Establishment and validation of a DNA damage repair gene based model for ovarian cancer typing and prognosis

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Abstract

Background

Under physiological conditions, DNA damage and repair are in a dynamic equilibrium. When this equilibrium is disrupted, the cell undergoes pathological changes, eventually the cell becomes cancerous. Ovarian cancer (OC) is a malignant disease with unique genomic characteristics, most of the chemotherapeutic agents currently used in ovarian cancer depend on the balance between damage and repair of DNA (DDR). DDR-related genes have potential value as prognostic indicators for ovarian cancer.

Results

DDR-related genes can well typing ovarian cancer patients, 16 genes associated with prognosis of ovarian cancer patients (CH25H, CCR7, CACNA1C, SLC4A8, CXCL11, UBD, TRPV4, RPS6KA2, FCGBP, TOMM20L, STX18, PI3, CMBL, ISG20, AKAP12, and PIGS) were screened as risk genes for the construction of ovarian cancer prognostic models.

Conclusion

Based on DDR-related genes for ovarian cancer typing and studying the prognostic relevance of differential genes between typing on ovarian cancer, 16 genes were screened for predicting poor prognosis of OC. To provide research directions for subsequent drug development and research basis for clinical application.

Background

Ovarian cancer (OC) is one of the most common causes of death in gynecologic malignancies. The screening, diagnosis and treatment of OC are still difficult, so the disease has a poor prognosis. DNA markers in tumors are currently a research focus in OC biomarker studies [1]. OC treatments are gradually evolving towards precision medicine, it is extremely important to obtain and improve predictive biomarkers [2]. Several tumor-targeted therapies have been added to OC treatment modalities, such as PARP inhibitors (poly ADP-ribose polymerase) and anti-VEGF monoclonal antibodies. The high efficiency and low toxicity of molecular targeted therapies have led to significant clinical benefits of OC treatment [3, 4]. Therefore, there is an urgent need for prognostic markers for the diagnosis and treatment of OC.

The DNA damage repair response (DDR) is a signaling cascade. When the body perceives a potential threat to genomic DNA, it immediately activates DNA damage repair mechanisms to induce a series of biological responses (induction of cell cycle arrest and apoptosis), thereby preventing normal cell carcinogenesis in a timely manner [5]. Abnormalities in key genes that maintain DDR in balance can increase tumor susceptibility, and somatic mutations defective in DDR have been found in a variety of

tumors [6, 7]. The mechanisms by which drugs (e.g., PARP inhibitors, platinum compounds, etc.) currently used in the clinical treatment of OC patients exert their anticancer effects are heavily dependent on the intracellular DDR response [8, 9]. Therefore, DDR is very important for the treatment of OC [10]. Based on the potential value of DDR as an independent prognostic indicator for OC, we predict that DNA damage-repair-related genes play an important role in the malignant progression of OC, it can be used as an independent prognostic indicator to predict poor prognosis in OC patients.

In this study, 379 OC tissue data from the TCGA database were screened for multiple typing using DDR damage-repair-related genes (DDR-Gene). subsequently, the typed prognosis-related differential genes (ITPD-Genes) were corrected with GEO data and the extracted intersection genes. TPDI-Gene was used to build a risk signature model, in which TCGA data were used as the training set and GEO data were used as the validation set. We further analyzed and validated the prognostic value and functional role of risk profile models in OC. This study confirmed our predictions, in which 16 risk genes (CH25H, CCR7, CACNA1C, SLC4A8, CXCL11, UBD, TRPV4, RPS6KA2, FCGBP, TOMM20L, STX18, PI3, CMBL, ISG20, AKAP12, PIGS) could be used as predictors of OC patients' adverse prognosis as an independent prognostic indicator.

Materials And Methods

Data collection

The transcriptomic and clinical data of 379 OC samples from the TCGA database were downloaded from the UCSC online website (http://www.genome.ucsc.edu/) and formatted (FPKM to TPM); “ovarian cancer survival” and “number of samples >200, and containing survival data” as filtering criteria. The GEO database (https://www.ncbi.nlm.nih.goc/geo/) was used to download the dataset GSE140082, which contains transcriptomic and clinical data for 380 OCs. The GSEA database (http://www.gsea-msigdb.org/gsea/index.jsp) was used to obtain 607 DDR-related genes.

