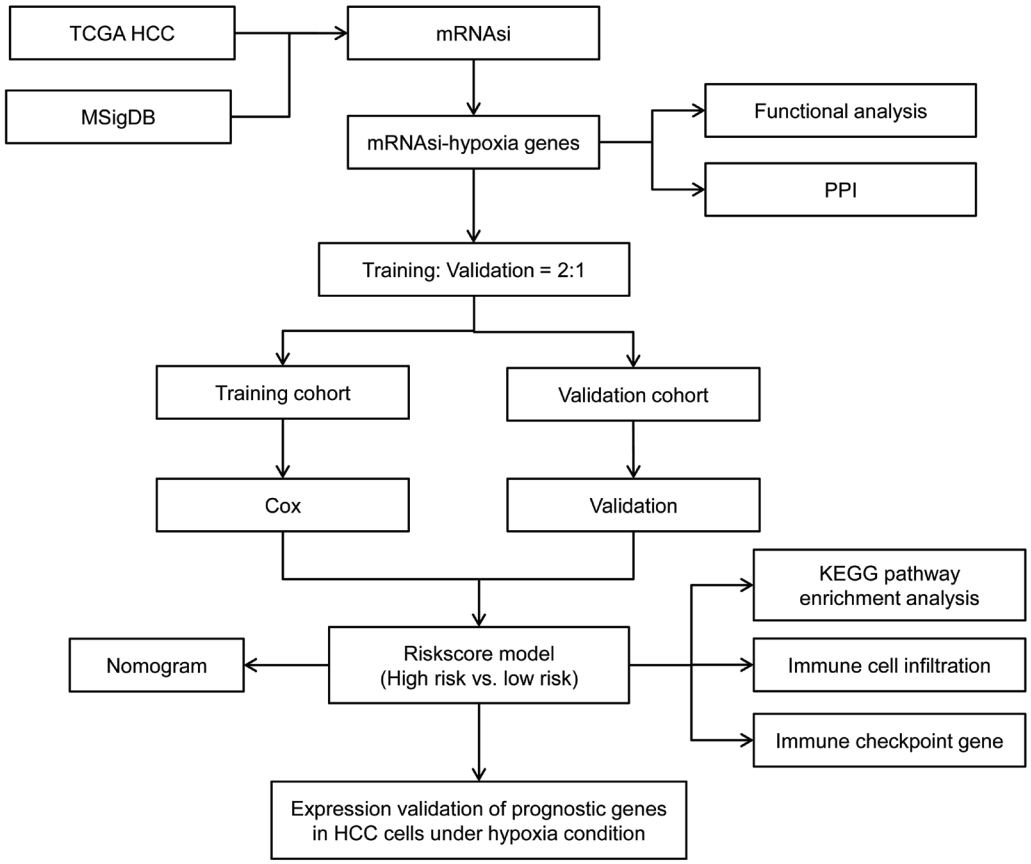

Figure S1 Workflow for the construction and validation of the three-prognostic stemness-hypoxia gene signature. HCC, hepatocellular carcinoma; KEGG, Kyoto Encyclopedia of Genes and Genomes; mRNAi, mRNA expression-based stemness index; MSigDB, Molecular Signatures Database; PPI, protein-protein interaction; TCGA, The Cancer Genome Atlas.

Table S1 Primers sequence

Gene	Forward sequence (5'-3')	Reverse sequence (5'-3')
CCNG2	TCTCGGGTTGTTGAACGTCTA	GTAGCCTCAATCAAACTCAGCC
PPARGC1A	TCTGAGTCTGTATGGAGTGACAT	CCAAGTCGTTCACATCTAGTTCA
PFKFB3	TTGGCGTCCCCACAAAAGT	AGTTGTAGGAGCTGTACTGCTT
SLC2A5	GAGGCTGACGCTTGTGCTT	CCACGTTGTACCCATACTGGA
RORA	ACTCCTGTCCTCGTCAGAAGA	CATCCCTACGGCAAGGCATTT
GAPDH	GGTGAAGGTCGGAGTCAACG	CAAAGTTGTCATGGATGHACC

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Table S2 Stemness-hypoxia-related genes

