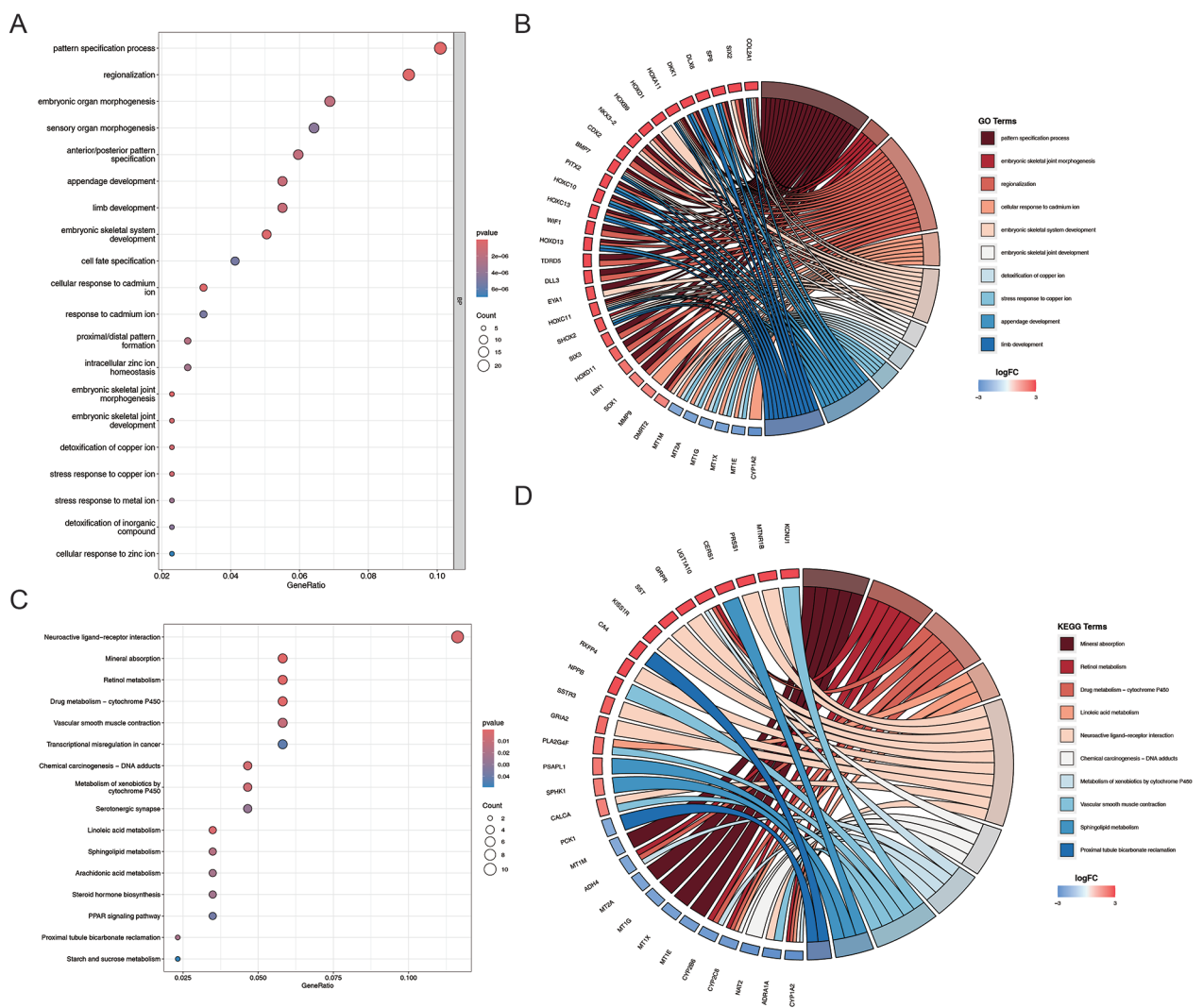
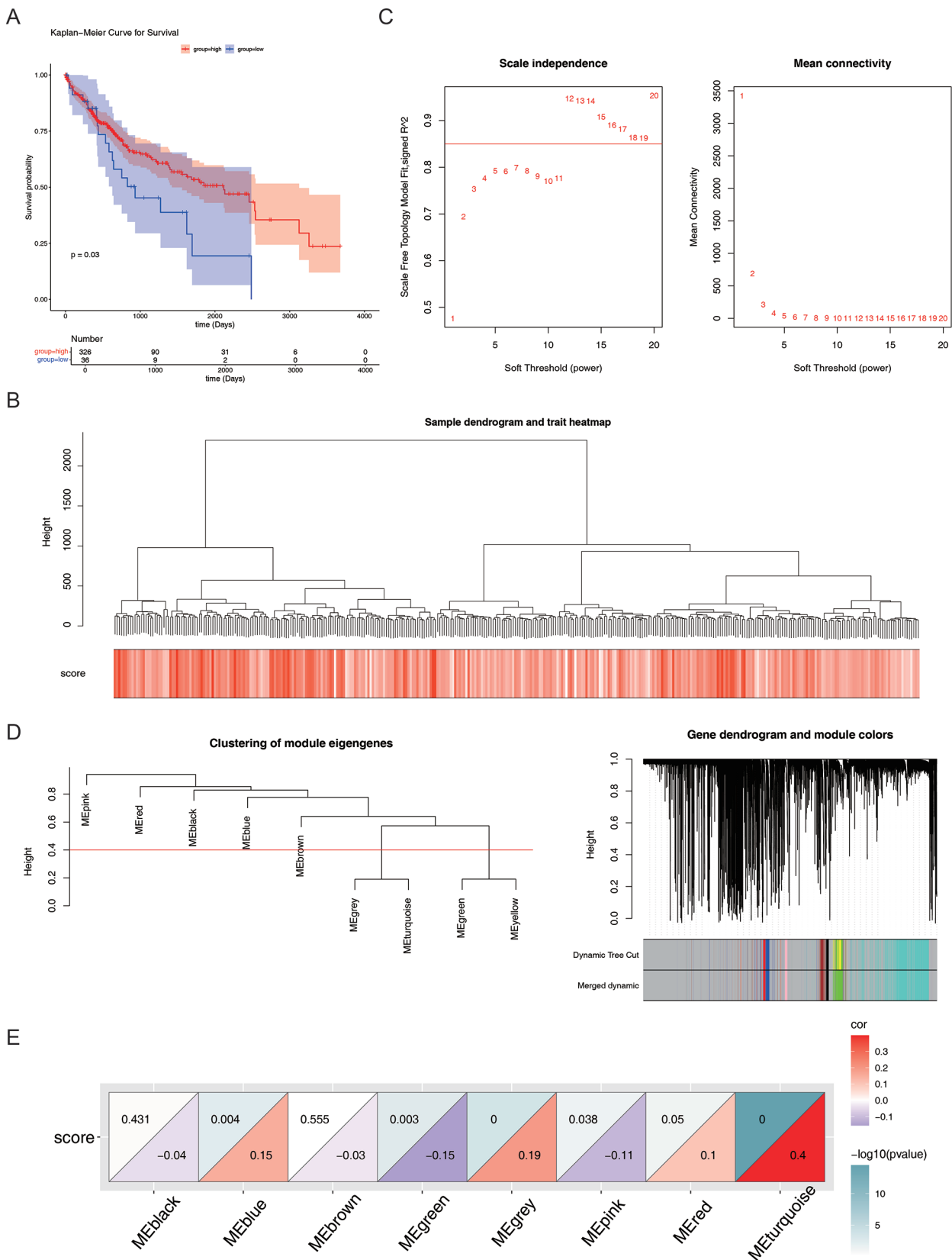


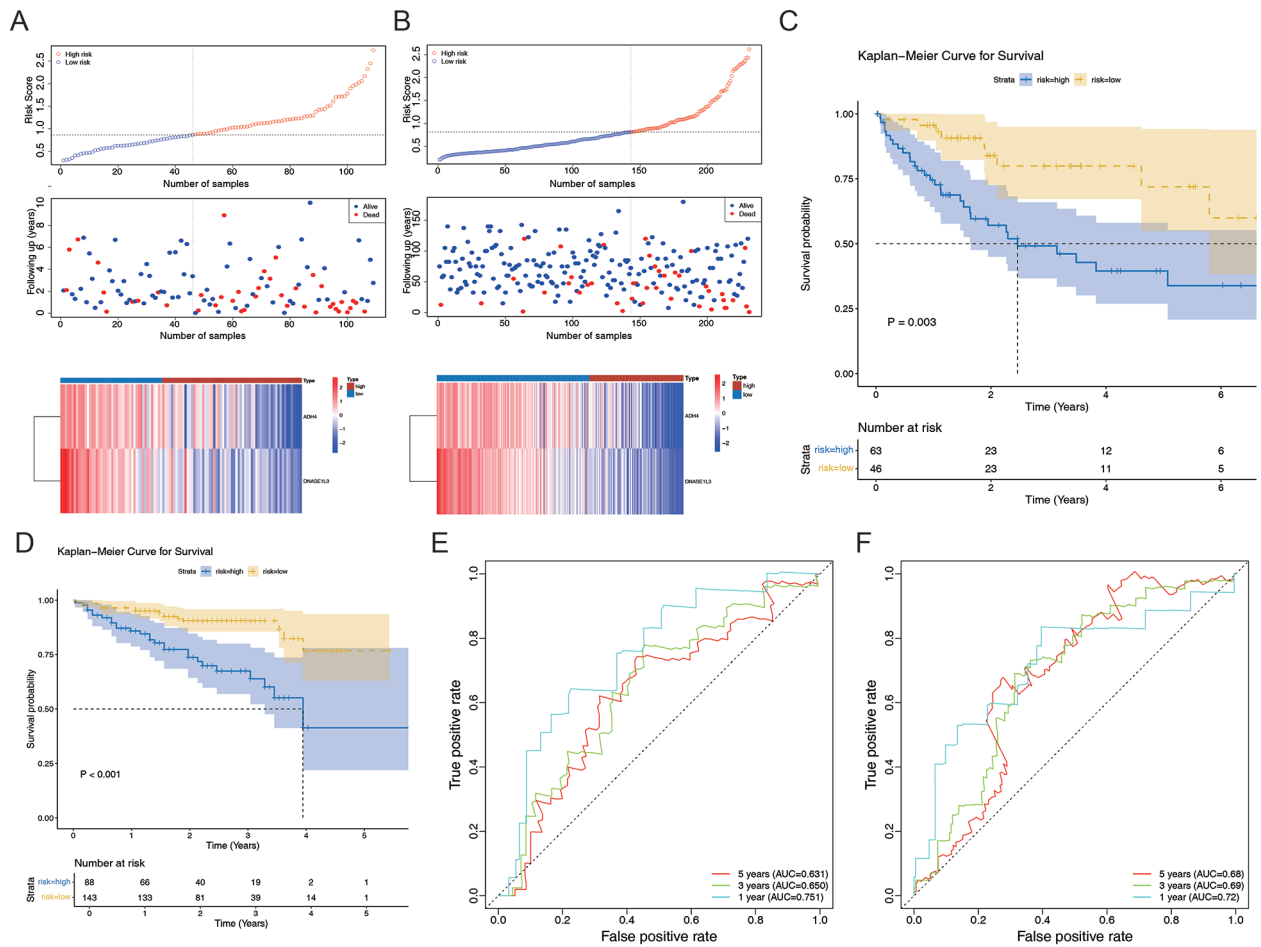
**Figure S1** Identification of the differentially expressed genes. (A) Volcano plot of the differentially expressed genes (tumor/normal). (B) Heatmap of the expression levels of the differentially expressed genes. HCC, hepatocellular carcinoma.



**Figure S2** Enrichment analysis of the candidate genes. (A) Bubble chart of the GO enrichment analysis results for the candidate genes. (B) Chord diagram of the GO enrichment analysis results for the candidate genes. (C) Bubble chart of the KEGG enrichment analysis results for the candidate genes. (D) Chord diagram of the KEGG enrichment analysis results for the candidate genes. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; FC, fold change.



