

Supplementary material

Figure S1

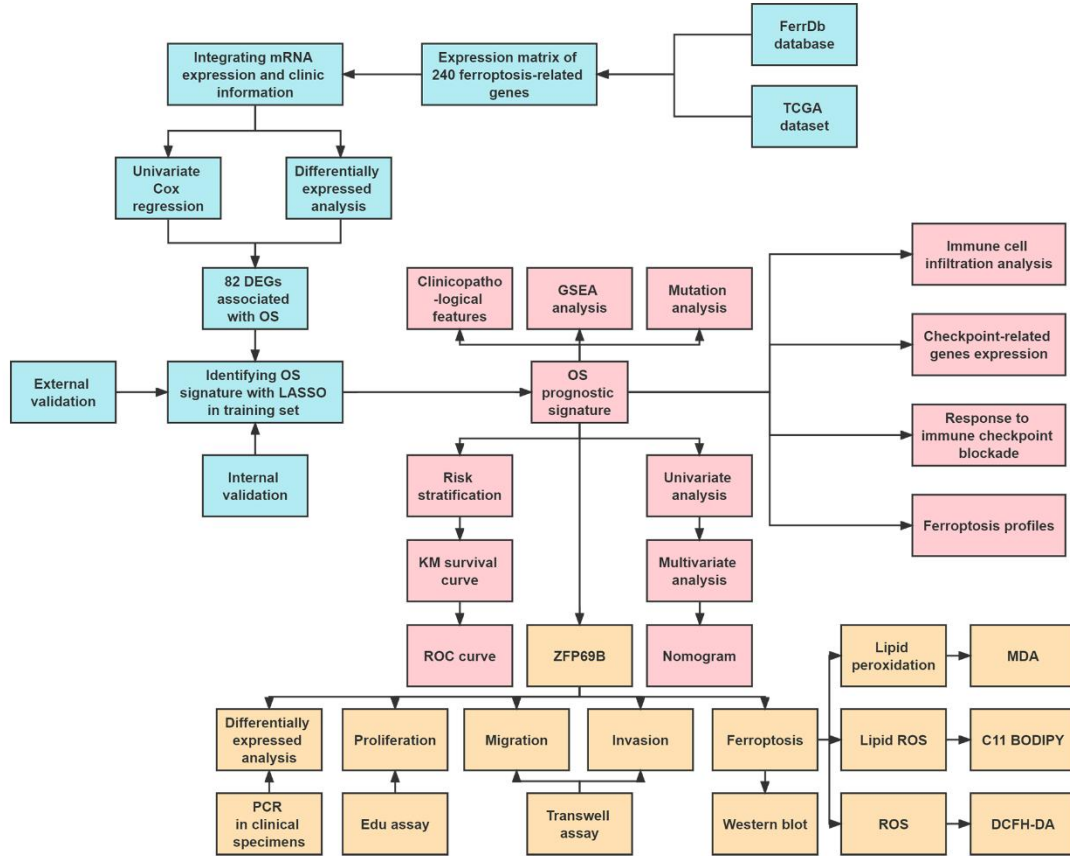


Figure S1 The work flow for this study.

