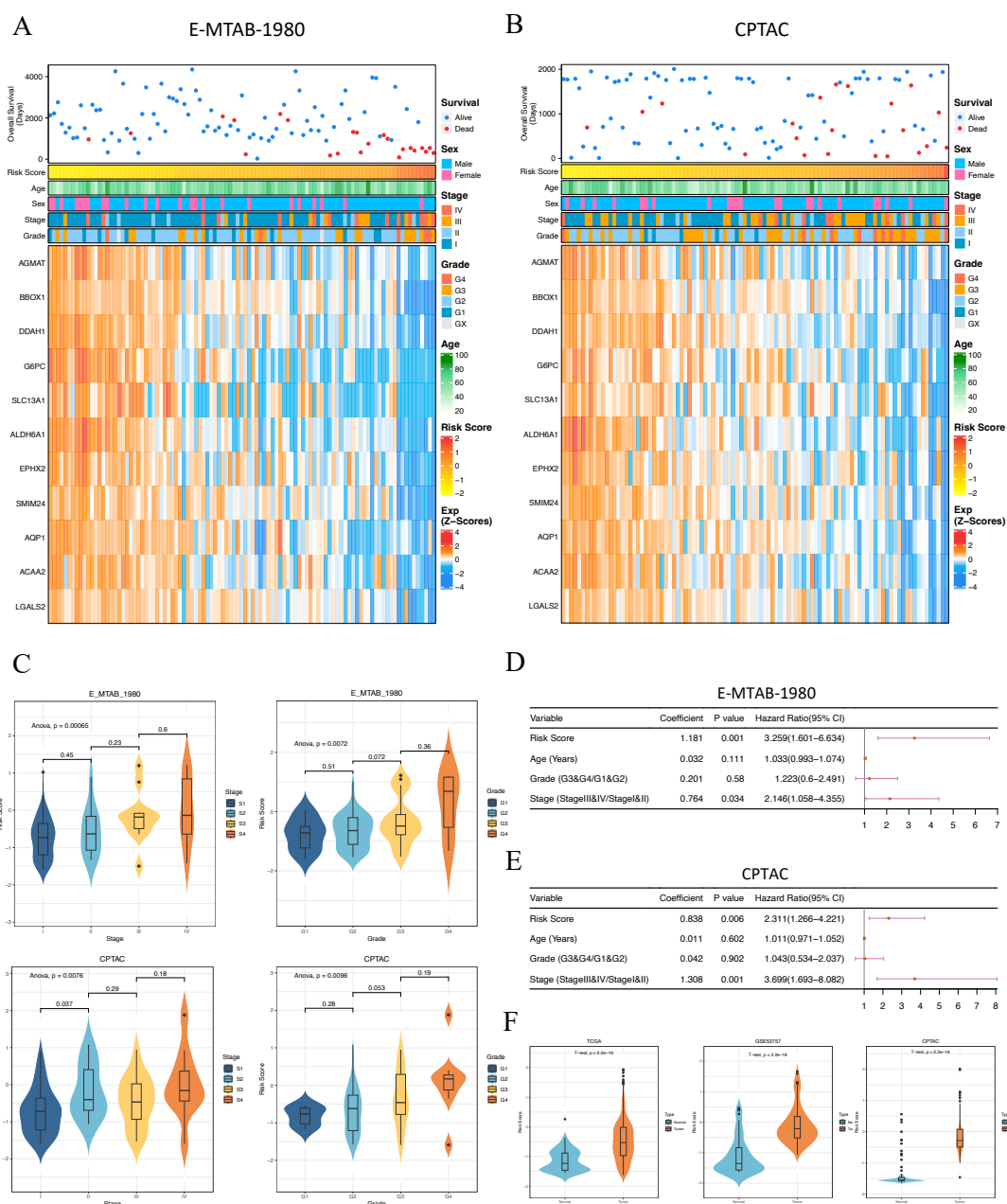
**Supplementary Figure 2 | Construction of co-expression networks for hdWGCNA and WGCNA and comparative analysis of TMRS genes expression in ccRCC samples versus adjacent normal tissues at transcriptional level.** **A.** Identification of the optimal soft-thresholding power for hdWGCNA. **B.** Cluster dendrogram of the hdWGCNA. **C.** Determination of the optimal soft-thresholding power for WGCNA. **D.** Cluster dendrogram of the WGCNA. **E.** The determination of iteration number in generalized boosted regression modelling. **F-H.** Comparative analysis of TMRS genes mRNA expression in ccRCC samples versus adjacent normal tissues within the TCGA (**F**), CPTAC (**G**), and GSE53757 (**H**) dataset.