Gene	P value	corValue
ACKR3	1.54e–11	–0.323
ADM	2.11e–05	–0.207
AK4	3.41e–05	0.202
AKAP12	2.60e–09	–0.287
ALDOA	7.28e–05	0.193
ALDOC	2.70e–07	0.249
AMPD3	1.12e–05	–0.214
ANKZF1	4.28e–15	0.372
ATF3	2.95e–12	–0.334
B3GALT6	1.97e–08	0.271
BCL2	1.06e–19	–0.426
BGN	6.11e–56	–0.672
BHLHE40	1.07e–19	–0.426
BNIP3L	7.74e–06	–0.218
BTG1	6.68e–04	–0.166
CAV1	1.48e–09	–0.291
CCNG2	3.34e–06	–0.226
CDKN1A	8.19e–06	–0.217
CHST2	4.73e–06	–0.223
CHST3	3.45e–19	–0.420
CITED2	1.56e–05	–0.210
COL5A1	1.59e–32	–0.538
CXCR4	1.49e–14	–0.365
DCN	4.79e–82	–0.768
DDIT3	4.72e–07	0.244
DDIT4	1.93e–05	–0.208
DUSP1	6.46e–21	–0.438
EDN2	1.51e–04	–0.185
EFNA1	2.66e–06	0.228
EFNA3	4.25e–16	0.385
EGFR	<0.001	–0.165
ENO1	9.65e–14	0.355
ERRFI1	1.04e–07	–0.258
ETS1	1.43e–49	–0.642
F3	8.10e–30	–0.518
FAM162A	9.23e–09	0.277
FBP1	1.96e–05	–0.208
FOS	6.88e–34	–0.548
FOSL2	1.08e–11	–0.325
FOXO3	4.22e–04	–0.172
GALK1	1.98e–14	0.364
GAPDH	7.32e–15	0.369
GPC1	2.66e–06	–0.228
GPC3	1.94e–14	0.364
GPC4	1.89e–07	–0.252
GPI	0.001	0.158
HAS1	1.63e–16	–0.390
HK1	4.70e–10	–0.300
HS3ST1	6.66e–16	–0.382
HSPA5	7.08e–06	0.218
IDS	4.33e–13	–0.346
IER3	8.63e–05	–0.192
IGFBP3	2.94e–10	–0.303
IL6	3.45e–15	–0.374
IRS2	7.95e–04	–0.164
JMJD6	1.49e–15	0.378
JUN	1.68e–10	–0.307
KLF6	5.40e–18	–0.407
KLF7	2.41e–24	–0.471
KLHL24	2.03e–05	–0.208
LDHC	0.002	0.154
LOX	9.47e–04	–0.162
LXN	2.68e–31	–0.529
MAFF	1.43e–10	–0.308
MT1E	3.02e–07	–0.248
MT2A	1.73e–09	–0.290
MYH9	3.38e–05	–0.202
NDRG1	1.05e–08	0.276
NEDD4L	1.44e–14	0.366
NFIL3	1.73e–06	–0.232
NR3C1	1.19e–05	–0.213
PAM	1.09e–11	–0.325
PCK1	5.46e–08	–0.263
PDGFB	1.35e–09	–0.292
PFKFB3	3.41e–20	–0.431
PFKP	2.42e–05	–0.206
PGF	7.08e–06	–0.218
PGM2	0.0021	–0.151
PKP1	1.33e–06	–0.235
PLAC8	3.79e–12	–0.332
PLAUR	1.03e–08	–0.276
PNRC1	1.45e–11	–0.323
PPARGC1A	1.29e–05	–0.212
PPP1R15A	2.25e–16	–0.388
PRDX5	2.25e–22	0.453
PRKCA	5.70e–05	0.196
PYGM	8.95e–12	–0.327
RORA	8.37e–08	–0.259
RRAGD	9.70e–12	0.326
SAP30	1.76e–11	0.322
SCARB1	8.76e–14	0.355
SDC2	5.19e–05	0.197
SDC3	2.02e–08	–0.271
SERPINE1	7.01e–13	–0.343
SLC25A1	8.93e–15	0.368
SLC2A3	4.83e–15	–0.372
SLC2A5	4.64e–05	0.199
SLC6A6	1.80e–08	–0.272
SRPX	4.11e–51	–0.650
STC1	5.91e–04	–0.168
TGFB3	2.94e–30	–0.521
TGM2	1.66e–09	–0.290
TIPARP	7.48e–10	–0.296
TMEM45A	2.30e–04	–0.180
TNFAIP3	1.63e–04	–0.184
TPBG	8.04e–07	–0.239
TPI1	3.33e–20	0.431
UGP2	2.69e–07	–0.249
ZFP36	1.81e–31	–0.530

