**Table S1** Marker gene sets for five carcinogenic pathways

| Symbol | Pathway |
| --- | --- |
| CCND1 | Cell.Cycle_activated |
| CCND2 | Cell.Cycle_activated |
| CCND3 | Cell.Cycle_activated |
| CCNE1 | Cell.Cycle_activated |
| CDK2 | Cell.Cycle_activated |
| CDK4 | Cell.Cycle_activated |
| CDK6 | Cell.Cycle_activated |
| E2F1 | Cell.Cycle_activated |
| E2F3 | Cell.Cycle_activated |
| YAP1 | Hippo_activated |
| TEAD1 | Hippo_activated |
| TEAD2 | Hippo_activated |
| TEAD3 | Hippo_activated |
| TEAD4 | Hippo_activated |
| WWTR1 | Hippo_activated |
| MYC | MYC_activated |
| MYCL1 | MYC_activated |
| MYCN | MYC_activated |
| CREBBP | NOTCH_activated |
| EP300 | NOTCH_activated |
| HES1 | NOTCH_activated |
| HES2 | NOTCH_activated |
| HES3 | NOTCH_activated |
| HES4 | NOTCH_activated |
| HES5 | NOTCH_activated |
| HEY1 | NOTCH_activated |
| HEY2 | NOTCH_activated |
| HEYL | NOTCH_activated |
| KAT2B | NOTCH_activated |
| NOTCH1 | NOTCH_activated |
| NOTCH2 | NOTCH_activated |
| NOTCH3 | NOTCH_activated |
| NOTCH4 | NOTCH_activated |
| PSEN2 | NOTCH_activated |
| LFNG | NOTCH_activated |
| NCSTN | NOTCH_activated |
| JAG1 | NOTCH_activated |
| APH1A | NOTCH_activated |
| FHL1 | NOTCH_activated |
| THBS2 | NOTCH_activated |
| MFAP2 | NOTCH_activated |
| RFNG | NOTCH_activated |
| MFAP5 | NOTCH_activated |
| JAG2 | NOTCH_activated |
| MAML3 | NOTCH_activated |
| MFNG | NOTCH_activated |
| CNTN1 | NOTCH_activated |
| MAML1 | NOTCH_activated |
| MAML2 | NOTCH_activated |
| PSEN1 | NOTCH_activated |
| PSENEN | NOTCH_activated |
| RBPJ | NOTCH_activated |
| RBPJL | NOTCH_activated |
| SNW1 | NOTCH_activated |
| ADAM10 | NOTCH_activated |
| APH1B | NOTCH_activated |