Clustering analysis of DDR-related genes in TCGA database

The expression of DDR-related genes in the TCGA database was obtained and clustering analysis was performed using the R package “ConsenSuClusterPlus”, which requires high intra-typical correlation and low inter-typical correlation. The accuracy of typing was verified using inter-typical survival analysis, heat map and PCA analysis. Gene Set Variation Analysis (GSVA) and single sample Gene Set Enrichment Analysis (ssGSEA) of typing were explored.

Inter-typical prognosis-related differential gene screening and typing

The R package “limma “VeneDiagram” was used to extract the inter-typical differential genes (ITD-Genes), and “logFC=3, adj.Pvalue=0.001 Pvalue=0.001” as the screening condition, 9323 ITD-Genes were screened. one-way COX analysis of ITD-Genes was performed using the R package “limma” “Survival”, and P< 0.05 was used as the screening condition, and 1014 inter-typical prognosis-related differential genes (ITPD-Genes) were obtained, and the above genes were clustered using the R package “ConsenSuClusterPlus”, and GO functional annotation and KEGG enrichment pathway analysis were performed between types.

Obtain intersection genes and prognostic genes between GEO and TCGA database for inter-typical prognosis-related genes

And based on the expression of ITPD-Genes obtained from TCGA data, the GSE140082 data set was corrected and the intersection genes were extracted by the R package “Sva” “limma”, and 349 intersection prognosis-related genes (IP-Genes) were obtained.

Construction and validation of the intersection prognostic gene prognostic model

Using the R package “glmnet” “Survival”, tumor samples were screened and gene correlation coefficients were calculated by the least absolute shrinkage and selection operator (LASSO) of the regression paradigm and multifactorial Cox analysis, where TCGA tumor samples were used as the training set and GEO data were used as the validation set to construct the model according to the modeling formula. Risk score = sum (expression of risk genes × corresponding coefficients). The accuracy of the prognostic model was verified using survival curve, risk heat map, ROC curve, and independent prognosis.

Immune infiltration, tumor microenvironment and drug sensitivity analysis of the risk model

The relative content of immune cells in the samples was calculated using the CIBERSORT package, and the correlation between the gene and immune cells was analyzed based on the relative content of all genes involved in the construction of the model and the immune cells in the tumor. The R package “estimate” was used to score the cellular matrix and immune cells and the combined environment, and the R package “reshape2\ ggpubr” was used to draw violin plots to describe the tumor microenvironment with high and low risk correlations. The R package “pRROphetic” was used to analyze whether there were differences in drug sensitivity between the high and low risk groups.

Online website to analyze gene and protein level expression in OC

The online website cBioPortal (http://cbioportal.org) was used to obtain gene mutation data of OC in the TCGA database. The Human Protein Atlas database (https://www.proteinatlas.org/) was used to obtain gene expression at the protein level.

Results

DDR-related genes can classify the tumor data in TCGA into two types

The workflow of this study is shown in the figure (Figure 1).The maximum value of clustering variable (k) was set to 9. The typing requirement was reached when k=2. DDR-related genes could well classify the tumor data in TCGA into two types (Figure 1A). The inter-typing survival analysis was statistically significant (p = 0.02) (Figure 1B). PCA plots indicated that bifurcation could well separate all data (Figure 1C). To verify the functional differences between the typing, the ssGSEA analysis showed that multiple immune cells were significantly different between typing (Figure 1D); GSVA analysis of the differential enrichment pathways between typing (Figure 1E) , the differential enrichment pathways between typing were mainly in the following areas: multiple neuromuscular-like disorders (Parkinson's, Huntington, and myocardial contraction), DNA damage repair (base excision repair, DNA replication, nucleotide excision repair), and metabolism and synthesis of related compounds (folate biosynthesis, glyoxylate and dicarboxylic acid metabolism, pyruvate metabolism).

Extraction of inter-typical prognosis-related differential genes and typing of tumor data in TCGA

Using “|logFC|=3, adj.Pvalue=0.001” as the condition, 9323 ITD-Genes were screened (Figure 2A). The typing condition was as above. The typing requirement was achieved when k=2, indicating that ITPD-Genes between typing could well classify the TCGA tumor data into two types (Figure 2B). Inter-typing survival analysis was statistically significant (p<0.001) (Figure 2C). P<0.05 was used as a screening index, One-way COX analysis of ITD-Genes yielded 1014 ITPD-Genes (Annex 1). ITPD-Genes were subjected to GO functional annotation (Figure 2D) and KEGG enrichment pathway analysis (Figure 2E).