Figure S2

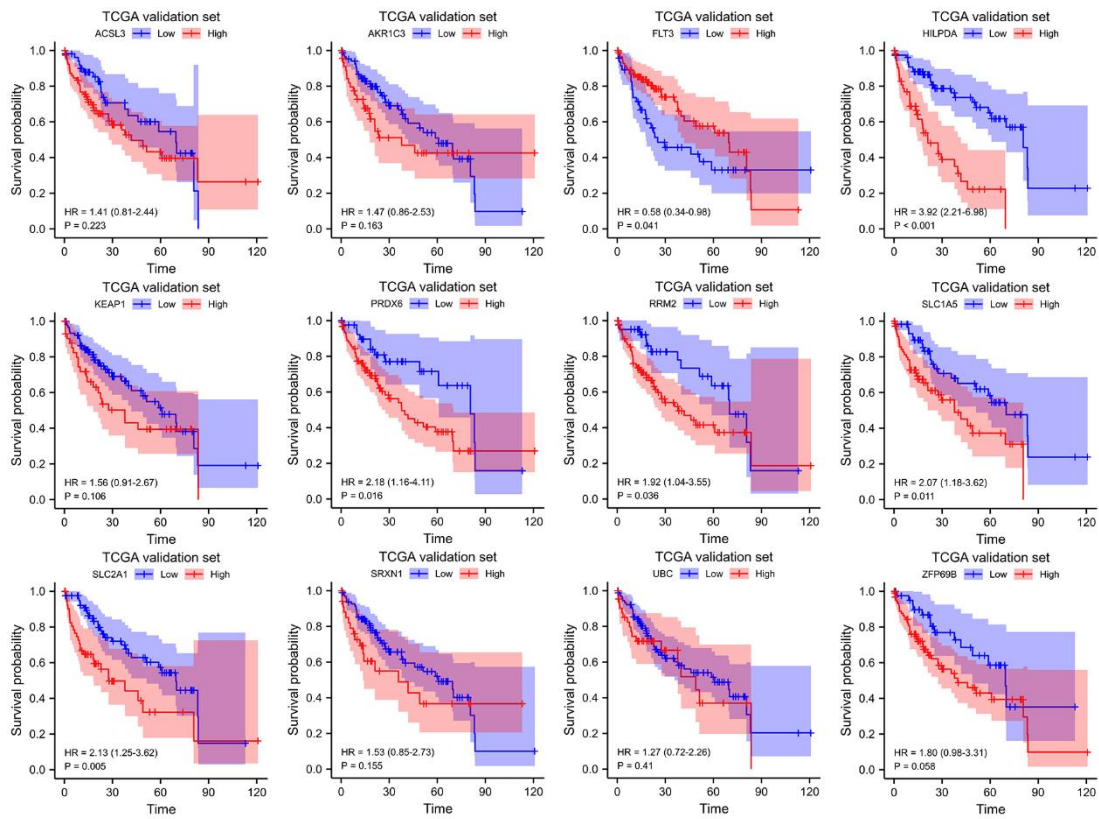


Figure S2 The KM survival curve for 12 FRGs in TCGA validation set.

Figure S3

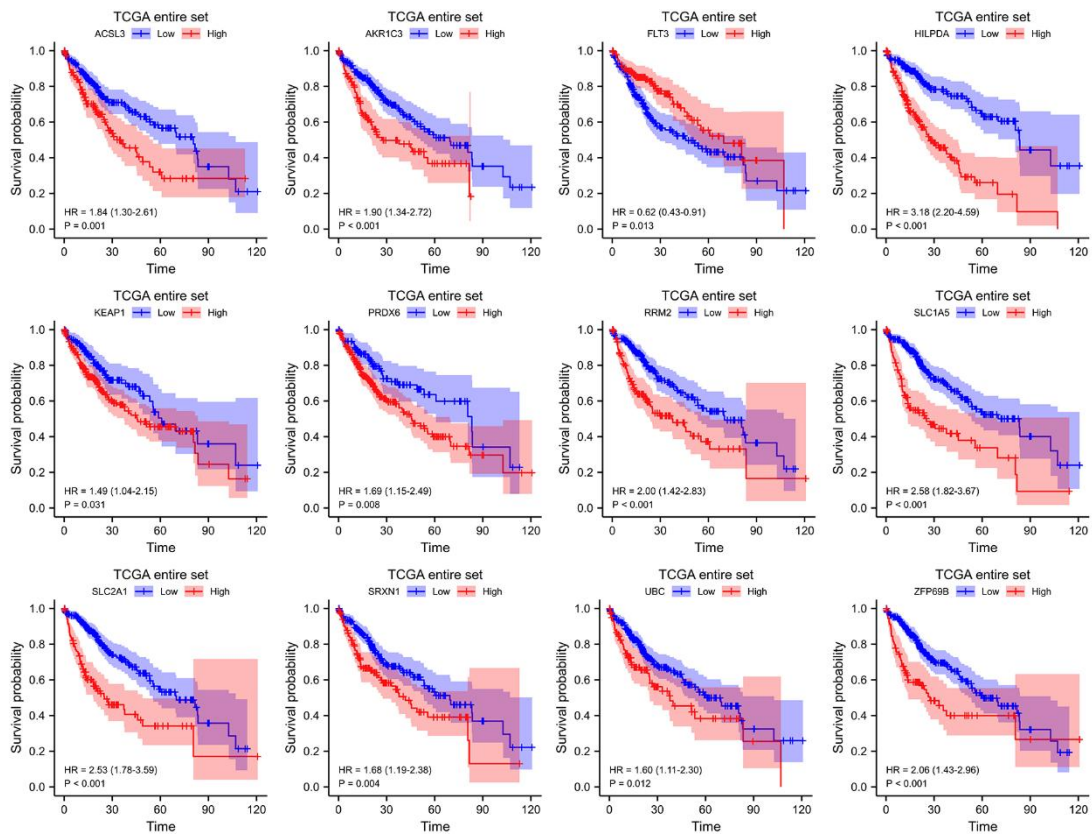


Figure S3 The KM survival curve for 12 FRGs in TCGA entire set.