| ADAM17 | NOTCH_activated |
| DLK1 | NOTCH_activated |
| DLL1 | NOTCH_activated |
| DLL3 | NOTCH_activated |
| DLL4 | NOTCH_activated |
| DNER | NOTCH_activated |
| DTX1 | NOTCH_activated |
| DTX2 | NOTCH_activated |
| DTX3 | NOTCH_activated |
| DTX3L | NOTCH_activated |
| DTX4 | NOTCH_activated |
| EGFL7 | NOTCH_activated |
| EIF4EBP1 | PI3K_activated |
| AKT1 | PI3K_activated |
| AKT2 | PI3K_activated |
| AKT3 | PI3K_activated |
| AKT1S1 | PI3K_activated |
| INPP4B | PI3K_activated |
| MAPKAP1 | PI3K_activated |
| MLST8 | PI3K_activated |
| MTOR | PI3K_activated |
| PDK1 | PI3K_activated |
| PIK3CA | PI3K_activated |
| PIK3CB | PI3K_activated |
| PIK3R2 | PI3K_activated |
| RHEB | PI3K_activated |
| RICTOR | PI3K_activated |
| RPTOR | PI3K_activated |
| RPS6 | PI3K_activated |
| RPS6KB1 | PI3K_activated |
| STK11 | PI3K_activated |
| CDKN1A | Cell.Cycle_repressed |
| CDKN1B | Cell.Cycle_repressed |
| CDKN2A | Cell.Cycle_repressed |
| CDKN2B | Cell.Cycle_repressed |
| CDKN2C | Cell.Cycle_repressed |
| RB1 | Cell.Cycle_repressed |
| STK4 | Hippo_repressed |
| STK3 | Hippo_repressed |
| SAV1 | Hippo_repressed |
| LATS1 | Hippo_repressed |
| LATS2 | Hippo_repressed |
| MOB1A | Hippo_repressed |
| MOB1B | Hippo_repressed |
| PTPN14 | Hippo_repressed |
| NF2 | Hippo_repressed |
| WWC1 | Hippo_repressed |
| TAOK1 | Hippo_repressed |
| TAOK2 | Hippo_repressed |
| TAOK3 | Hippo_repressed |
| CRB1 | Hippo_repressed |
| CRB2 | Hippo_repressed |
| CRB3 | Hippo_repressed |
| LLGL1 | Hippo_repressed |
| LLGL2 | Hippo_repressed |
| HMCN1 | Hippo_repressed |
| SCRIB | Hippo_repressed |
| HIPK2 | Hippo_repressed |
| FAT1 | Hippo_repressed |
| FAT2 | Hippo_repressed |