Prognostic model construction and validation

The 349 IP-Genes were further analyzed using lasso regression and multifactorial Cox. The expression and gene correlation coefficients of 16 key genes were obtained (CH25H, CCR7, CACNA1C, SLC4A8, CXCL11, UBD, TRPV4, RPS6KA2, FCGBP, TOMM20L, STX18, PI3, CMBL, ISG20 AKAP12, PIGS).The

modeling equation: Risk-Score= (0.001247) *CH25H+(-0.003417)* CCR7+(0.017031)*CACNA1C+ (-0.008297)*SLC4A8+(-0.003082)*CXCL11+(-0.003726)*UBD+(0.004255)*TRPV4.+ (0.003507)*RPS6KA2+(0.005019)*FCGBP+(-0.004344)*TOMM20L+(-0.001889)*STX18+ (0.002769)*PI3+(-0.000619)*CMBL+(-0.000359)*ISG20+(0.000582)*AKAP12+(0.000396)*PIGS. According to the formula, risk values were calculated for each case. Patients were divided into high-risk and low-risk groups, using the median risk score as the boundary. The results of survival analysis between high and low risk groups in both the TCGA training set and the GEO validation set showed $p<0.05$, which was statistically significant (Figure 3A-B). The risk heat map of the model suggested that the number of patient deaths gradually increased and the number of survivors gradually decreased as the patient risk gradually increased (Figure 3C-D). Column line plot of the predicted 1, 2 , and 3 year survival rates of patients applying the TCGA training set, in which there were significant differences between patient age, stage, and risk score (Figure 4A). The calibration curve converged to the midline, indicating the reliability of the column plots in predicting survival (Figure 4B). The DCA curve indicates that the predictive capability of the model we constructed is similar to the capability of the column line graph (Figure 4C). The area under the ROC curve for the predictive ability of our constructed model was smaller than the column line plot but larger than the other clinicopathological features, the AUC=0.72(Figure 4D). Both the univariate and multifactor independent prognosis of the TCGA training set showed the smallest p-value for the risk model, $p<0.001$ (Figure 4F-G). Columnar plot of the application of the GEO validation set for predicting 1, 2, and 3 year patient survival, where there were significant differences between patient age and risk scores (Figure 5A). The calibration curve tends to the middle line, indicating the reliability of the column line plot in predicting survival (Figure 5B), and the DCA curve indicates that the predictive ability of our constructed model is similar to the column line plot ability (Figure 5C). Both univariate and multifactorial independent prognosis showed the smallest p-value for the risk model, $p<0.001$ (Figure 5D-E).

Risk model constructed based on DDR-related genes for immune, stem cell correlation and drug sensitivity analysis

In the typing of TCGA tumors based on DDR-related genes and ITPD-Genes between typing, the differences between high and low risk groups were statistically significant, $p<0.001$ (Figure 6A-B). The results of the correlation heat map of risk model genes and immune cells showed that risk genes were significantly correlated with multiple immune cells (Figure 6C). The results of stem cell correlation analysis showed that with risk score was positively correlated with stem cell index, ($R=0.14$, $p=0.013$) (Figure 6D). Immunoscoring of the tumor microenvironment showed significant differences in the tumor cell stromal environment between high and low risk groups (Figure 6E). The results of drug sensitivity analysis between high and low risk groups revealed significant differences in anti-OC drugs such as methotrexate, mitomycin C and cisplatin between high and low risk groups (Figure 6F).

Risk gene study

Mutation frequency analysis of 16 risk genes according to the cBioPortal online website showed that the mutation rate of FCGBP gene was 12%, CACNA1C gene was 10%, CMBL gene was 8%, UBD gene was 5%, PI3 gene was 4%, ISG20, AKAP12, STX18, RPS6KA2 gene was 3%, CXCL11, PIGS gene was 2.1%, TRPV4 gene was 1.9%, CH25H gene was 1.6%, CCR7 gene was 1.4%, SLC4A8 gene was 1.3%, TOMM20L gene was 0.4%, and the mutation types were mainly amplification mutations (Figure 7A). The top 5 risk genes of mutation frequency were further explored according to the HPA database for differential expression between normal ovarian epithelium and OC inter-tissue protein levels, among which UBD gene was not yet relevant in ovarian cancer epithelium and tumors in the HPA database (Figure 7B).