**Figure S3** Identification of Key Modules. (A) Kaplan-Meier curve: This shows the differences in MTDM scores. (B) Sample clustering. The upper part of the figure shows branches representing samples, with the vertical axis representing the height of hierarchical clustering. The lower part indicates the sample types. From the figure, it can be observed that the training set samples show good overall clustering. (C) Scale-Free soft threshold distribution plot. The x-axis represents the weight parameter (power value). The left y-axis represents the scale-free fit index (signed  $R^2$ ), where the higher the squared correlation coefficient, the closer the network approaches a scale-free distribution. The right y-axis represents the average of all gene adjacency functions in the corresponding gene modules. (D) Module clustering dendrogram. Genes are classified into various modules through hierarchical clustering, with different colors representing different modules. The gray color represents genes that cannot be classified into any module by default. (E) Heatmap of Module-Clinical Traits correlation. The x-axis represents different modules, and the y-axis represents MTDM scores. Each square represents the correlation coefficient and significance p-value between a module and MTDM score. The upper part shows p-values, and the lower part shows correlation coefficients. The deeper the color, the stronger the correlation.



**Figure S4** Validation of the risk model. (A) Risk curves for the high- and low-risk groups in TCGA-LIHC test set. (B) Risk curves for the high- and low-risk groups in the Liver Cancer-RIKEN, JP project (LIRI-JP) validation set. (C) Kaplan-Meier survival curves for TCGA-LIHC test set. (D) Kaplan-Meier survival curves for the LIRI-JP validation set. (E) ROC curves for TCGA-LIHC test set. (F) ROC curves for the LIRI-JP validation set. TCGA-LIHC, The Cancer Genome Atlas-liver hepatocellular carcinoma; ROC, receiver operating characteristic.

**Table S1** Pathway information of Gene Ontology (GO) enrichment analysis

Category	Subcategory	ID	Description	GeneRatio	BgRatio	P value	Padjust	q value	Gene ID	Count
Organismal systems	Digestive system	hsa04978	Mineral absorption	5/86	60/8,662	0.000305	0.000305	0.034487	MT1E/MT1G/MT1M/MT1X/MT2A	5
Metabolism	Metabolism of cofactors and vitamins	hsa00830	Retinol metabolism	5/86	68/8,662	0.000547	0.000547	0.034487	ADH4/CYP1A2/CYP2B6/CYP2C8/UGT1A10	5
Metabolism	Xenobiotics biodegradation and metabolism	hsa00982	Drug metabolism - cytochrome P450	5/86	72/8,662	0.000712	0.000712	0.034487	ADH4/CYP1A2/CYP2B6/CYP2C8/UGT1A10	5
Metabolism	Lipid metabolism	hsa00591	Linoleic acid metabolism	3/86	30/8,662	0.003161	0.003161	0.096065	CYP1A2/CYP2C8/PLA2G4F	3
Environmental Information Processing	Signaling molecules and interaction	hsa04080	Neuroactive ligand-receptor interaction	10/86	367/8,662	0.003307	0.003307	0.096065	ADRA1A/CALCA/GRIA2/GRPR/KISS1R/MTNR1B/PRSS1/RXFP4/SST/SSSTR3	10