| FAT3 | Hippo_repressed |
| FAT4 | Hippo_repressed |
| DCHS1 | Hippo_repressed |
| DCHS2 | Hippo_repressed |
| CSNK1E | Hippo_repressed |
| CSNK1D | Hippo_repressed |
| AJUBA | Hippo_repressed |
| LIMD1 | Hippo_repressed |
| WTIP | Hippo_repressed |
| MGA | MYC_repressed |
| MNT | MYC_repressed |
| MXD1 | MYC_repressed |
| MXD3 | MYC_repressed |
| MXD4 | MYC_repressed |
| MXI1 | MYC_repressed |
| ARRDC1 | NOTCH_repressed |
| CNTN6 | NOTCH_repressed |
| KDM5A | NOTCH_repressed |
| NOV | NOTCH_repressed |
| NRARP | NOTCH_repressed |
| ITCH | NOTCH_repressed |
| SPEN | NOTCH_repressed |
| FBXW7 | NOTCH_repressed |
| HDAC2 | NOTCH_repressed |
| CUL1 | NOTCH_repressed |
| NCOR1 | NOTCH_repressed |
| NCOR2 | NOTCH_repressed |
| HDAC1 | NOTCH_repressed |
| NUMB | NOTCH_repressed |
| CIR1 | NOTCH_repressed |
| NUMBL | NOTCH_repressed |
| RBX1 | NOTCH_repressed |
| SAP30 | NOTCH_repressed |
| SKP1 | NOTCH_repressed |
| CTBP1 | NOTCH_repressed |
| CTBP2 | NOTCH_repressed |
| DEPDC5 | PI3K_repressed |
| DEPTOR | PI3K_repressed |
| NPRL2 | PI3K_repressed |
| NPRL3 | PI3K_repressed |
| PIK3R1 | PI3K_repressed |
| PIK3R3 | PI3K_repressed |
| PPP2R1A | PI3K_repressed |
| PTEN | PI3K_repressed |
| TSC1 | PI3K_repressed |
| TSC2 | PI3K_repressed |

**Table S2** The list of 129 immunomodulators used in this study

| Chemokines | Interleukins | Interferons | Other cytokines |
|---|---|---|---|
| CXCL10 | IL21R | IFNG | IDO1 |
| CCL11 | IL12B | IFNB1 | LTA |
| CXCL13 | IL21 | IFNAR2 | FASLG |
| CXCL9 | IL9R | IFNGR2 | TNF |
| CXCL11 | IL26 | IFNA8 | CSF2 |
| CCR8 | IL27 | IFNA1 | CSF2RB |
| CCL17 | IL29 | IFNE | CSF2RA |
| CCL20 | IL2RB | IFNA5 | VEGFA |
| CCR4 | IL12RB1 | | TGFBR1 |