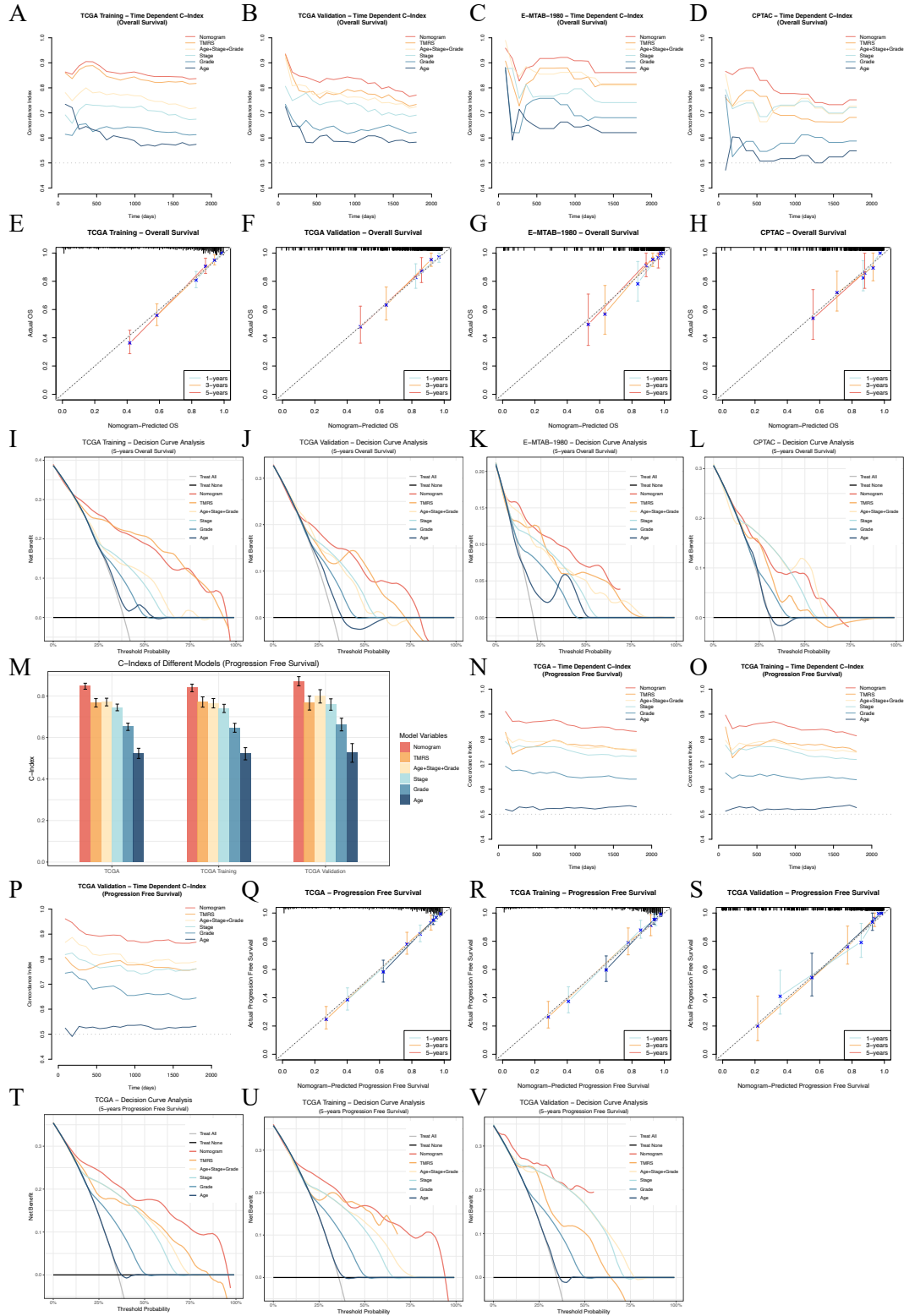
**Supplementary Figure 3 | TMRS genes' protein expression and correlation with mRNA levels in ccRCC. A.** Comparative analysis of TMRS protein expression in ccRCC vs. adjacent normal tissues using CPTAC proteome data. **B.** Immunohistochemical analysis of TMRS genes in normal and tumor tissues based on HPA database. **C.** Correlation analysis between mRNA and protein expression levels of TMRS genes utilizing the CPTAC database.



