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A novel defined risk signature of endoplasmic reticulum stress-related genes for predicting the prognosis and immune infiltration status of ovarian cancer

Key words: Ovarian cancer (OvCa), Endoplasmic reticulum (ER) stress, Risk signature, Prognosis, Immune infiltration

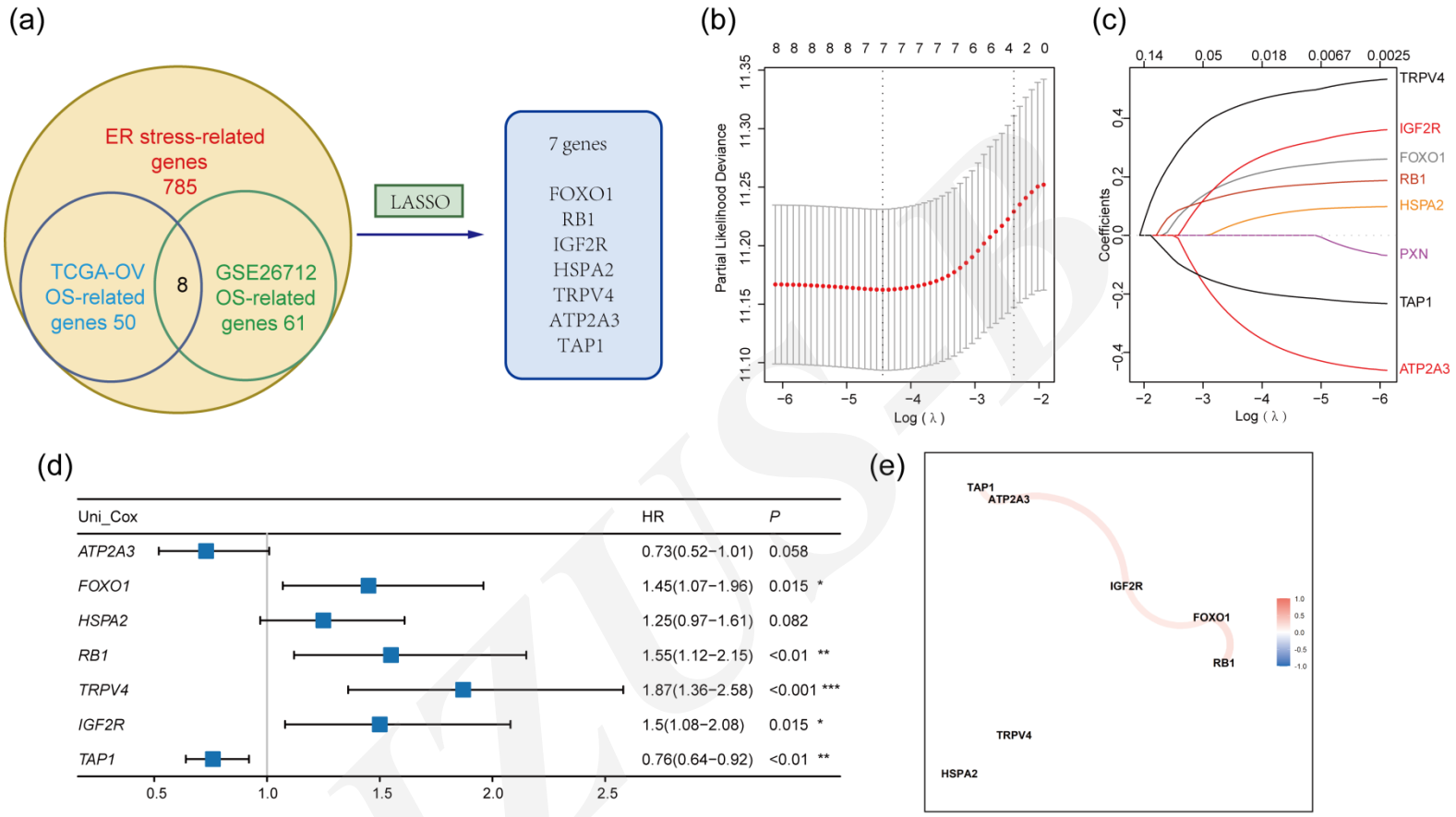


Fig. 1 Identifying prognostic genes for developing a risk signature. (a) Workflow diagram of seven genes screen. (b) LASSO coefficient profiles of the eight genes in TCGA cohort. (c) Selection of the optimal parameter (λ) in the LASSO model. (d) Seven genes were chosen to establish a prognosis signature. (e) The correlation network of the seven genes. P<0.05 were considered statistically significant. ER: endoplasmic reticulum; OvCa: ovarian cancer; TCGA: The Cancer Genome Atlas; LASSO: least absolute shrinkage and selection operator; *FOXO1*: forkhead box O1; *RB1*: retinoblastoma gene; *IGF2R*: insulin like growth factor 2 receptor; HSPA2: heat-shock protein family A member 2; *TRPV4*: transient receptor potential cation channel subfamily V member 4; *ATP2A3*: ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 3; *TAP1*: ATP binding cassette subfamily B member; HR: hazard ratio.