| CCL18 | IL10 | | FAS |
| CCL25 | IL24 | | TGFB3 |
| CXCR4 | IL7R | | CSF1 |
| CXCR3 | IL18 | | PDGFC |
| CCL26 | IL32 | | ARG1 |
| CCR3 | IL2RG | | VEGFC |
| CCR7 | IL8 | | VEGFB |
| CCR5 | IL2RA | | PDGFRB |
| CCR2 | IL12RB2 | | TGFBR2 |
| XCL2 | IL1A | | PDGFRA |
| CCL5 | IL22 | | EPOR |
| CCL4 | IL10RA | | PDGFA |
| CCR6 | IL23A | | CSF3 |
| CCR1 | IL31RA | | EGFR |
| CCL3 | IL1R2 | | PDGFD |
| CCL22 | IL28A | | EGF |
| CCL8 | IL28B | | TPO |
| XCL1 | IL1B | | TGFBR3 |
| CXCR6 | IL27RA | | |
| CCL1 | IL11 | | |
| CXCL16 | IL20RB | | |
| CXCR1 | IL12A | | |
| CXCR2 | IL16 | | |
| CCR9 | IL10RB | | |
| PF4 | IL6R | | |
| CXCL6 | IL10RB | | |
| CX3CL1 | IL6R | | |
| CCR10 | IL3RA | | |
| CX3CR1 | IL4R | | |
| CXCR7 | IL1R1 | | |
| CCL16 | IL34 | | |
| CXCL14 | IL17D | | |
| CXCL12 | IL6 | | |
| CCL21 | IL11RA | | |
| PPBP | IL5 | | |
| CCL14 | IL17RD | | |
| CCL28 | IL33 | | |
| | IL20RA | | |
| | IL17B | | |
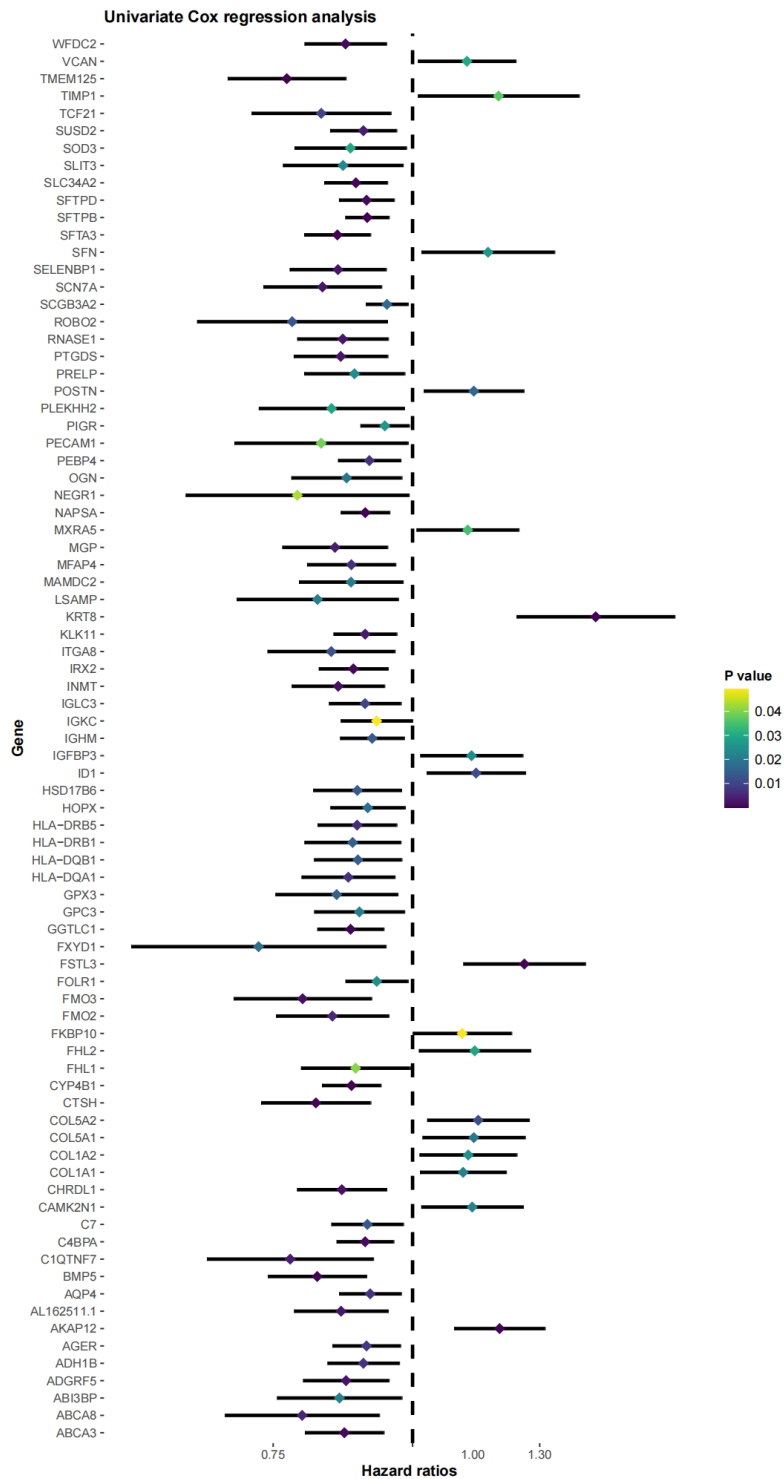
**Figure S1** Forest plot of survival-associated genes obtained with univariate Cox analysis.
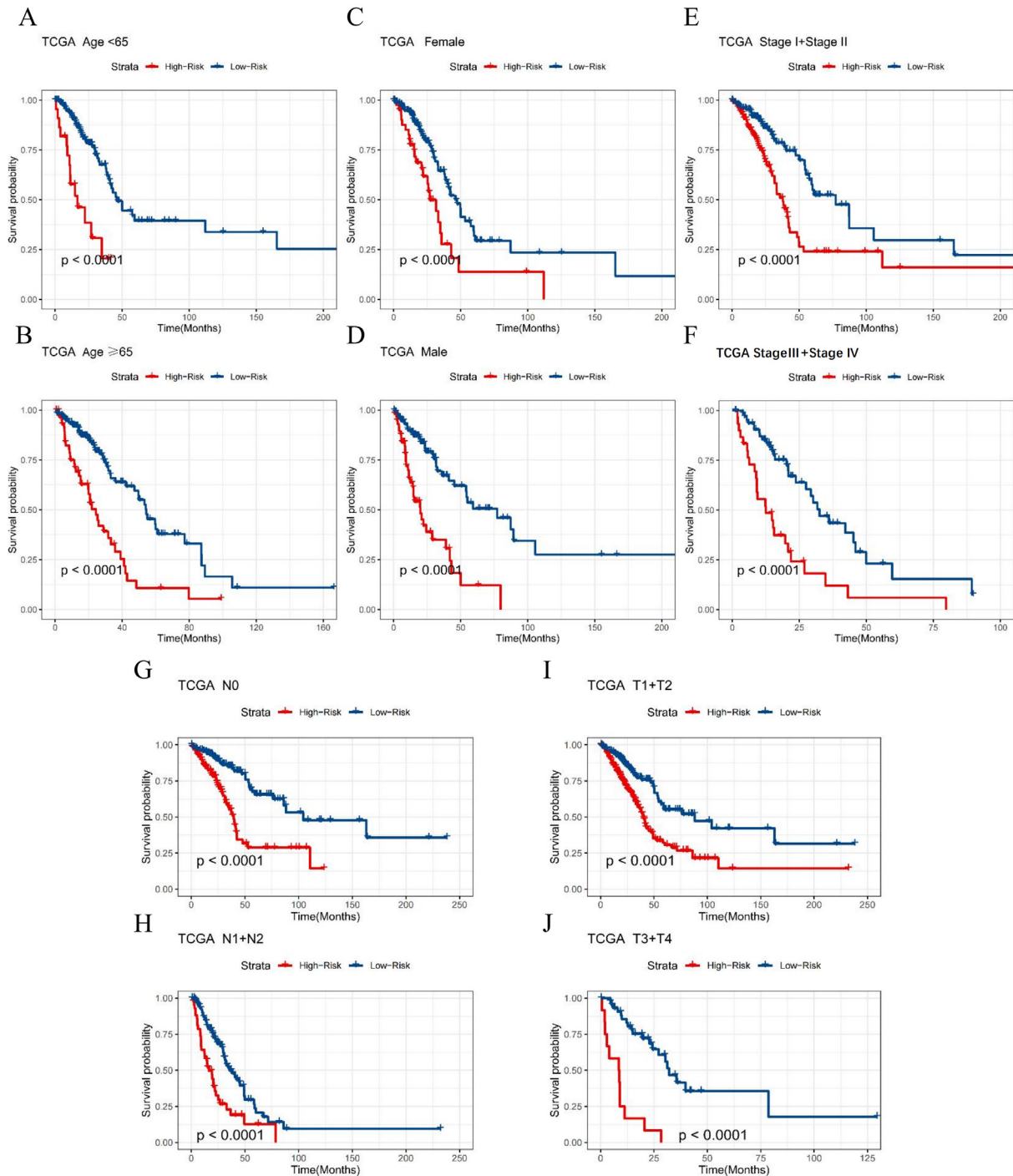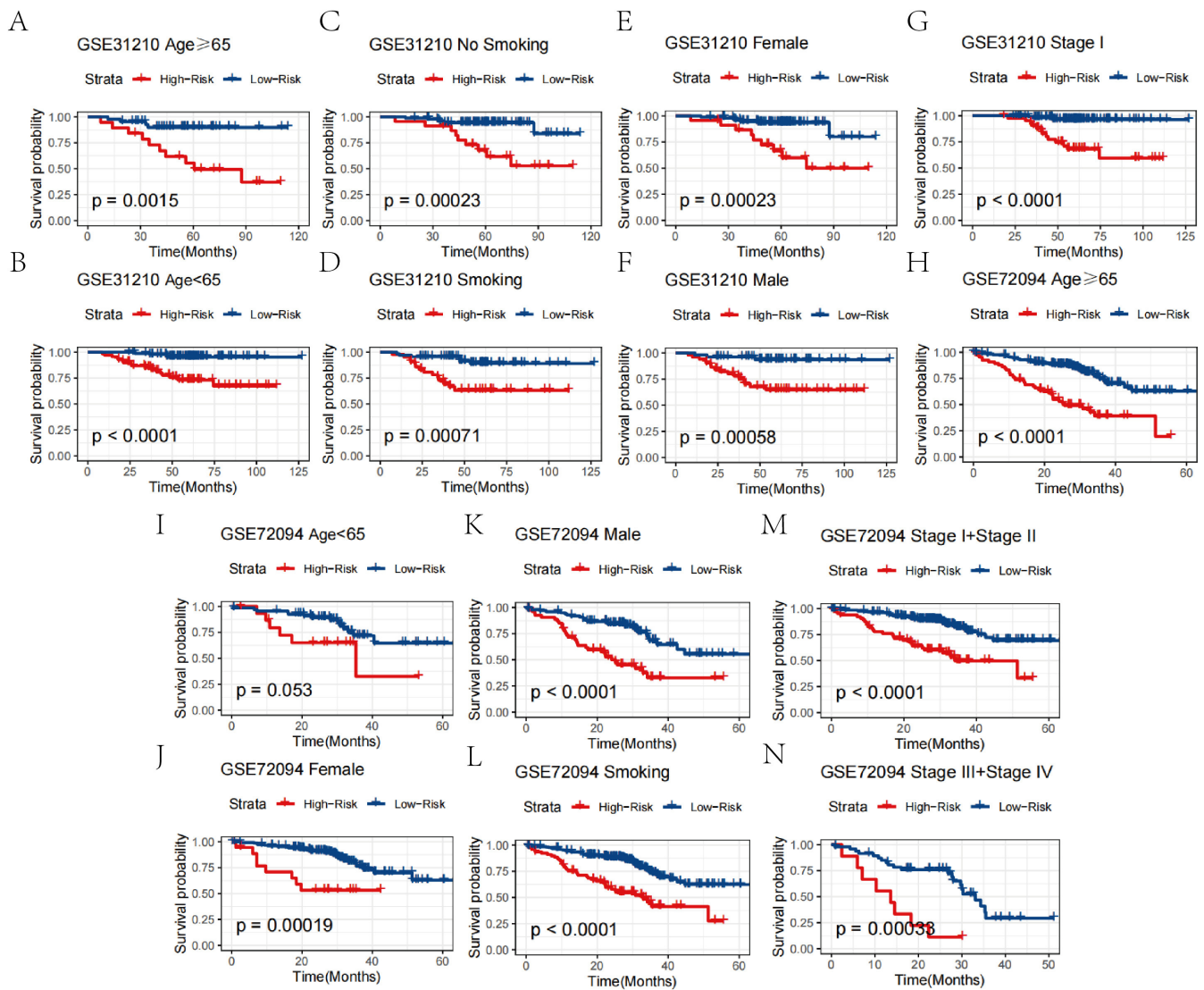
**Figure S2** Validation of the prediction power of the signature in different subgroups of the TCGA cohort based on clinical variables. Kaplan-Meier overall survival analysis based on risk scores in TCGA database for the following subgroups: (A) aged <65 years, (B) aged ≥65 years, (C) female, (D) male, (E) at early stages (I + II), (F) at advanced stages (III + IV), (G) without lymph node metastasis, (H) with lymph node metastasis, (I) at early T stages (T1 + T2), and (J) at advanced T stages (T3 + T4). TCGA, The Cancer Genome Atlas.