**Supplementary Figure 4 | Association of TMRS Gene Expression with Clinical Characteristics in ccRCC.** A-C. Association between the mRNA level of TMRS genes and disease stages across TCGA (A), E-MTAB-1980 (B), and CPTAC (C) database. D-F. Relationship between the mRNA level of TMRS genes and histological grade within TCGA (D), E-MTAB-1980 (E), and CPTAC (F) database. G-H. Association of TMRS genes' protein level with disease stages (G) and histological grade (H) within CPTAC proteome data.

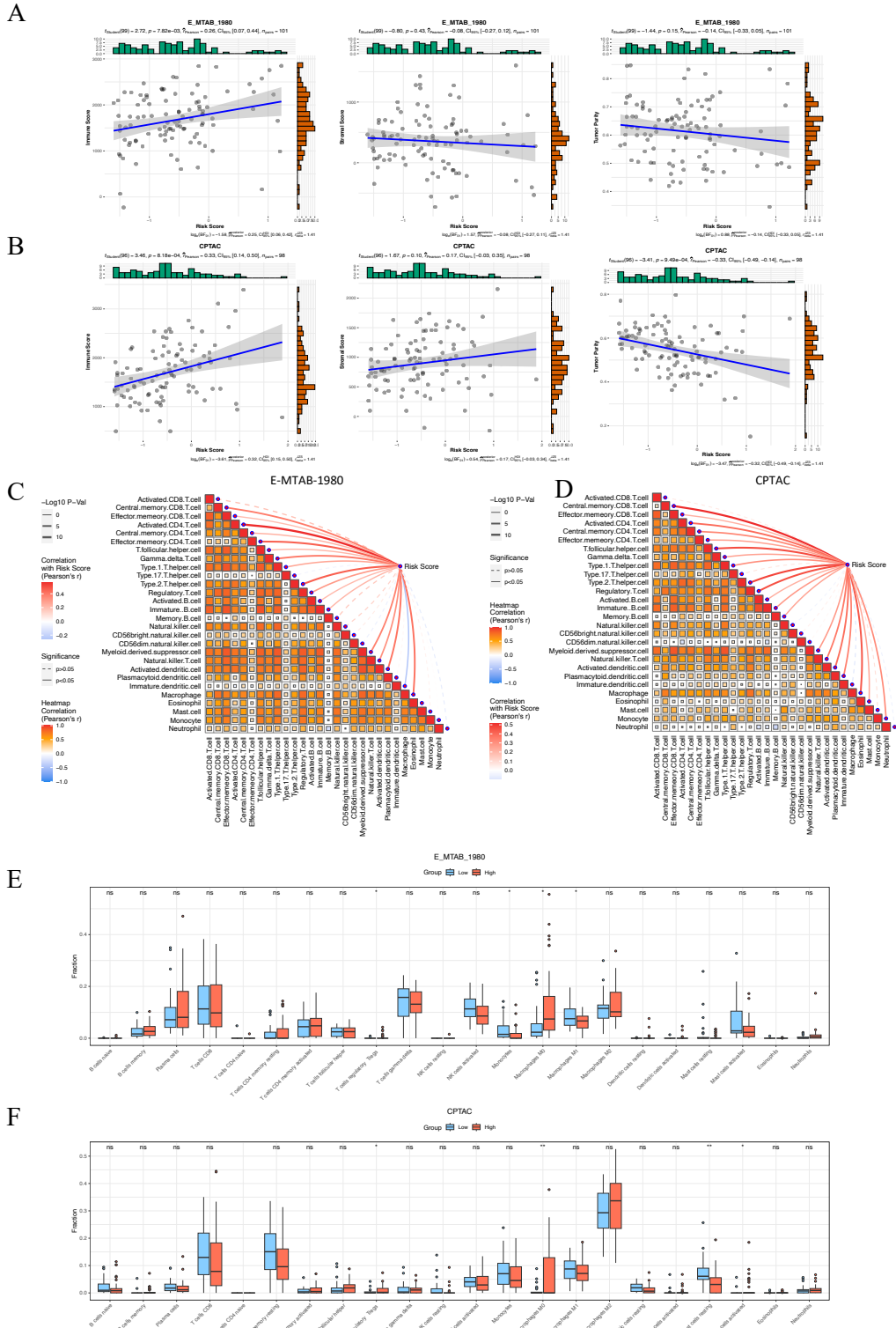


**Supplementary Figure 5 | Association between TMMRS risk score and clinicopathological characteristics of ccRCC.** A-B Heatmaps depicting the relationship between TMMRS and clinicopathological features in E-MTAB-1980 (A) and CPTAC (B) datasets. C. Tendency of increased TMMRS in ccRCC samples with advanced stages and grades in