Discussion

Among gynecologic malignant diseases, OC has a high incidence and mortality rate. The lack of effective screening strategies for the population makes the diagnosis and treatment of OC difficult, so there is an urgent need to find new screening methods and various biomarkers [11]. OC has a unique and complex genomic profile, new methods based on molecular genomics for predicting early diagnosis and prevention of OC deserve further development [12, 13]. Furthermore, the high recurrence rate of OC has led to the fact that the treatment of OC is no longer limited to surgical cytoreduction. Recently developed tumor-targeted therapies such as immunosuppressive agents have shown excellent performance in OC treatment [14–16]. Studies have shown that all OC patients have a defect in at least one of the major DDR pathways [17]. Therefore, the use of DDR-related genes as a predictive prognostic marker for OC deserves to be investigated in depth.

In this study, we performed typing and screening of TCGA tumors based on DDR-related genes. In combination with OC survival data, the aim was to identify the genes with the most relevant inter-typical differences in OC prognosis for use in the construction of risk models. We performed GO functional annotation and KEGG pathway enrichment analysis of 1014 ITPD-Genes, where the BP component is mainly enriched in the following: protein, ATP and RNA binding, protein serine/threonine/tyrosine kinase activity; CC components are mainly enriched in the following aspects: cytoplasm, nucleus, cytoplasm, nucleoplasm, and cell membrane; MF components are mainly enriched in the following aspects: positive and negative regulation of transcription by RNA polymerase II promoter, signal transduction, protein phosphorylation, and positive regulation of GTPase activity. KEGG pathway enrichment analysis: [cell] endocytosis, Salmonella infection, regulation of the actin cytoskeleton, proteoglycans in cancer, chemokine signaling pathway. Next we further corrected the TCGA and GEO data and obtained 349 IP-Genes. IP-Genes were analyzed by lasso regression and multi-factor COX to screen for relevant genes and calculate their expression and coefficients. Risk profile models were constructed for 16 genes using TCGA tumor data as the training set and GEO tumor data as the validation set, (CH25H, CCR7, CACNA1C, SLC4A8, CXCL11, UBD, TRPV4, RPS6KA2, FCGBP, TOMM20L, STX18, PI3, CMBL, ISG20, AKAP12, PIGS). DDR-associated genes well typed ovarian cancer tumors, and the difference in high and low risk between typing was statistically significant. The risk model showed a significant correlation with multiple immune cells, and the stromal immune scoring was higher in the high-risk group than in the low-risk group, indicating that the high-risk group had more immune cells in the tumor stroma than the low-risk group. As

the risk increased, the number of neutrophils also gradually increased to exert anti-tumor effects. Significant differences in the IC50 values of various drugs used to treat OC between the high and low risk groups. To further investigate the importance of these 16 risk genes in OC, we analyzed the mutations of 16 genes in OC using the cBioPortal online website, in which FCGBP showed extremely high mutations, followed by CACNA1C. The expression of risk genes at the protein level was analyzed using the HPA online database, showing only the top 5 fractions with the highest mutation frequencies. UBD genes were not shown as they were not yet found in the HPA database for relevant studies in ovarian cancer.

Although the study screening gene pathways were very different, some of our constructed risk model genes were also screened as prognostic predictors of ovarian cancer in other ovarian cancer risk model studies, which further side validating the high accuracy of our constructed model: Fc Gamma Binding Protein (FCGBP)[18],Calcium Voltage-Gated Channel Subunit Alpha1 C (CACNA1C)[19],Ubiquitin D(UBD)[20, 21],Peptidase Inhibitor 3(PI3)[22, 23],Interferon Stimulated Exonuclease Gene 20 (ISG20)[24–26],A-Kinase Anchoring Protein 12(AKAP122)[26, 27],Ribosomal Protein S6 Kinase A2(RPS6KA2)[28],C-X-C Motif Chemokine Ligand 11(CXCL11)[21, 29–34],Transient Receptor Potential Cation Channel Subfamily V Member 4(TRPV4)[35],Cholesterol 25-Hydroxylase(CH25H)[23, 36],Solute Carrier Family 4 Member 8(SLC4A8)[37]However, the following genes have not been identified in ovarian cancer studies: Translocase Of Outer Mitochondrial Membrane 20 Like (TOMM20L), C-C Motif Chemokine Receptor 7(CCR7), Phosphatidylinositol Glycan Anchor Biosynthesis Class S(PIGS), Syntaxin 18(STX18), Carboxymethylenebutenolidase Homolog (CMBL)have not been found to be studied in ovarian cancer.