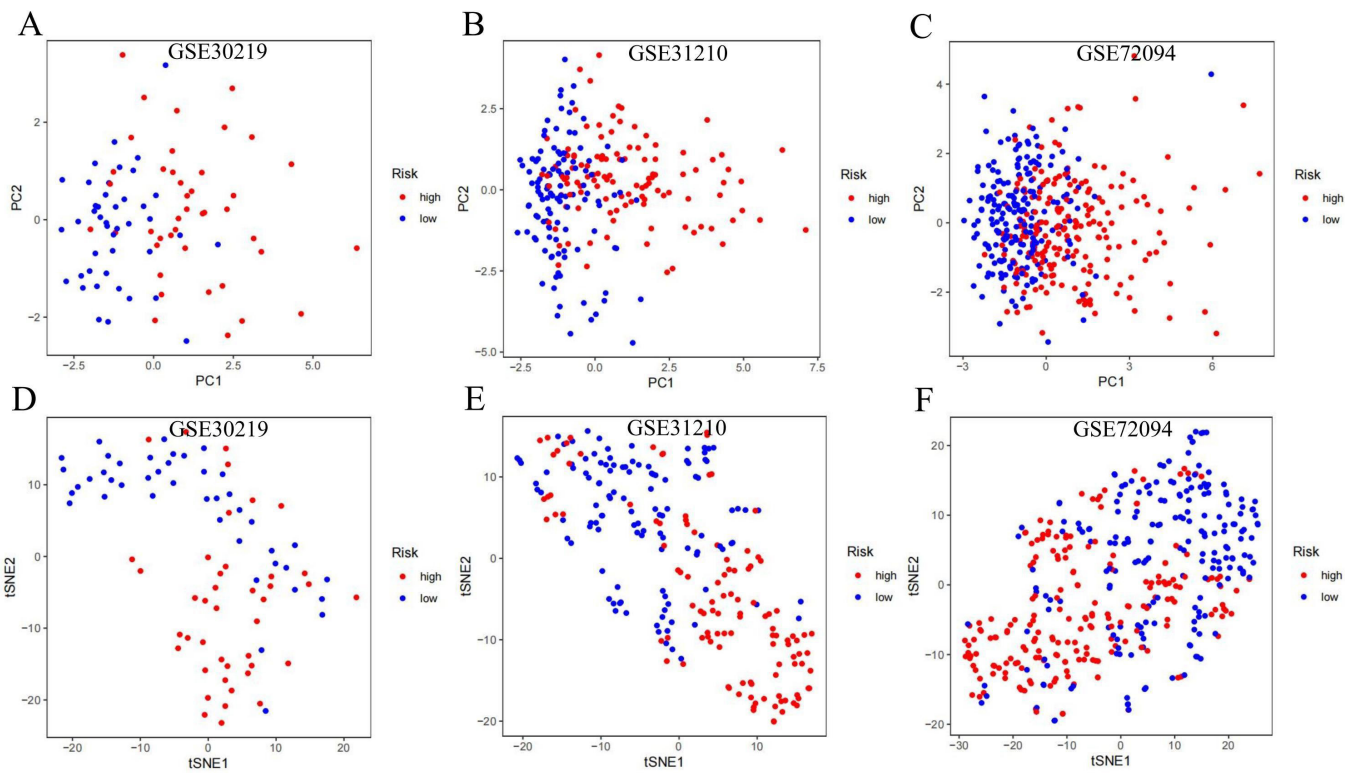
**Figure S3** The PCA and tSNE analysis in the 3 validation cohorts. (A-C) PCA analysis and (D-F) tSNE analysis in the GSE30219, GSE31210, and GSE72094 cohorts. PCA, principal component analysis; tSNE, t-distributed stochastic neighbor embedding.

**Figure S4** Validation of the prediction power of the signature in different subgroups of the GEO cohorts based on clinical variables. Kaplan-Meier overall survival analysis of the GSE31210 cohort for the following subgroups:(A) aged ≥65 years, (B) aged <65 years, (C) non-smoking, (D) smoking, (E) female, (F) male, and (G) at stage I. Kaplan-Meier overall survival curves based on risk score in the GSE72094 cohort for the following subgroups: (H) aged ≥65 years, (I) aged <65 years, (J) female, (K) male, (L) smoking, (M) at early stages (I + II), and (N) at advanced stages (III + IV). GEO, Gene Expression Omnibus.