Figure S4

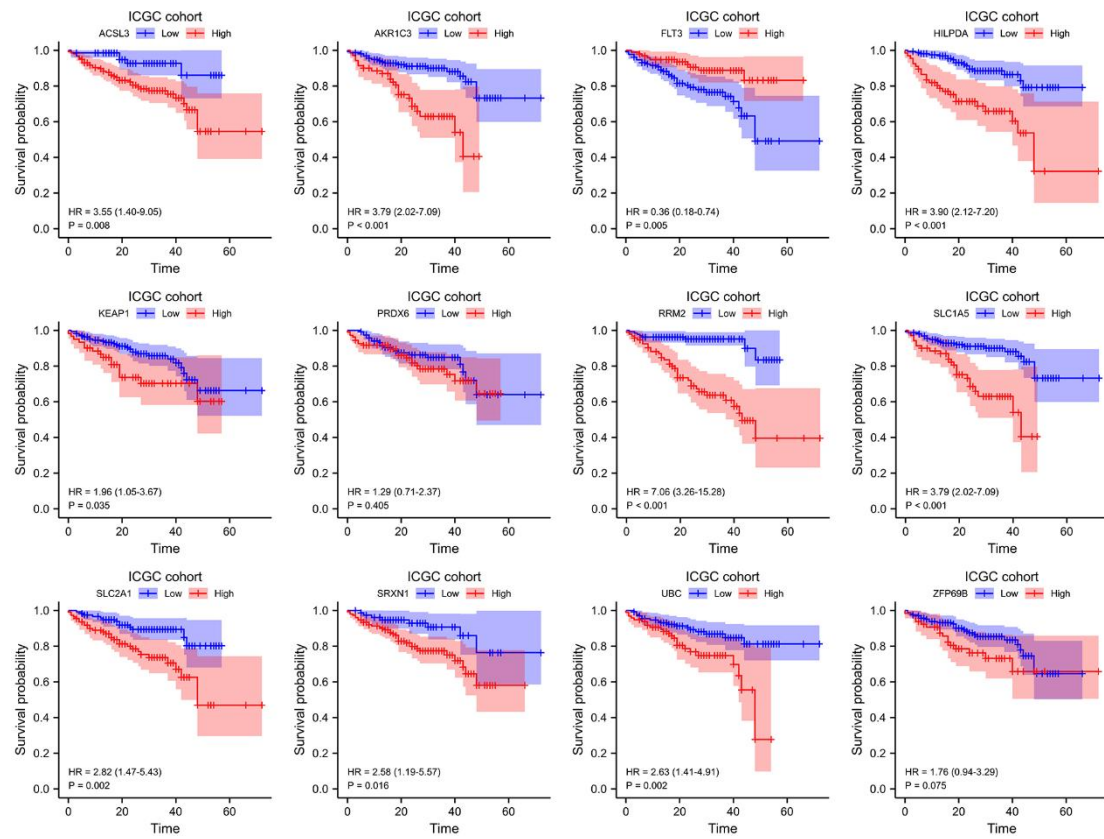


Figure S4 The KM survival curve for 12 FRGs in ICGC cohort.