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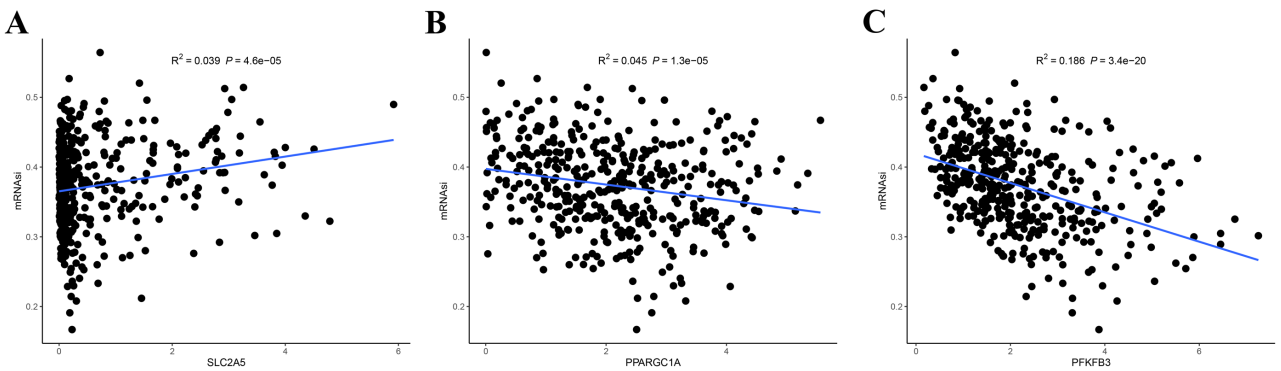

Figure S2 Association between mRNAsi and hypoxia genes. The Pearson's correlation coefficient between mRNAsi and the expression levels of representative hypoxia-related genes: (A) *SLC2A5*; (B) *PPARGC1A*; (C) *PFKFB3*. HCC, hepatocellular carcinoma; mRNAsi, mRNA expression-based stemness index; *PFKFB3*, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; *PPARGC1A*, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *SLC2A5*, solute carrier family 2 member 5.