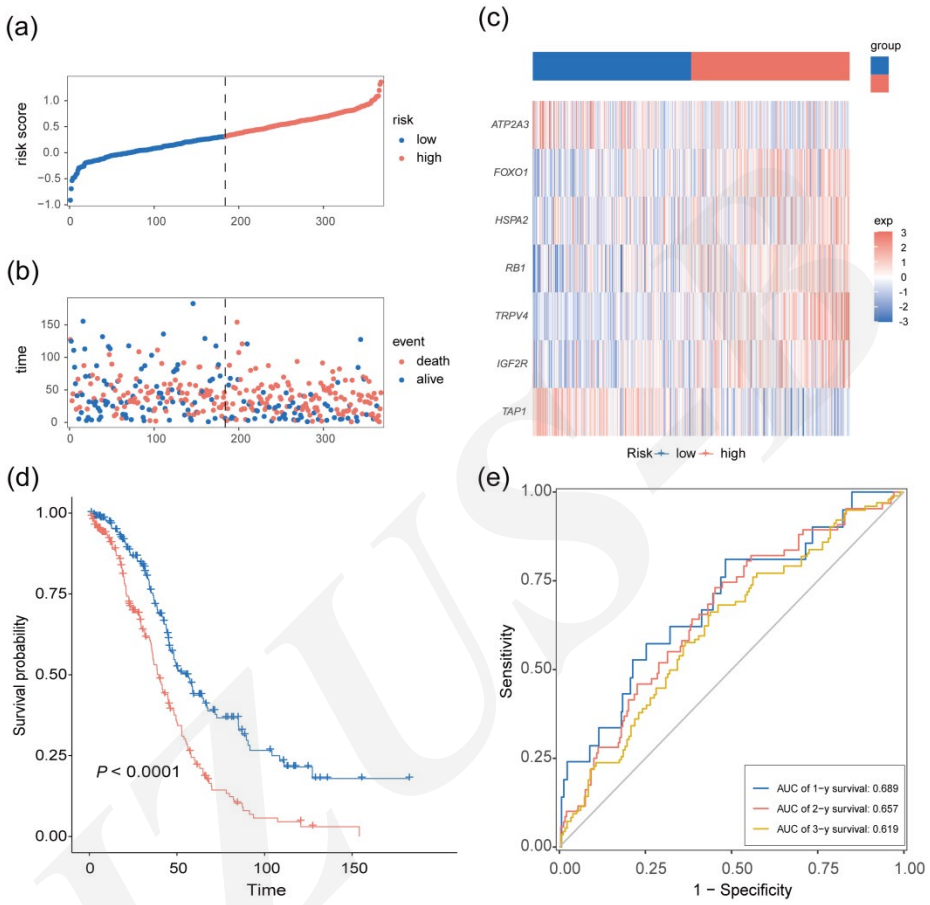


Fig. 2 Training of ER stress-related risk signature for OvCa in TCGA cohort. (a) Risk score for OvCa. (b) Survival status for each case. (c) Heatmap of gene expression between low- and high-risk groups. (d) KM curves for the OS of patients in the low- and high-risk group based on risk score. (e) Time-dependent ROC curves demonstrated the predictive efficiency. ER: endoplasmic reticulum; OvCa: ovarian cancer; TCGA: The Cancer Genome Atlas; KM: Kaplan-Meier; OS: overall survival; ROC: receiver operating characteristic; *FOXO1*: forkhead box O1; *RB1*: retinoblastoma gene; *IGF2R*: insulin like growth factor 2 receptor; HSPA2: heat-shock protein family A member 2; *TRPV4*: transient receptor potential cation channel subfamily V member 4; *ATP2A3*: ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 3; *TAP1*: ATP binding cassette subfamily B member.