Figure S5

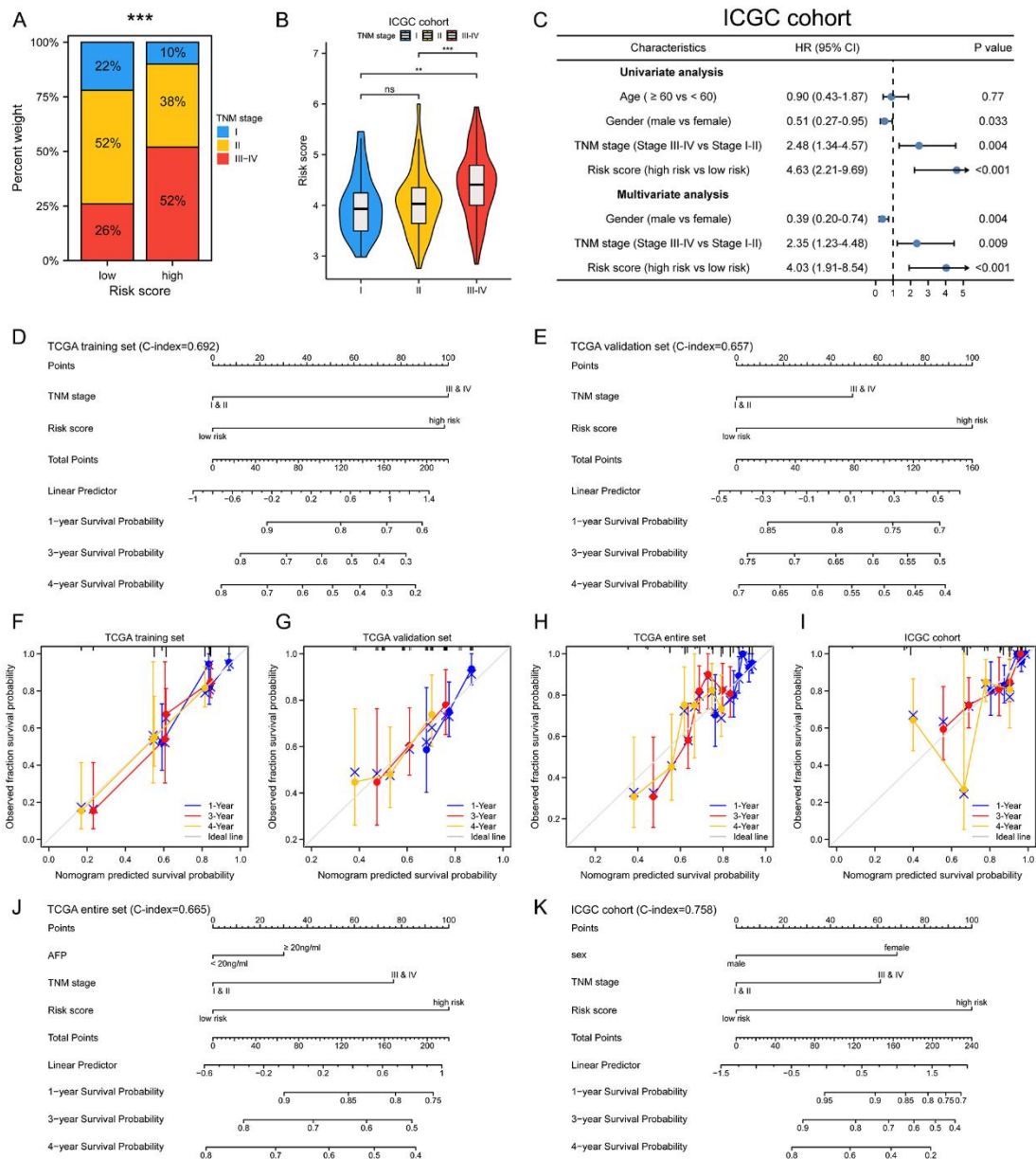


Figure S5 Development of nomograms to predict OS of HCC patients. (A-B) Correlation between risk score and TNM stage in ICGC cohort. **(C)** Univariate and multivariate Cox regression analyses in different TCGA cohorts. Nomograms predicting OS in TCGA training set **(D)**, TCGA validation set **(E)**, TCGA entire set **(J)** and ICGC cohort **(K)**. **(F-I)** Calibration curves for predicting 1-year, 3-year and 4-year OS in different cohorts. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure S6