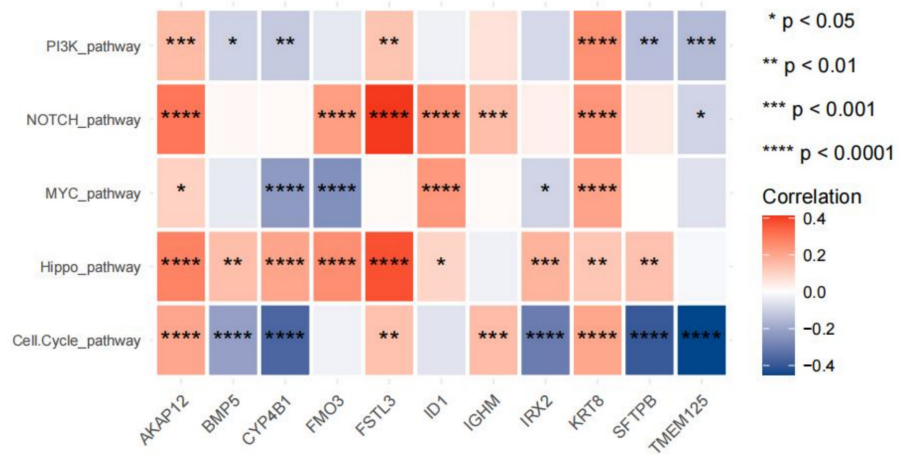
**Figure S5** The thermogram shows the association between the 5 oncogenic signaling pathways and the 11 CAF marker genes.
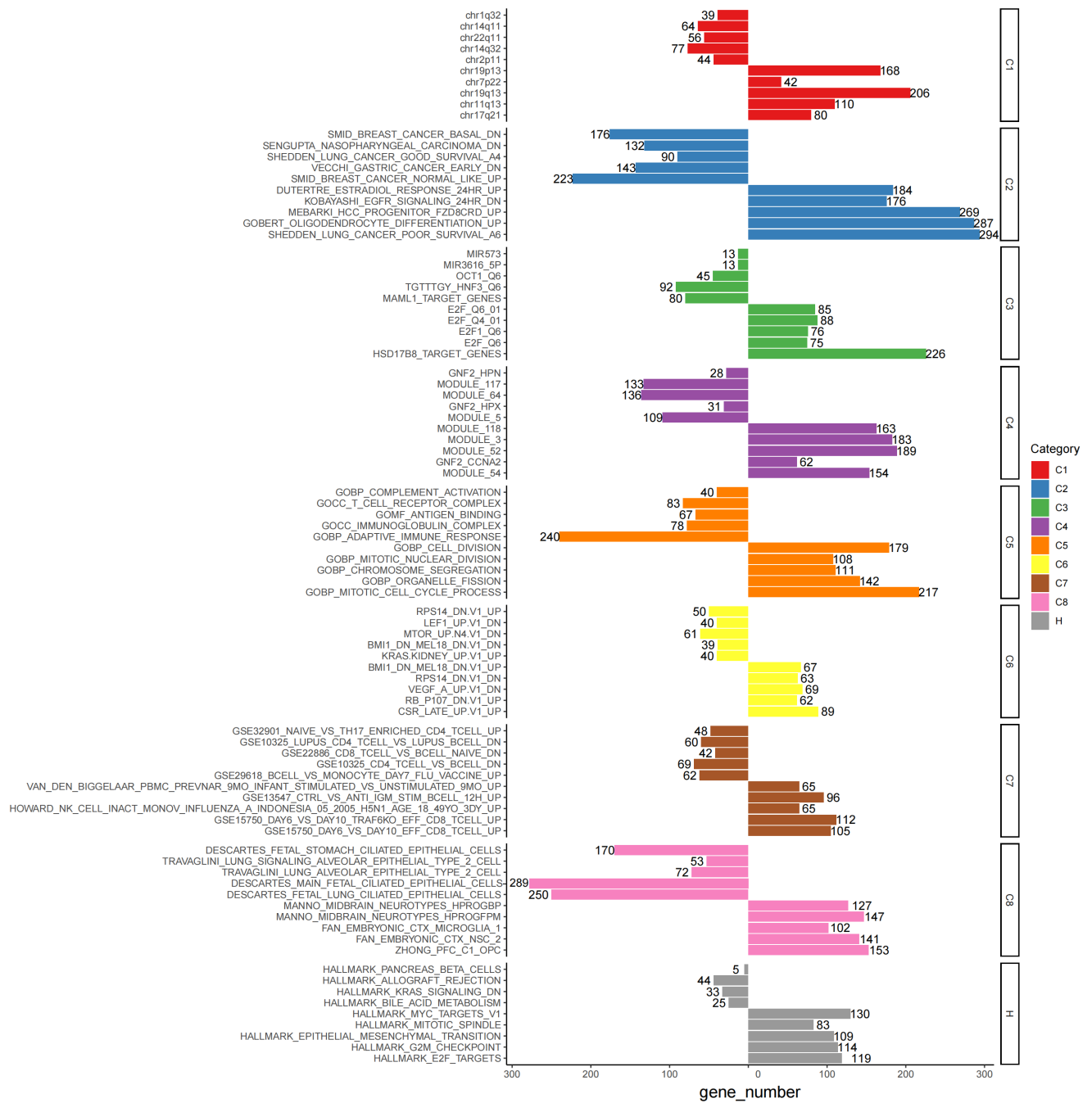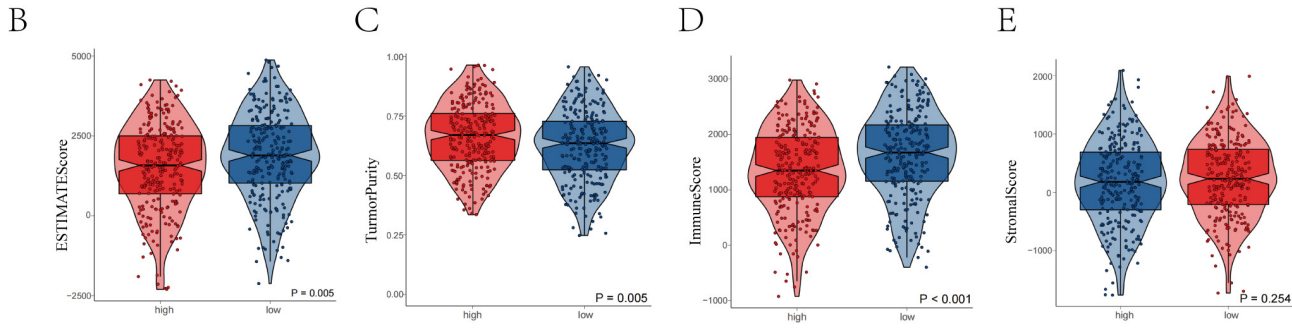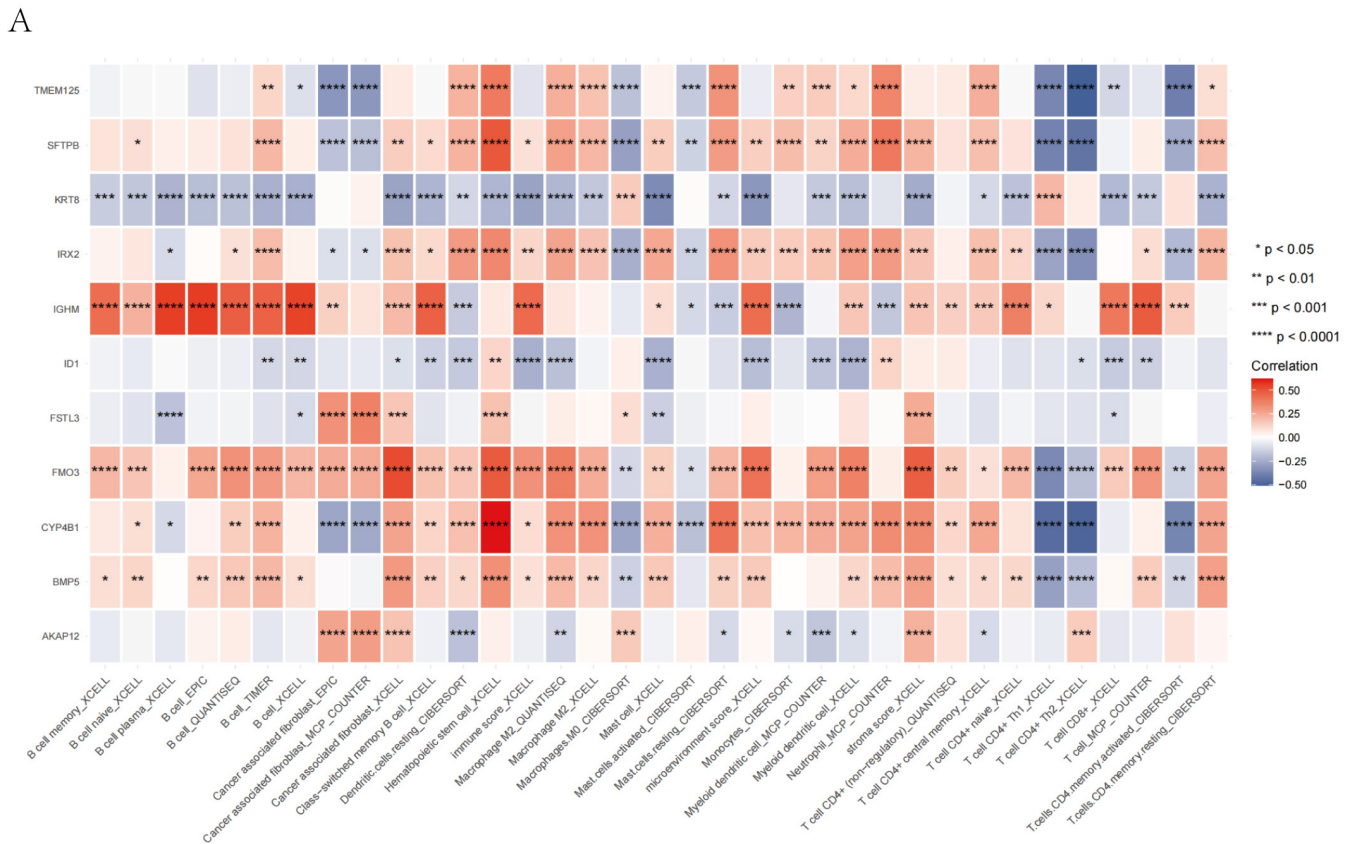
**Figure S6** Histogram of gene set enrichment analysis based on MsigDB.

**Figure S7** Thermogram showing the association between the marker genes and biological signaling pathways according to GSVA. CAF, cancer-associated fibroblast; GSVA, gene set variation analysis.