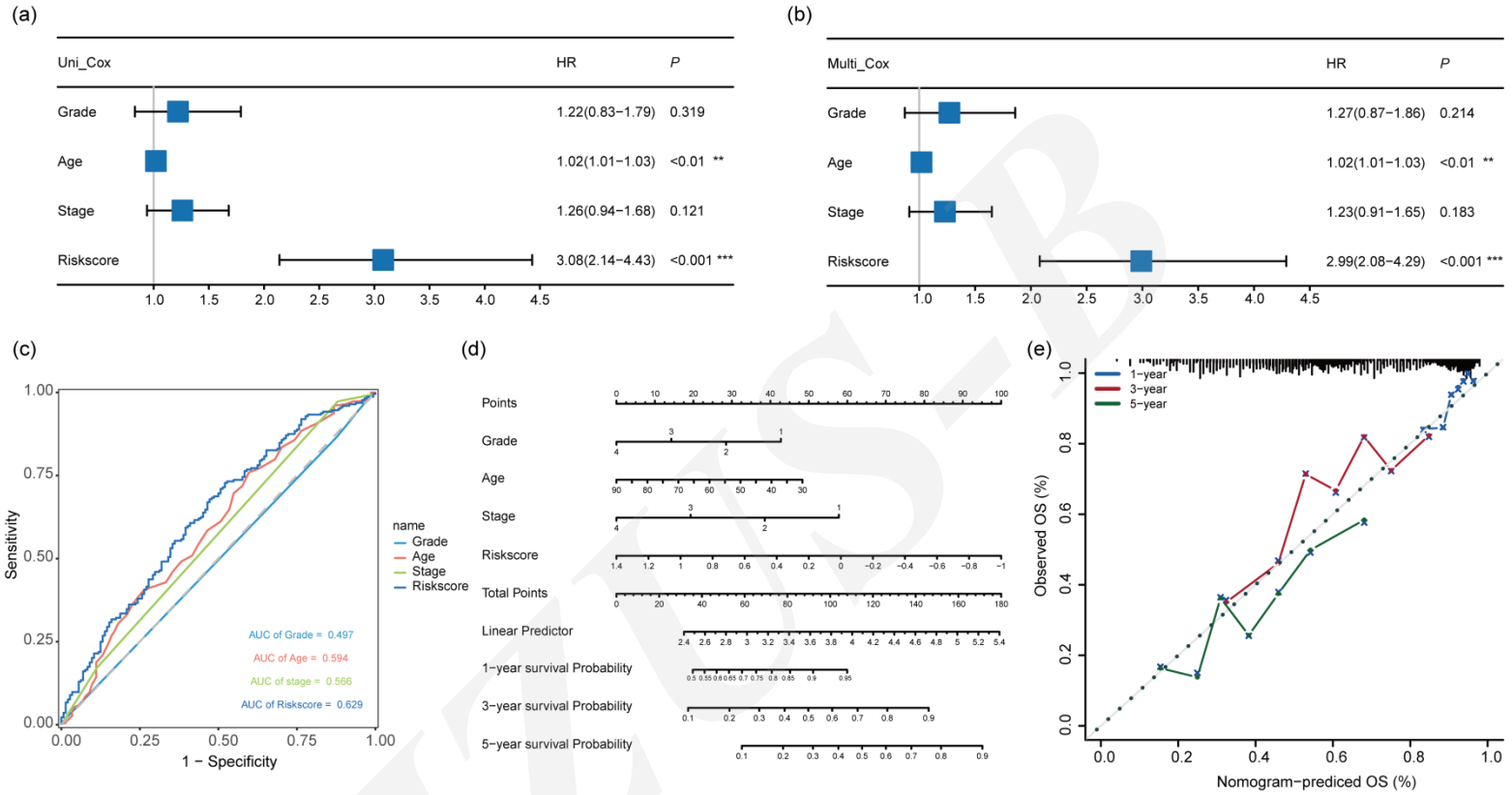


Fig. 3 Independent prognostic value of the ER stress-related risk signature in TCGA cohort. (a) Univariate analysis for TCGA cohort. (b) Multivariate analysis for TCGA cohort. (c) Multi-indicator ROC curves for risk score, age, stage, and tumor grade. (d) Nomogram combining seven gene markers in TCGA cohort. (e) The calibration curves for internal verification nomogram in the TCGA cohort. *P*<0.05 were considered statistically significant. ER: endoplasmic reticulum; TCGA: The Cancer Genome Atlas; ROC: receiver operating characteristic; HR: hazard ratio; AUC: area under the curve; OS: overall survival.