This is the first study to type ovarian cancer based on DDR-related genes and to investigate the prognostic relevance of genes that differ between types in ovarian cancer. Investigating the potential relevance of DDR-related genes on the prognosis of ovarian cancer. In this study, TCGA tumor data were utilized to construct the model and validated with GEO tumor data to increase the credibility of the model. Both typing results for the tumors showed significant differences between high and low risk, thus validating the accuracy of DDR-related genes for ovarian cancer staging. Among the risk genes we constructed, 11 genes have been screened in different study models and 5 of them have not been found to be studied in ovarian cancer. Therefore, this study provides direction and theoretical basis for future studies of prognostic predictors in OC.

Conclusion

In conclusion, our study showed that DDR is closely associated with the prognosis of OC. The model constructed based on 16 ITPD-Genes is an independent risk factor for predicting OC. This study provides a new genetic marker for the prediction of prognosis in OC patients. To provide a research basis for further study of the relationship between the above risk genes and immune function in OC patients, and to provide rational drugs for the treatment of risk gene-induced diseases in OC patients, which has certain guiding significance for clinical application.

Abbreviations

DNA damage repair gene DDR

the inter-typical differential genes ITD-Genes

the inter-typical prognosis-related differential genes ITPD-Genes

the intersection prognosis-related genes IP-Genes

Declarations

Ethical approval and consent to participate (not applicable)

Consent to publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The original data supporting the conclusions of this manuscript will be available by the author without undue reservation.

Competing interests

All authors do not have any possible conflicts of interest.

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Authors' contributions

Prof. HYJ and Director LJ guided and reviewed the article; CSR and LY analyzed and interpreted all the data, and YP, LJ, HQ□WYL and DR helped to obtain the data. All read and approved the final manuscript.