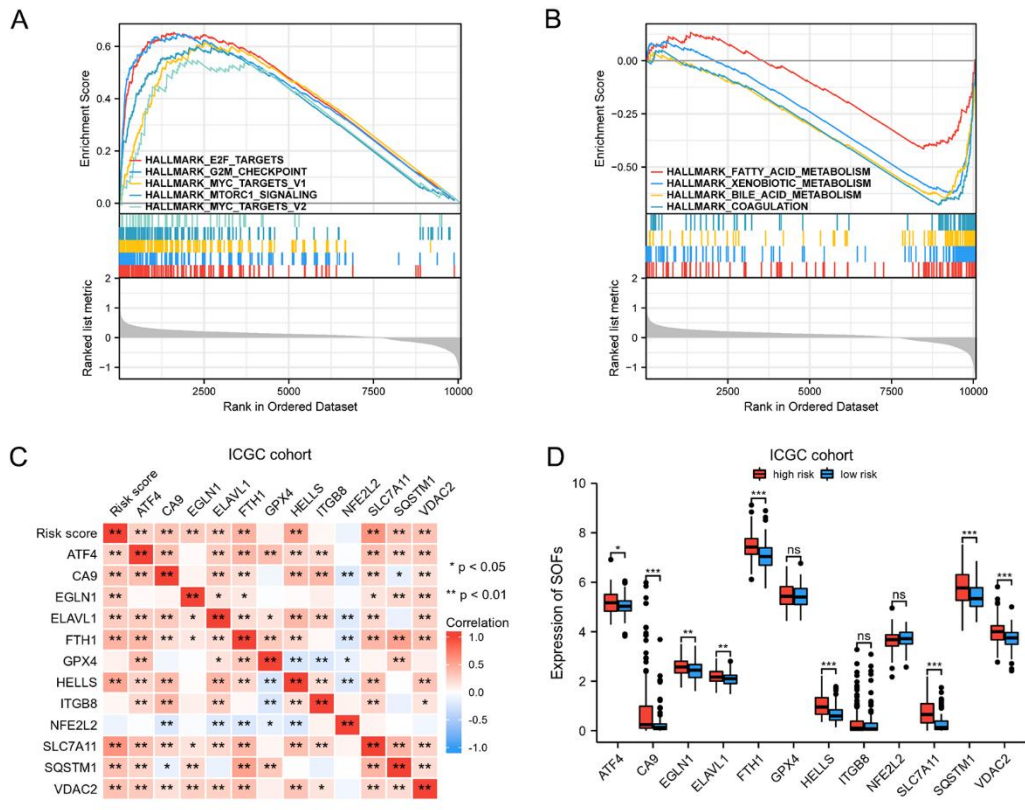


Figure S6 Pathway enrichment and transcriptional changes of SOFs in different subgroups. (A-B) GSEA enrichment analyses for different risk group of ICGC cohort. (C-D) The correlation between risk score and SOFs and transcriptional changes in SOFs in different subgroups of ICGC cohort. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure S7