**Figure S8** Correlation between the signature and immune cell infiltration in the TME. (A) Heatmap showing the correlation of the 11 CAF marker genes with immune cell infiltration characteristics. (B) Comparison of ESTIMATE scores, (C) tumor purity scores, (D) immune scores, and (E) stromal scores of the high-risk and low-risk groups. CAF, cancer-associated fibroblast; TME, the tumor microenvironment.

A


B
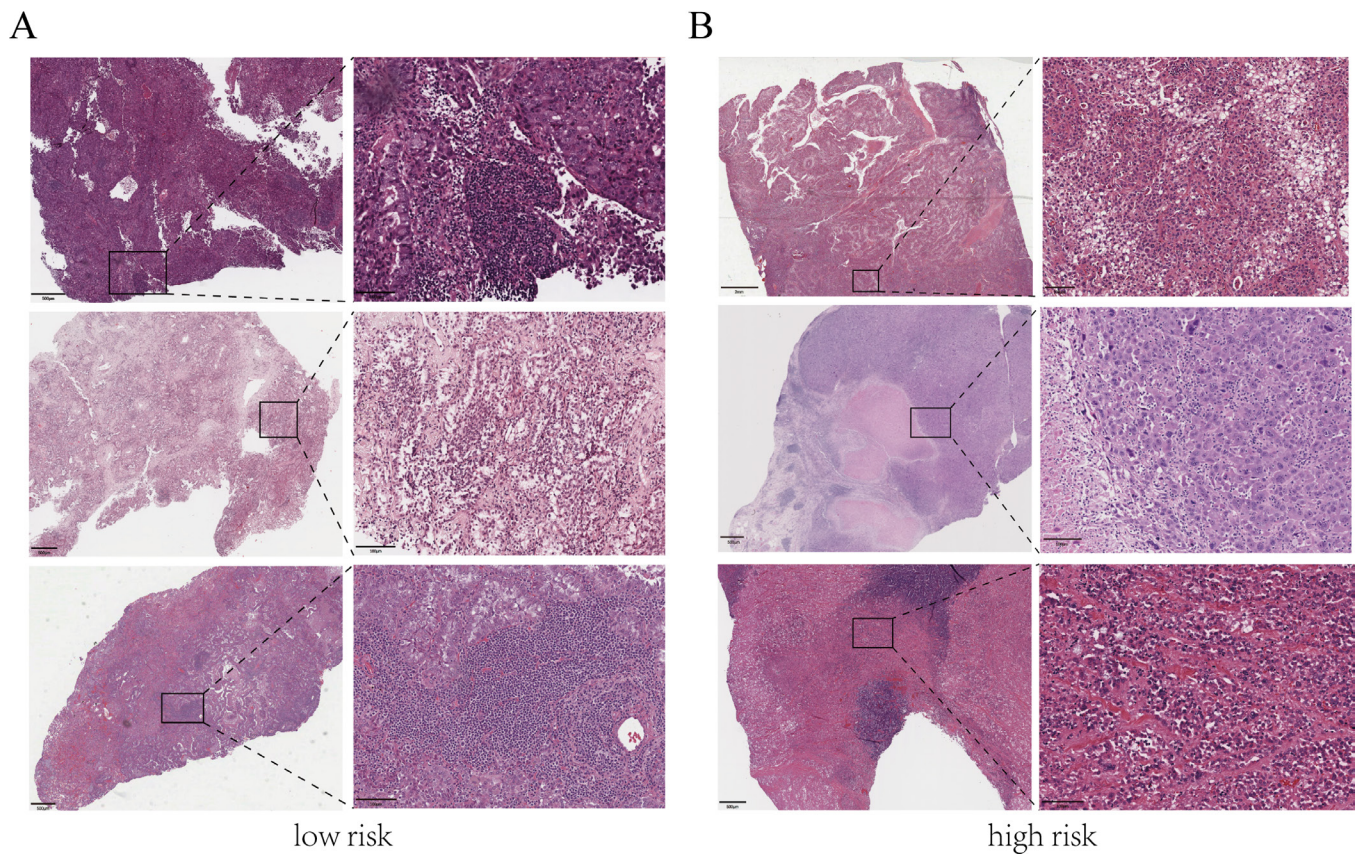

low risk

high risk

**Figure S9** Representative images of HE staining of the (A) low-risk and (B) high-risk patients in TCGA database (TCGA pathology slides). HE staining, hematoxylin-eosin staining; TCGA, The Cancer Genome Atlas.