E-MTAB-1980 and CPTAC datasets. D-E. TMMRS demonstrated significant independent prognostic value for patients' overall survival in E-MTAB-1980 (D) and CPTAC (E) datasets. F. Elevated TMMRS in tumor samples compared to adjacent normal samples across TCGA, CPTAC, and GSE53757 datasets.



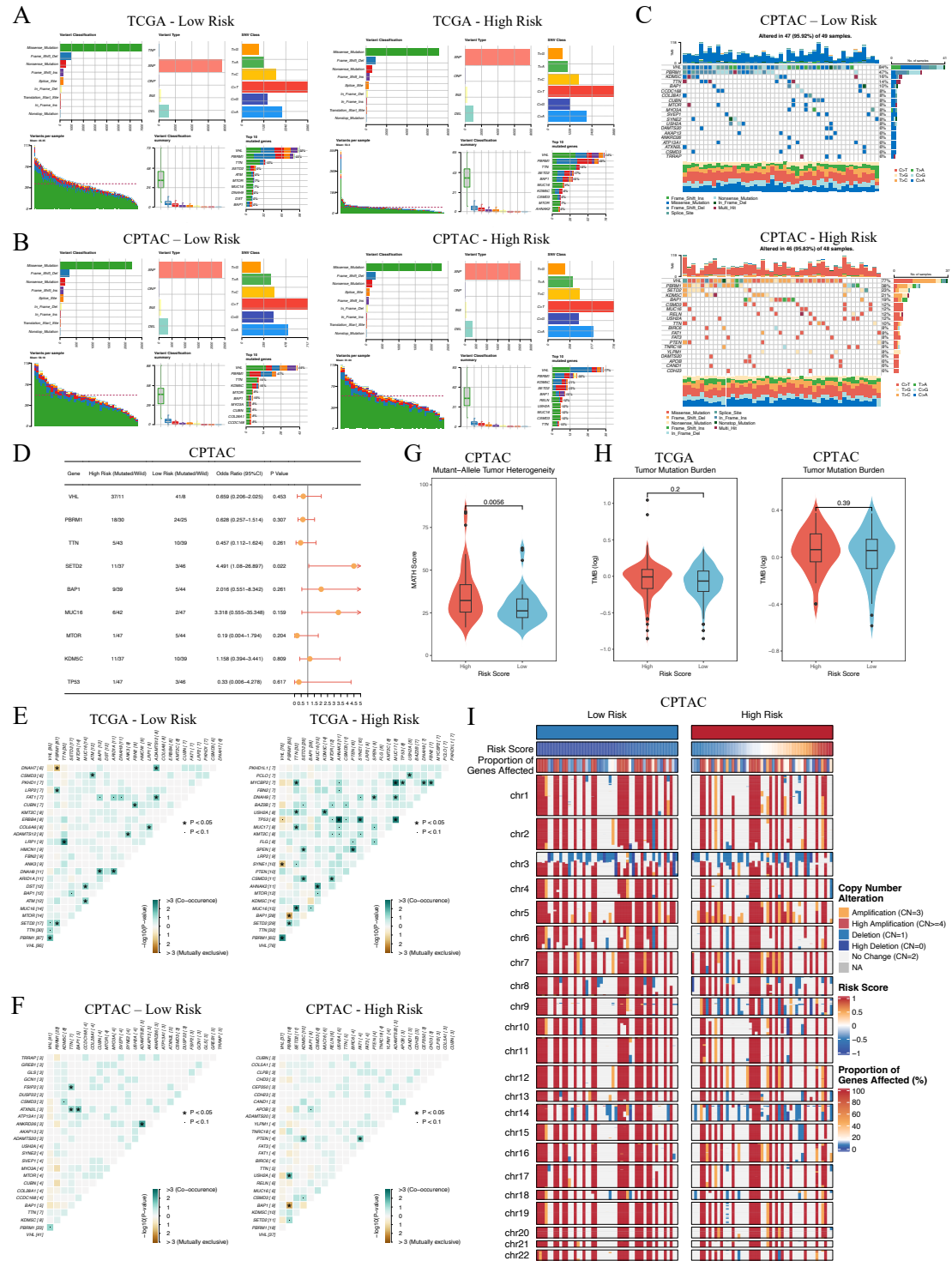
**Supplementary Figure 6 | The performance of nomograms in predicting the prognosis of patients.** A-D. Time-dependent C-index of the nomogram for predicting OS within the TCGA training set (A), TCGA validation set (B), E-MTAB-1980 dataset (C), and CPTAC dataset (D). E-H. Calibration curve of the nomogram for 1-year, 3-year, and 5-year OS predictions within the TCGA training set (E), TCGA validation set (F), E-MTAB-1980 dataset (G), and CPTAC dataset (H). I-L. Decision curve analysis (DCA) demonstrating the net benefit of utilizing the nomogram,