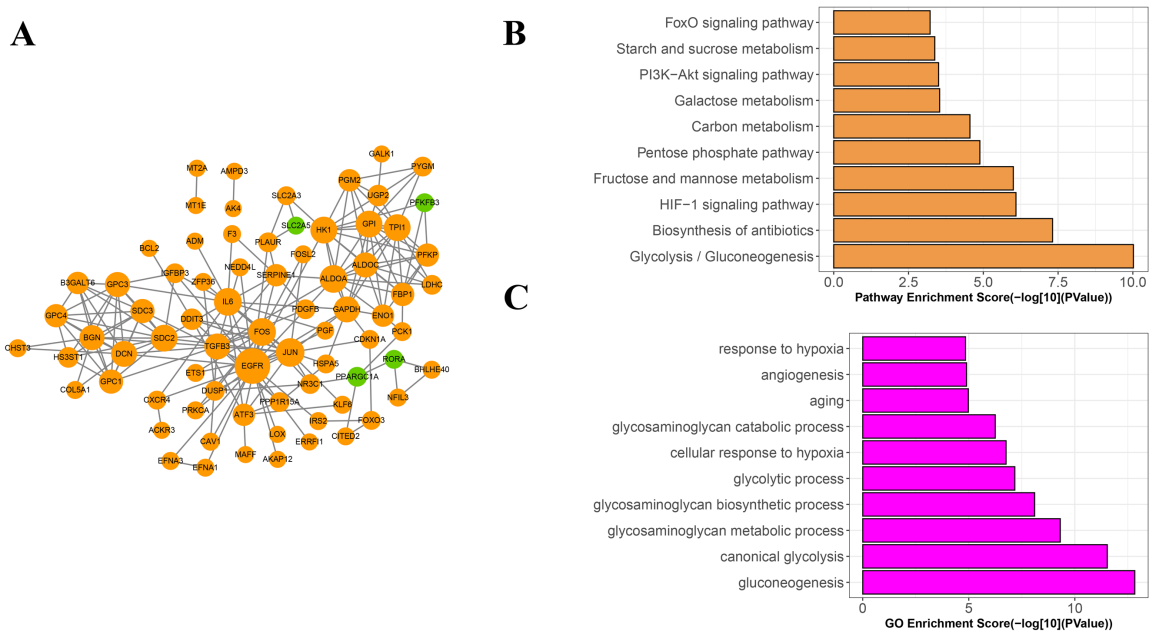

Figure S3 PPI network, KEGG pathways enrichment, and GO analyses of stemness-hypoxia genes. (A) This PPI network consists of 75 nodes and 194 edges. the green nodes represent the model genes, while the yellow nodes represent the non-model genes. (B) The upper panel represents the enriched KEGG pathways of stemness-hypoxia genes. (C) The lower panel represents the biological process annotation of stemness-hypoxia genes. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein-protein interaction.

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Table S3 Univariate Cox analysis revealed 37 genes correlated significantly with LIHC prognosis

Gene	Hazard ratio (HR)	95% CI	P value
ENO1	1.816677	1.4678–2.248479	4.08e–08
EFNA3	1.912636	1.469095–2.490087	1.45e–06
NDRG1	1.429841	1.22715–1.666011	4.55e–06
JMJD6	2.189042	1.558712–3.074272	6.14e–06
ALDOA	1.437298	1.218729–1.695065	1.63e–05
GAPDH	1.805355	1.377195–2.366627	1.89e–05
SAP30	1.84732	1.353695–2.520947	0.000109
PPARGC1A	0.696423	0.574967–0.843535	0.000215
TPI1	1.754272	1.299316–2.368532	0.000243
IER3	1.267965	1.107902–1.451153	0.000564
DDIT3	1.427837	1.157247–1.761698	0.000893
PFKP	1.250806	1.092933–1.431484	0.001151
PFKFB3	1.262512	1.095661–1.454772	0.001268
ANKZF1	1.943078	1.29653–2.912044	0.001291
RORA	0.59073	0.41867–0.833501	0.002728
GPC1	1.315255	1.097638–1.576015	0.002983
SERPINE1	1.181603	1.052354–1.326726	0.004752
SDC3	1.429977	1.114008–1.835566	0.004994
RRAGD	1.391715	1.103477–1.755245	0.005245
SLC2A5	1.329337	1.088046–1.624137	0.005342
PCK1	0.884273	0.809518–0.965931	0.00635
BNIP3L	1.44357	1.095572–1.902106	0.009094
MAFF	1.353806	1.0779–1.700334	0.009185
FBP1	0.862004	0.76645–0.96947	0.013242
IGFBP3	1.214472	1.037483–1.421654	0.015613
PLAUR	1.320705	1.052772–1.656828	0.016194
TMEM45A	1.180229	1.030501–1.351712	0.016664
ADM	1.237518	1.036829–1.477053	0.018246
AK4	1.35445	1.052175–1.743565	0.018538
CCNG2	1.487772	1.047811–2.112467	0.026347
PPP1R15A	1.293199	1.029231–1.624866	0.027292
ETS1	0.751951	0.580823–0.973498	0.030478
NEDD4L	1.405098	1.021627–1.932507	0.036479
TPBG	1.391399	1.017944–1.901865	0.038312
B3GALT6	1.439067	1.010481–2.049434	0.043616
PRDX5	1.398866	1.008983–1.939405	0.04405
SCARB1	1.329691	1.004345–1.76043	0.046564

CI, confidence interval.