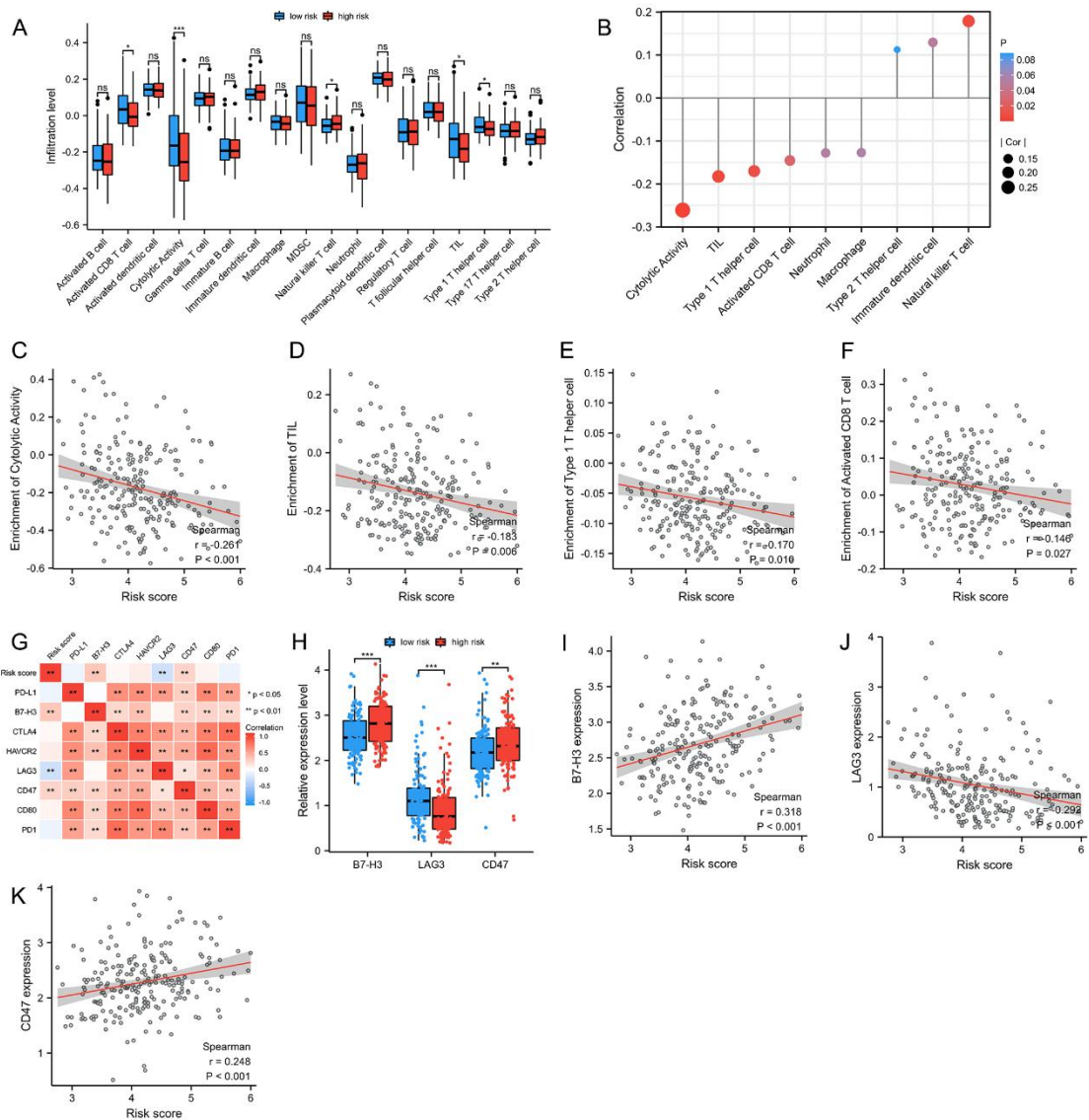


Figure S7 The difference of immune cell infiltration and ICIs related-genes in different risk groups of ICGC cohort. (A) The landscape of 18 immune cell infiltration proportions for ICGC cohort. **(B)** Correlation between immune cell infiltration level and risk score. Risk score was significantly negatively correlated with cytolytic activity **(C)**, TIL **(D)**, Th1 cell **(E)**, and activated CD8 T cell **(F)**. **(G-K)** Risk score was positively associated with B7-H3 and CD47 and negatively associated with LAG3. *p*-values were showed as follows: * *p* < 0.05, ** *p* < 0.01, *** *p* < 0.001.

Figure S8

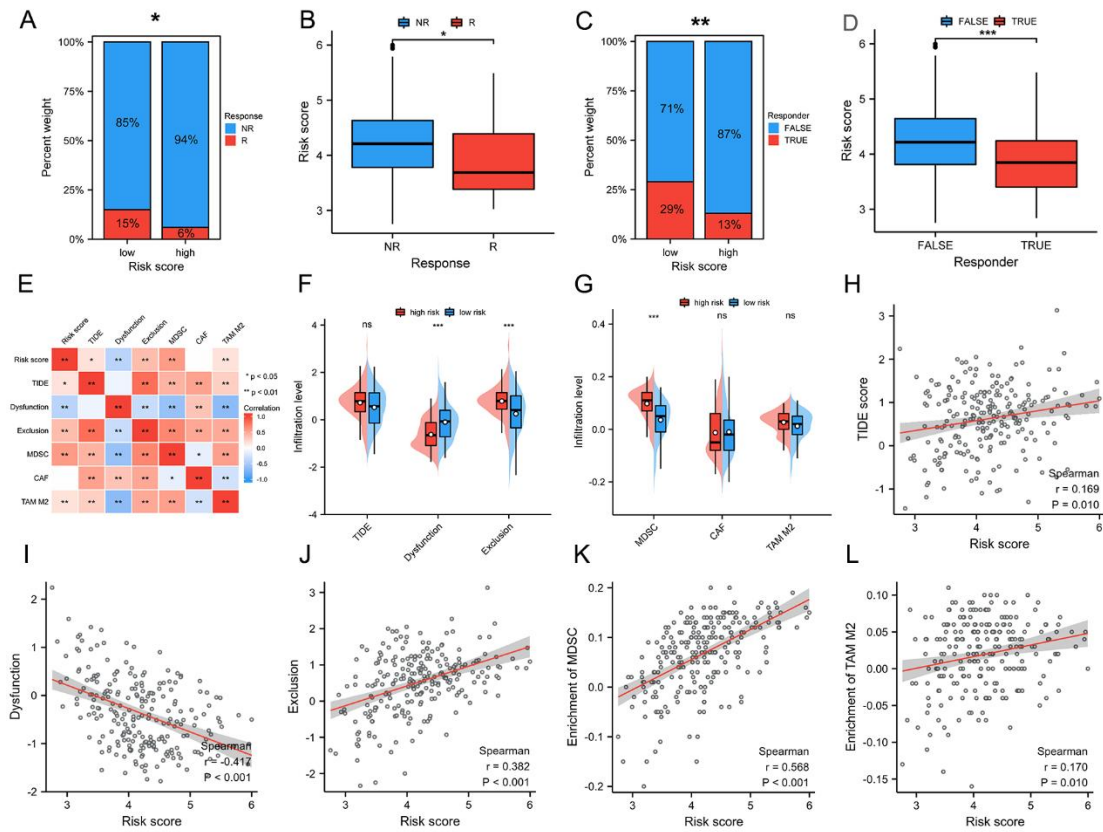


Figure S8 Signature predicts immunotherapy response. Therapeutic response to ICB therapy from ImmuneCellAI (A-B) and TIDE score (C-D). (E-L) Risk scores were positively correlated with TIDE score, T cell exclusion, MDSC and TAM M2 but negatively correlated with T cell dysfunction. p -values were showed as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplementary tables

Table S1: Univariate Cox regression analysis result of OS-genes

Genesymbol	Coefficient	HR	CI	P-value
SLC2A1	0.618	1.854	1.483-2.318	<0.001
CDO1	-0.188	0.829	0.731-0.939	0.003
ABCC1	0.458	1.581	1.234-2.026	<0.001
SRXN1	0.766	2.150	1.537-3.009	<0.001
CARS1	0.755	2.127	1.371-3.299	0.001
LONP1	0.655	1.926	1.182-3.137	0.008