Human Diseases	Cancer: overview	hsa05204	Chemical carcinogenesis - DNA adducts	4/86	70/8,662	0.005048	0.005048	0.122209	CYP1A2/CYP2C8/NAT2/UGT1A10	4
Metabolism	Xenobiotics biodegradation and metabolism	hsa00980	Metabolism of xenobiotics by cytochrome P450	4/86	78/8,662	0.007397	0.007397	0.153502	ADH4/CYP1A2/CYP2B6/UGT1A10	4
Organismal Systems	Circulatory system	hsa04270	Vascular smooth muscle contraction	5/86	134/8,662	0.010535	0.010535	0.191292	ADRA1A/CALCA/KCNU1/NPPB/PLA2G4F	5
Metabolism	Lipid metabolism	hsa00600	Sphingolipid metabolism	3/86	54/8,662	0.016287	0.016287	0.262877	CERS1/PSAPL1/SPHK1	3
Organismal Systems	Excretory system	hsa04964	Proximal tubule bicarbonate reclamation	2/86	23/8,662	0.021534	0.021534	0.28413	CA4/PCK1	2
Metabolism	Lipid metabolism	hsa00590	Arachidonic acid metabolism	3/86	61/8,662	0.022494	0.022494	0.28413	CYP2B6/CYP2C8/PLA2G4F	3
Metabolism	Lipid metabolism	hsa00140	Steroid hormone biosynthesis	3/86	62/8,662	0.023472	0.023472	0.28413	CYP1A2/SRD5A2/UGT1A10	3
Organismal Systems	Nervous system	hsa04726	Serotonergic synapse	4/86	115/8,662	0.027236	0.027236	0.304339	CYP2C8/HTR3A/KCNN2/PLA2G4F	4
Organismal Systems	Endocrine system	hsa03320	PPAR signaling pathway	3/86	75/8,662	0.038254	0.038254	0.396919	FABP4/FABP6/PCK1	3
Human Diseases	Cancer: overview	hsa05202	Transcriptional misregulation in cancer	5/86	193/8,662	0.042625	0.042625	0.412793	EYA1/HMGA2/HOXA11/MMP9/PAX3	5
Metabolism	Carbohydrate wmetabolism	hsa00500	Starch and sucrose metabolism	2/86	36/8,662	0.049369	0.049369	0.448217	GYS2/MGAM2	2

**Table S2** Pathway information of Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

Category	Subcategory	ID	Description	Gene ratio	Bg ratio	P value	Padjust	q value	Gene ID	Count
Organismal Systems	Digestive system	hsa04978	Mineral absorption	5/86	60/8,662	$3.1 \times 10^{-4}$	0.00030515169844615	0.0344869011370706	MT1E/MT1G/MT1M/MT1X/MT2A	5
Metabolism	Metabolism of cofactors and vitamins	hsa00830	Retinol metabolism	5/86	68/8,662	$5.4 \times 10^{-4}$	0.000547354219279346	0.0344869011370706	ADH4/CYP1A2/CYP2B6/CYP2C8/UGT1A10	5
Metabolism	Xenobiotics biodegradation and metabolism	hsa00982	Drug metabolism - cytochrome P450	5/86	72/8,662	$7.1 \times 10^{-4}$	0.000712229480004719	0.0344869011370706	ADH4/CYP1A2/CYP2B6/CYP2C8/UGT1A10	5
Metabolism	Lipid metabolism	hsa00591	Linoleic acid metabolism	3/86	30/8,662	$3.1 \times 10^{-4}$	0.00316122781156017	0.0960646863904857	CYP1A2/CYP2C8/PLA2G4F	3
Environmental Information Processing	Signaling molecules and interaction	hsa04080	Neuroactive ligand-receptor interaction	10/86	367/8,662	$3.3 \times 10^{-3}$	0.00330657435039715	0.0960646863904857	ADRA1A/CALCA/GRIA2/GRPR/KISS1R/MTNR1B/PRSS1/RXFP4/SST/SSSTR3	10
Human Diseases	Cancer: overview	hsa05204	Chemical carcinogenesis - DNA adducts	4/86	70/8,662	$5.0 \times 10^{-3}$	0.00504776993233932	0.122209166782952	CYP1A2/CYP2C8/NAT2/UGT1A10	4
Metabolism	Xenobiotics biodegradation and metabolism	hsa00980	Metabolism of xenobiotics by cytochrome P450	4/86	78/8,662	0.00739701401973945	0.00739701401973945	0.153501945071285	ADH4/CYP1A2/CYP2B6/UGT1A10	4