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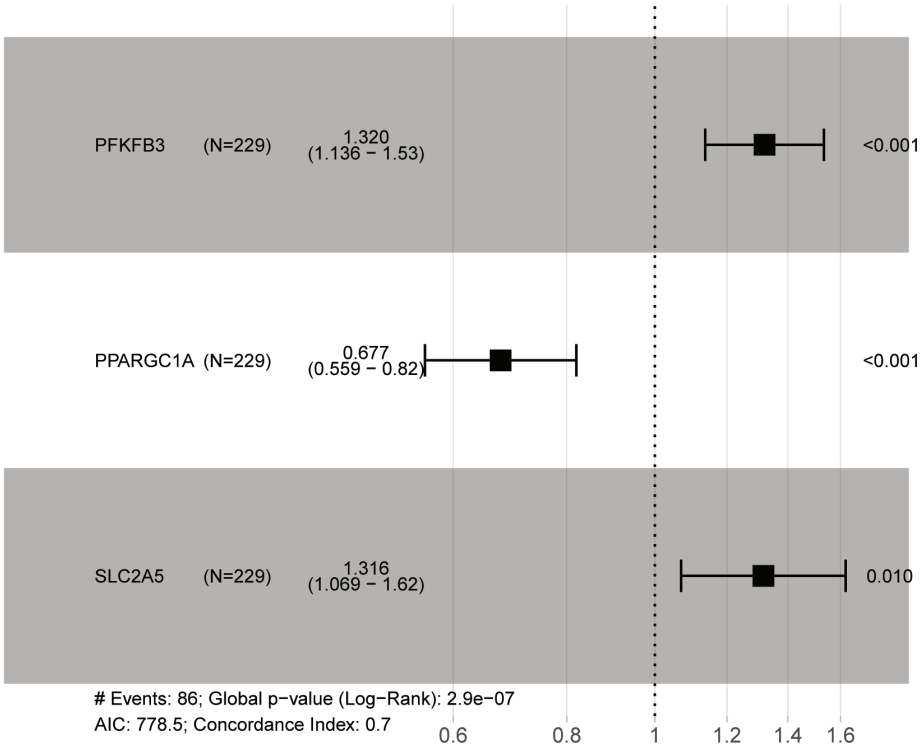

Figure S4 Hazard ratio for each prognostic stemness-hypoxia gene. *PPARGC1A*, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *SLC2A5*, solute carrier family 2 member 5.

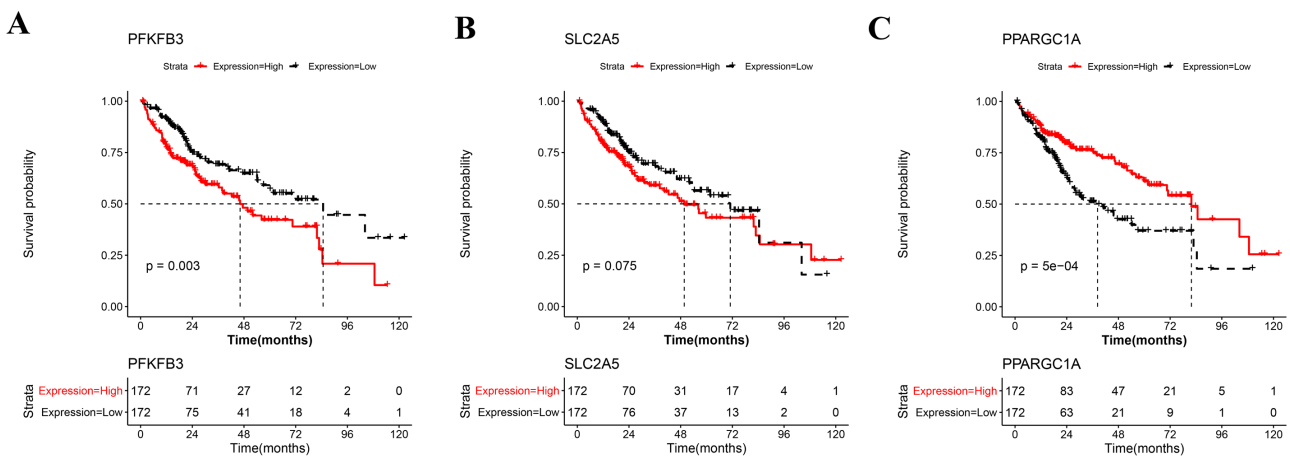

Figure S5 KM survival analysis for the prognostic genes. KM survival curve was analyzed based on the expression of *PFKFB3* (A), *SLC2A5* (B), *PPARGC1A* (C). KM, Kaplan-Meier; *PFKFB3*, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; *PPARGC1A*, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; *SLC2A5*, solute carrier family 2 member 5.