OTUB1	0.793	2.210	1.346-3.630	0.002
CISD2	0.562	1.754	1.044-2.947	0.034
FLT3	-2.415	0.089	0.014-0.587	0.012
PEBP1	-0.300	0.741	0.551-0.996	0.047
HRAS	0.447	1.564	1.169-2.091	0.003
NOX1	0.539	1.714	1.072-2.742	0.025
VEGFA	0.453	1.573	1.149-2.153	0.005
DNAJB6	0.955	2.600	1.405-4.812	0.002
GPT2	-0.215	0.807	0.679-0.959	0.015
ATG16L1	0.932	2.541	1.302-4.956	0.006
FTL	0.261	1.298	1.039-1.623	0.022
UBC	0.532	1.703	1.009-2.873	0.046
MT3	0.512	1.668	1.245-2.235	0.001
OXSR1	0.653	1.920	1.164-3.167	0.011
RRM2	0.497	1.644	1.304-2.073	<0.001
ATG7	1.537	4.653	2.102-10.297	<0.001
GABARAPL1	-0.341	0.711	0.561-0.900	0.005
SAT1	-0.413	0.662	0.454-0.963	0.031
HELLS	0.659	1.933	1.313-2.845	0.001
CHMP5	0.506	1.659	1.029-2.674	0.038
ASNS	0.386	1.471	1.167-1.853	0.001
HILPDA	0.523	1.688	1.367-2.085	<0.001
AIFM2	0.468	1.596	1.116-2.282	0.010
NRAS	0.843	2.323	1.580-3.416	<0.001
TRIB3	0.290	1.337	1.077-1.659	0.008
PCK2	-0.193	0.824	0.687-0.990	0.038
SQSTM1	0.464	1.591	1.260-2.009	<0.001
MYB	1.626	5.083	1.987-13.002	0.001
PRDX1	0.729	2.072	1.463-2.934	<0.001
STMN1	0.510	1.665	1.330-2.085	<0.001
SLC3A2	0.375	1.454	1.021-2.071	0.038
RPL8	0.247	1.280	1.027-1.596	0.028
SLC1A4	0.521	1.683	1.239-2.287	0.001
AURKA	0.400	1.492	1.177-1.892	0.001
EIF2S1	1.293	3.645	1.967-6.755	<0.001
FANCD2	0.790	2.203	1.469-3.303	<0.001
ALB	-0.120	0.886	0.795-0.989	0.031
RELA	0.805	2.236	1.156-4.326	0.017
MAPK1	0.494	1.639	1.083-2.481	0.020
PGD	0.587	1.799	1.376-2.353	<0.001
HSF1	0.456	1.578	1.130-2.204	0.007
IL33	-0.331	0.718	0.533-0.968	0.030
ATF4	0.514	1.672	1.142-2.450	0.008
KEAP1	0.653	1.921	1.095-3.371	0.023

SLC2A6	0.270	1.311	1.030-1.668	0.028
ATG3	1.223	3.398	1.846-6.254	<0.001
G6PD	0.503	1.653	1.405-1.945	<0.001
TFRC	0.375	1.454	1.102-1.919	0.008
TFR2	-0.188	0.829	0.715-0.960	0.012
PRKAA2	0.334	1.397	1.068-1.827	0.015
MAFG	0.839	2.314	1.634-3.277	<0.001
FTH1	0.509	1.663	1.203-2.300	0.002
SRC	0.320	1.378	1.088-1.744	0.008
HMOX1	0.285	1.330	1.092-1.618	0.005
ACSL3	0.569	1.766	1.245-2.504	0.001
VDAC2	0.744	2.104	1.330-3.327	0.001
NQO1	0.141	1.152	1.052-1.260	0.002
TXNIP	-0.204	0.815	0.676-0.982	0.032
PRDX6	0.481	1.617	1.098-2.382	0.015
MAPK3	0.647	1.910	1.259-2.898	0.002
NCF2	0.395	1.485	1.190-1.852	<0.001
SLC38A1	0.412	1.509	1.236-1.843	<0.001
ATG5	0.865	2.375	1.324-4.259	0.004
ZFP69B	2.042	7.703	3.776-15.716	<0.001
SLC7A11	0.556	1.744	1.358-2.241	<0.001
CDKN2A	0.312	1.366	1.106-1.688	0.004
YY1AP1	0.718	2.051	1.309-3.211	0.002
ATG13	1.040	2.830	1.510-5.304	0.001
CAPG	0.273	1.313	1.107-1.558	0.002
AKR1C3	0.356	1.427	1.118-1.821	0.004
DDIT3	0.295	1.343	1.055-1.710	0.016
CISD1	0.708	2.030	1.298-3.174	0.002
SLC1A5	0.449	1.566	1.326-1.850	<0.001
TXNRD1	0.450	1.568	1.261-1.950	<0.001
NF2	0.493	1.638	1.008-2.661	0.046
ELAVL1	0.809	2.245	1.223-4.119	0.009