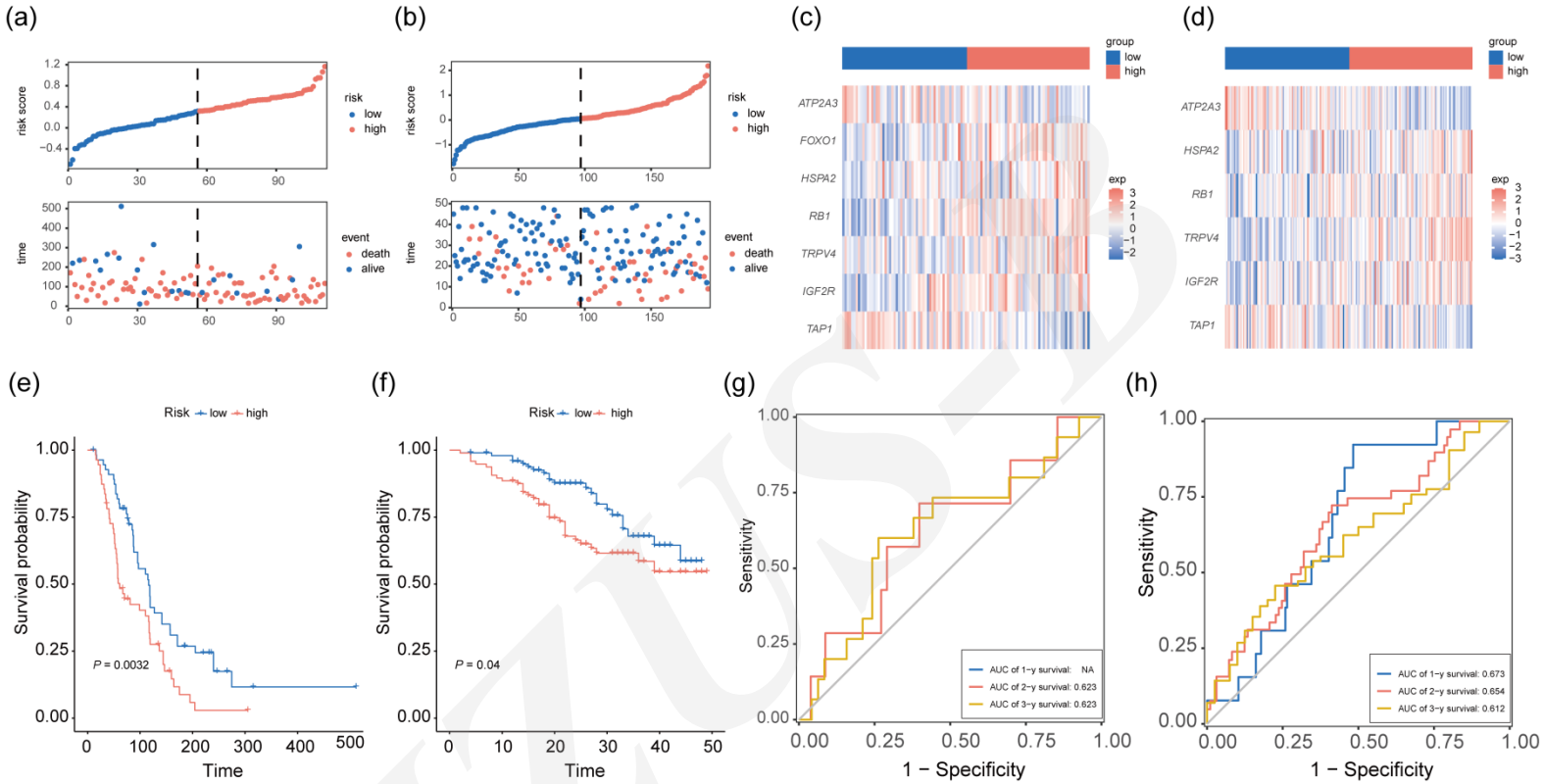


Fig. 4 Validation of ER stress-related risk signature in ICGC and GEO cohorts. (a) Risk score (upper) and distribution of survival status (lower) for OvCa in ICGC cohort. (b) Risk score (upper) and distribution of survival status (lower) for OvCa in GEO cohort. (c and d) Heatmaps of gene expression between low- and high-risk groups in ICGC and GEO cohorts, respectively. (e and f) KM curves for the OS of patients between low- and high-risk groups in ICGC and GEO cohort, respectively. (g and h) Time-dependent ROC curves for OvCa in ICGC and GEO cohorts, respectively. $P<0.05$ were considered statistically significant. ER: endoplasmic reticulum; ICGC: International Cancer Genome Consortium; GEO: Gene Expression Omnibus; OvCa: ovarian cancer; KM: Kaplan-Meier; OS: overall survival; ROC: receiver operating characteristic; AUC: area under the curve; HR: hazard ratio; NA: not available.

Fig. 5 Functional enrichment of the ER stress-related risk signature. (a–c) Differential expression of ER stress markers in TCGA, ICGC, and GEO cohorts between different groups. (d) Bubble graph for GO enrichment. (e) Bubble graph for KEGG pathways. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns: no significance. ER: endoplasmic reticulum; TCGA: The Cancer Genome Atlas; ICGC: International Cancer Genome Consortium; GEO: Gene Expression Omnibus; GO: Ontology analysis; KEGG: Kyoto Encyclopedia of Genes and Genomes analysis.