Organismal Systems	Circulatory system	hsa04270	Vascular smooth muscle contraction	5/86	134/8,662	0.0105349257767203	0.0105349257767203	0.191292073314132	ADRA1A/CALCA/KCNU1/NPPB/PLA2G4F	5
Metabolism	Lipid metabolism	hsa00600	Sphingolipid metabolism	3/86	54/8,662	0.0162869341421862	0.0162869341421862	0.262876831768619	CERS1/PSAPL1/SPHK1	3
Organismal Systems	Excretory system	hsa04964	Proximal tubule bicarbonate reclamation	2/86	23/8,662	0.0215338253684595	0.0215338253684595	0.284130417565935	CA4/PCK1	2
Metabolism	Lipid metabolism	hsa00590	Arachidonic acid metabolism	3/86	61/8,662	0.0224936985844383	0.0224936985844383	0.284130417565935	CYP2B6/CYP2C8/PLA2G4F	3
Metabolism	Lipid metabolism	hsa00140	Steroid hormone biosynthesis	3/86	62/8,662	0.0234716431902294	0.0234716431902294	0.284130417565935	CYP1A2/SRD5A2/UGT1A10	3
Organismal Systems	Nervous system	hsa04726	Serotonergic synapse	4/86	115/8,662	0.0272361025782412	0.0272361025782412	0.304338636096946	CYP2C8/HTR3A/KCNN2/PLA2G4F	4
Organismal Systems	Endocrine system	hsa03320	PPAR signaling pathway	3/86	75/8,662	0.0382537756736786	0.0382537756736786	0.396918875411101	FABP4/FABP6/PCK1	3
Human Diseases	Cancer: overview	hsa05202	Transcriptional misregulation in cancer	5/86	193/8,662	0.0426253360853891	0.0426253360853891	0.412792728405873	EYA1/HMGA2/HOXA11/MMP9/PAX3	5
Metabolism	Carbohydrate metabolism	hsa00500	Starch and sucrose metabolism	2/86	36/8,662	0.0493688662000757	<a href="https://dx.doi.org/10.21037/tcr-2025-546">https://dx.doi.org/10.21037/tcr-2025-546</a> 0.0493688662000757	0.448217337869109	GYS2/MGAM2	2

**Table S3** Drug sensitivity analysis of high and low risk groups

Chemical number	P
BI.2536	$1.4 \times 10^{-12}$
A.443654	$5.0 \times 10^{-12}$
ABT.888	$9.9 \times 10^{-11}$
SL.0101.1	$1.9 \times 10^{-10}$
GW843682X	$2.6 \times 10^{-10}$
S.Trityl.L.cysteine	$2.8 \times 10^{-10}$
JW.7.52.1	$7.6 \times 10^{-10}$
JNK.Inhibitor.VIII	$1.8 \times 10^{-8}$
BI.D1870	$3.3 \times 10^{-7}$
PD.173074	$1.1 \times 10^{-6}$
CCT018159	$2.6 \times 10^{-6}$
PF.4708671	$2.7 \times 10^{-6}$
VX.680	$1.1 \times 10^{-5}$
KU.55933	$2.2 \times 10^{-5}$
Salubrinal	$2.2 \times 10^{-5}$
BIRB.0796	$2.5 \times 10^{-5}$
BIBW2992	$5.3 \times 10^{-5}$
Paclitaxel	$9.6 \times 10^{-5}$
CMK	$1.1 \times 10^{-4}$
RO.3306	$1.8 \times 10^{-4}$
Obatoclax.Mesylate	$1.8 \times 10^{-4}$
Rapamycin	$3.0 \times 10^{-4}$
QS11	$5.7 \times 10^{-4}$
AZD.2281	$6.9 \times 10^{-4}$
MS.275	$8.1 \times 10^{-4}$
TW.37	$8.5 \times 10^{-4}$
Camptothecin	$1.2 \times 10^{-3}$
CGP.60474	$1.7 \times 10^{-3}$
Mitomycin.C	$1.7 \times 10^{-3}$
Parthenolide	$1.8 \times 10^{-3}$
Gemcitabine	$2.2 \times 10^{-3}$
ZM.447439	$3. \times 10^{-3}$
CGP.082996	$6.9 \times 10^{-3}$
Z.LLNle.CHO	$7.5 \times 10^{-3}$
ATRA	$9.3 \times 10^{-3}$
Metformin	$9.7 \times 10^{-3}$
Epothilone.B	0.013
Shikonin	0.015
FTI.277	0.017
IPA.3	0.020
Cisplatin	0.021
Docetaxel	20.026
Nilotinib	0.027
ABT.263	0.031
PLX4720	0.034
GSK.650394	0.036
Doxorubicin	0.049
Sorafenib	0.049