Table S2: Clinicopathological features of the samples included in this study

Clinical characteristics	TCGA cohort (n = 364)		ICGC cohort (n = 230)	
	Total	Percentage	Total	Percentage
Age				
< 60	164	45.05%	44	19.13%
≥60	200	54.95%	186	80.87%
Gender				
Female	118	32.42%	61	26.52%
Male	246	67.58%	169	73.48%
Race				
White	181	49.73%		

Asian	155	42.58%		
Family History				
Negative	204	56.04%		
Positive	111	30.49%		
Serum AFP				
< 20ng/ml	147	40.38%		
≥ 20ng/ml	128	35.16%		
Total bilirubin				
< 1.0mg/dl	215	59.07%		
≥ 1.0mg/dl	84	23.08%		
Albumin				
< 3.5g/dl	69	18.96%		
≥ 3.5g/dl	226	62.09%		
Adjacent hepatitis				
Negative	117	32.14%		
Positive	114	31.32%		
Fibrosis				
Negative	74	20.33%		
Fibrosis	57	15.66%		
Cirrhosis	77	21.15%		
Vascular invasion				
Negative	204	56.04%		
Positive	106	29.12%		
T				
T1+T2	269	73.90%		
T3+T4	91	25.00%		
TNM staging				
I–II	253	69.51%	140	60.87%
III–IV	85	23.35%	90	39.13%
Tumor grade				
I–II	211	57.97%		
III–IV	130	35.71%		
Child-Pugh classification				
A	216	59.34%		
B+C	22	6.04%		

Table S3: Relationship between risk score and other clinicopathological features in TCGA cohort for OS.

Clinicopathological variables	Training set (n = 228)			Validation set (n = 136)			Entire cohort (n = 364)		
	Low risk	High risk	p value	Low risk	High risk	p value	Low risk	High risk	p value
Age									
< 60	52	47	0.504	29	36	0.229	81	83	0.833
≥60	62	67		39	32		101	99	

Gender										
Female	38	34	0.569	23	23	1.000	61	57	0.654	
Male	76	80		45	45		121	125		
Race										
White	56	56	0.884	35	34	0.560	89	92	0.926	
Asian	49	51		25	30		77	78		
Family History										
Negative	65	59	0.244	35	45	0.242	102	102	0.593	
Positive	32	41		21	17		52	59		
Serum AFP										
< 20ng/ml	49	41	0.620	35	22	0.011	84	63	0.089	
≥ 20ng/ml	40	39		18	31		60	68		
Total bilirubin										
< 1.0mg/dl	67	60	0.535	46	42	0.981	113	102	0.454	
≥ 1.0mg/dl	34	25		13	12		48	36		
Albumin										
< 3.5g/dl	22	23	0.419	13	11	0.645	34	35	0.493	
≥ 3.5g/dl	77	61		43	45		122	104		
Adjacent hepatitis										
Negative	45	27	0.133	29	16	0.168	74	43	0.057	
Positive	35	35		22	22		58	56		
Fibrosis										
Negative	28	18	0.665	16	12	0.997	45	29	0.727	
Fibrosis	19	18		12	9		31	26		
Cirrhosis	25	21		18	13		43	34		
Vascular invasion										
Negative	69	63	0.689	42	30	0.051	111	93	0.127	
Positive	31	32		17	26		48	58		
T										
T1+T2	93	79	0.015	52	46	0.194	146	123	0.003	
T3+T4	19	35		15	22		33	58		
TNM staging										
I-II	89	72	0.014	50	42	0.189	140	113	0.001	
III-IV	19	34		14	20		30	55		
Tumor grade										
I-II	83	68	0.034	50	28	<0.001	113	98	0.003	
III-IV	30	45		16	39		48	82		
Child-Pugh classification										
A	75	59	0.348	42	40	1.000	118	98	0.411	
B+C	6	8		4	4		10	12		

Bold values indicate $p < 0.05$.

Table S4: Relationship between risk score and other clinicopathological features in ICGC cohort for OS.

Clinicopathological variables	ICGC cohort (n = 230)		
	Low risk	High risk	<i>p</i> value
Age			
< 60	87	16	<0.001
≥60	28	99	
Gender			
Female	31	30	0.881
Male	84	85	
TNM staging			
I–II	85	55	<0.001
III–IV	30	60	

Bold values indicate $p < 0.05$.