TMRS, and other clinical features for predicting OS within the TCGA training set **(I)**, TCGA validation set **(J)**, E-MTAB-1980 dataset **(K)**, and CPTAC dataset **(L)**. **M**. Concordance Index (C-index) Comparison of nomograms, TMRS, and other clinical parameters for predicting PFS. **N-P**. Time-dependent C-index of the nomogram for predicting PFS within the whole TCGA dataset **(N)**, TCGA training set **(O)**, and TCGA validation set **(P)**. **Q-S**. Calibration curve of the nomogram for 1-year, 3-year, and 5-year PFS predictions within the whole TCGA dataset **(Q)**, TCGA training set **(R)**, and TCGA validation set **(S)**. **T-V**. Decision curve analysis (DCA) demonstrating the net benefit of utilizing the nomogram, TMRS, and other clinical features for predicting PFS within the whole TCGA dataset **(T)**, TCGA training set **(U)**, and TCGA validation set **(V)**.



**Supplementary Figure 7 | Immune landscape of patients with different TMRS risk scores within E-MTAB-1980 and CPTAC dataset. A-B.** ESTIMATE algorithm indicated elevated immune infiltration and reduced tumor purity in patients with high TMRS risk scores in E-MTAB-1980 (A) and CPTAC (B) datasets. **C-D.** Association between TMRS risk scores and abundance of various immune cells in the tumor microenvironment assessed by ssGSEA algorithm in E-MTAB-1980 (C) and CPTAC (D) datasets. **E-F.** CIBERSORT algorithm unveiled the composition of