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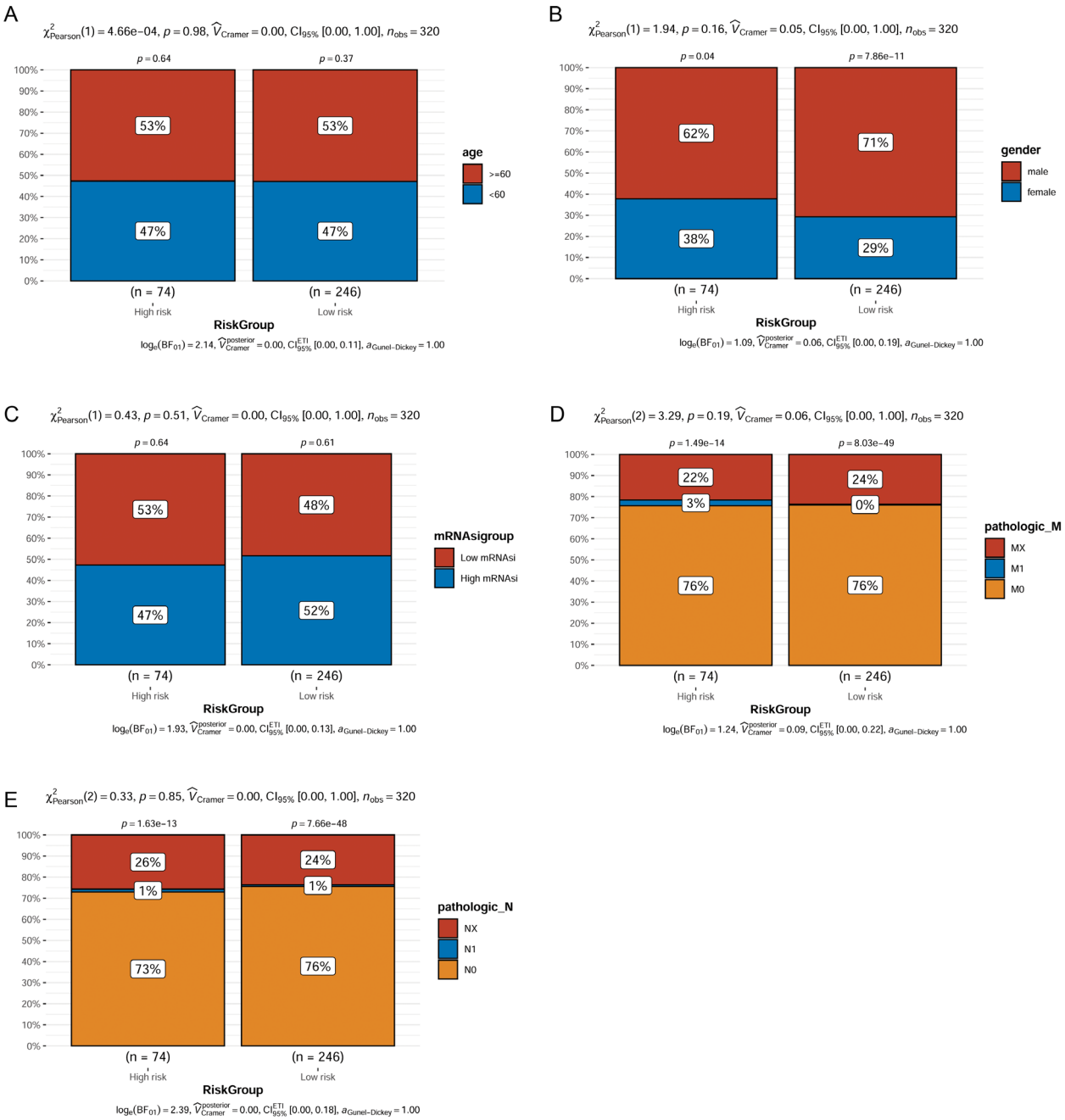

Figure S6 Clinical feature analysis. The ratio of age (A), gender (B), mRNAsi (C), pathologic M stage (D), pathologic N stage (E) in the high-risk and low-risk groups. mRNAsi, mRNA expression-based stemness index.

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