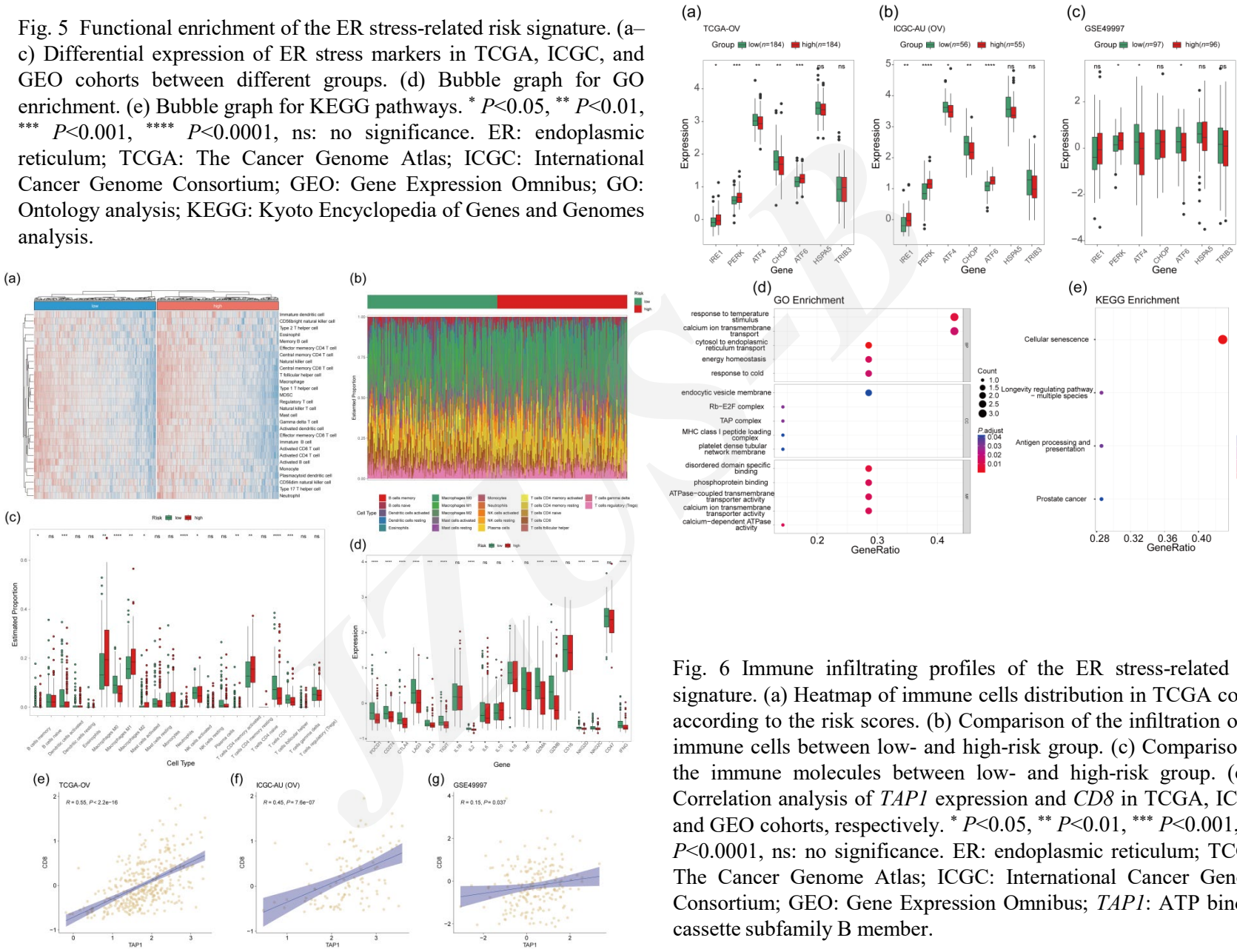


Fig. 6 Immune infiltrating profiles of the ER stress-related risk signature. (a) Heatmap of immune cells distribution in TCGA cohort according to the risk scores. (b) Comparison of the infiltration of 22 immune cells between low- and high-risk group. (c) Comparison of the immune molecules between low- and high-risk group. (e–g) Correlation analysis of *TAP1* expression and *CD8* in TCGA, ICGC, and GEO cohorts, respectively. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns: no significance. ER: endoplasmic reticulum; TCGA: The Cancer Genome Atlas; ICGC: International Cancer Genome Consortium; GEO: Gene Expression Omnibus; *TAP1*: ATP binding cassette subfamily B member.