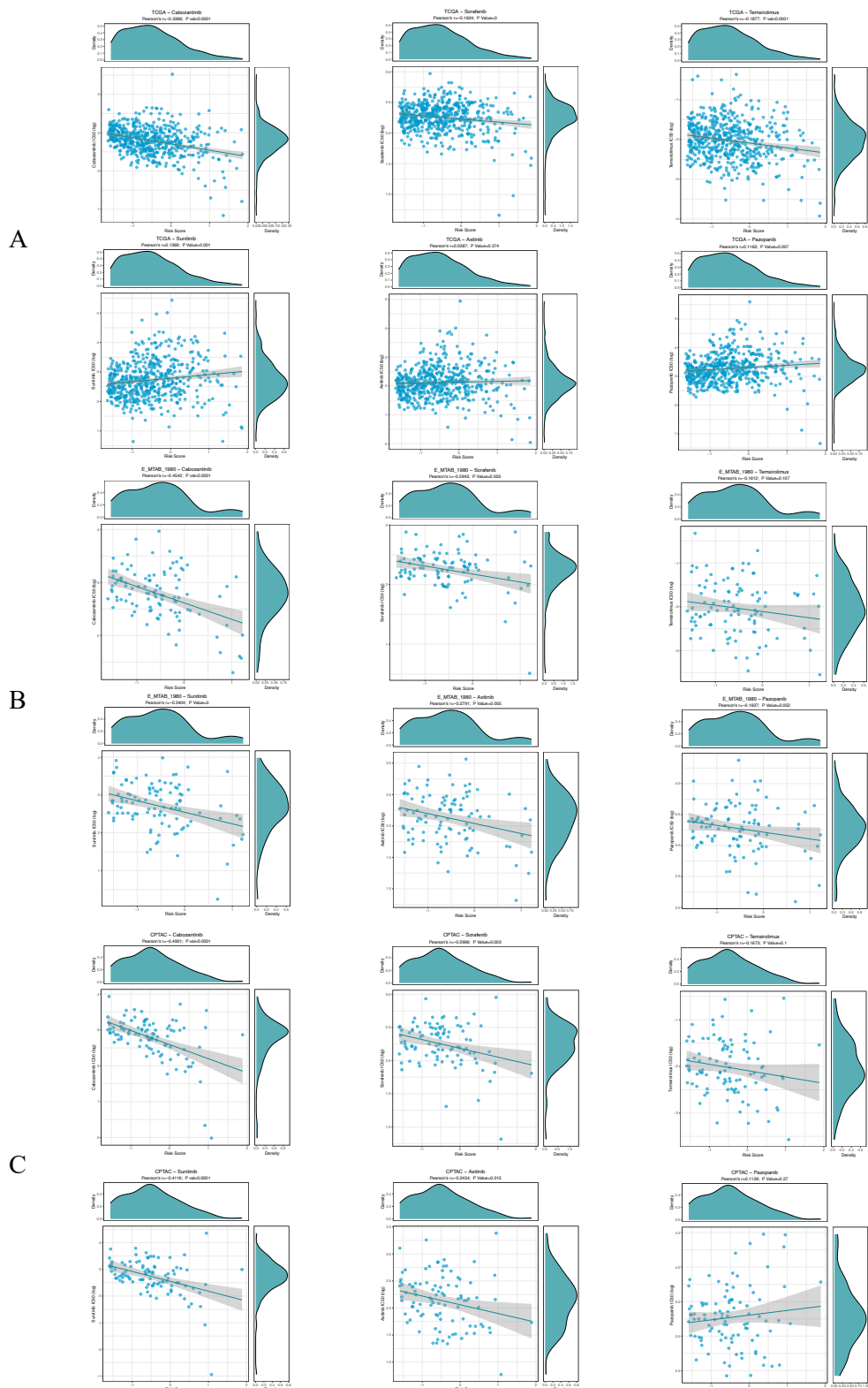
immune cell populations in patients categorized by TMRS risk scores within E-MTAB-1980 (E) and CPTAC (F) dataset.



**Supplementary Figure 8 | Association of TMRS with genomic features in ccRCC. A-B.** Comparative summary plots illustrating genomic mutations across high and low TMRS risk groups within the TCGA (A) and CPTAC (B) datasets. C. Waterfall plots highlighting the top 20 genes with



the highest mutation frequencies among patients categorized by high and low TMRS risk scores in the CPTAC dataset. **D.** Evaluation of gene mutation frequency variances between high and low TMRS risk score groups in the CPTAC dataset, conducted using Fisher's exact test. **E-F.** Identification of mutually exclusive or co-occurring genetic events within high and low TMRS risk score groups in the TCGA (**E**) and CPTAC (**F**) datasets. **G.** Patients classified under the high TMRS risk score exhibit significantly elevated mutant allele tumor heterogeneity (MATH) scores in the CPTAC dataset. **H.** Comparative analysis of tumor mutation burden between high and low-risk groups across the TCGA and CPTAC datasets, revealing no notable differences. **I.** Overview of the gene level copy number variation landscape in patients with varying TMRS risk scores in the CPTAC dataset. The horizontal axis of the heatmap represents individual patients, while the vertical axis displays genes ordered by their chromosomal positions.



**Supplementary Figure 9 | Correlation between TMRS and sensitivity of six commonly used targeted therapies. A-C.** Correlation between TMRS risk scores and the log-transformed half-maximal inhibitory concentration (IC50) values of six targeted therapies commonly utilized in ccRCC treatment, as predicted by OncoPredict across three datasets: TCGA (A), E-MTAB-1980 (B), and CPTAC (C).