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Figures

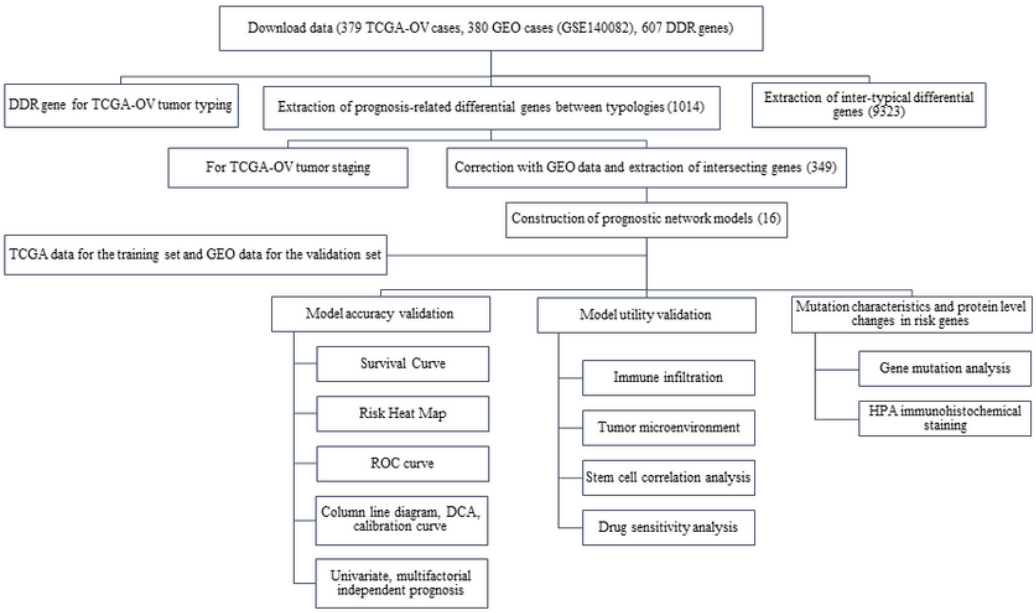

Figure 1

Flow chart of the study

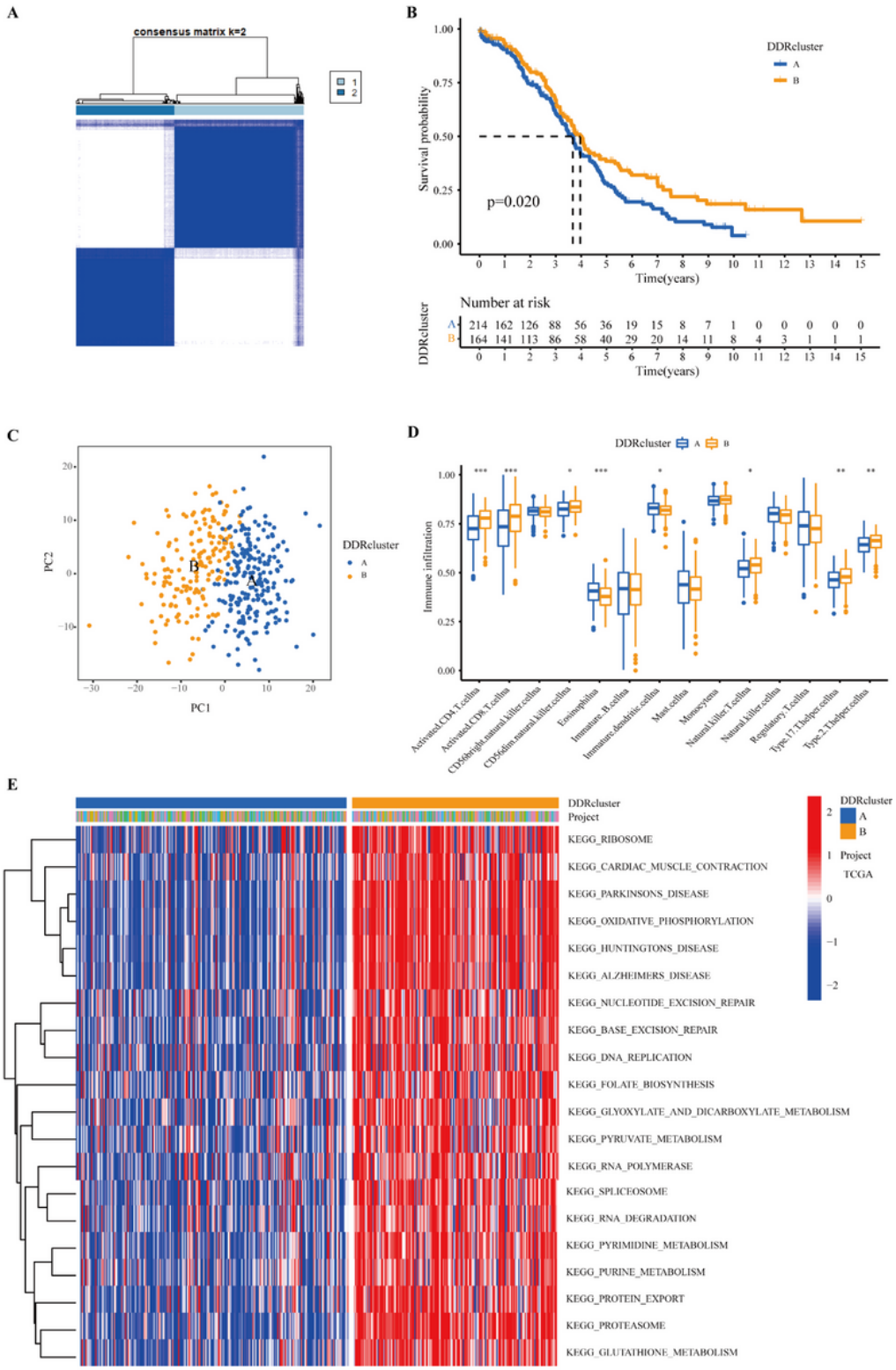

Figure 2

Figure 1 Typing of TCGA tumors by DDR-related genes:A 379 patients were better classified into two subgroups by DDR-related genes according to the consensus matrix (k=2); B Inter-typical survival analysis (TCGA patients were divided into two groups based on DDR gene, denoted by A, B); C inter-typing principal component analysis, PCA plots; D inter-typing immune cell infiltration analysis; E inter-typing GSVA enrichment analysis

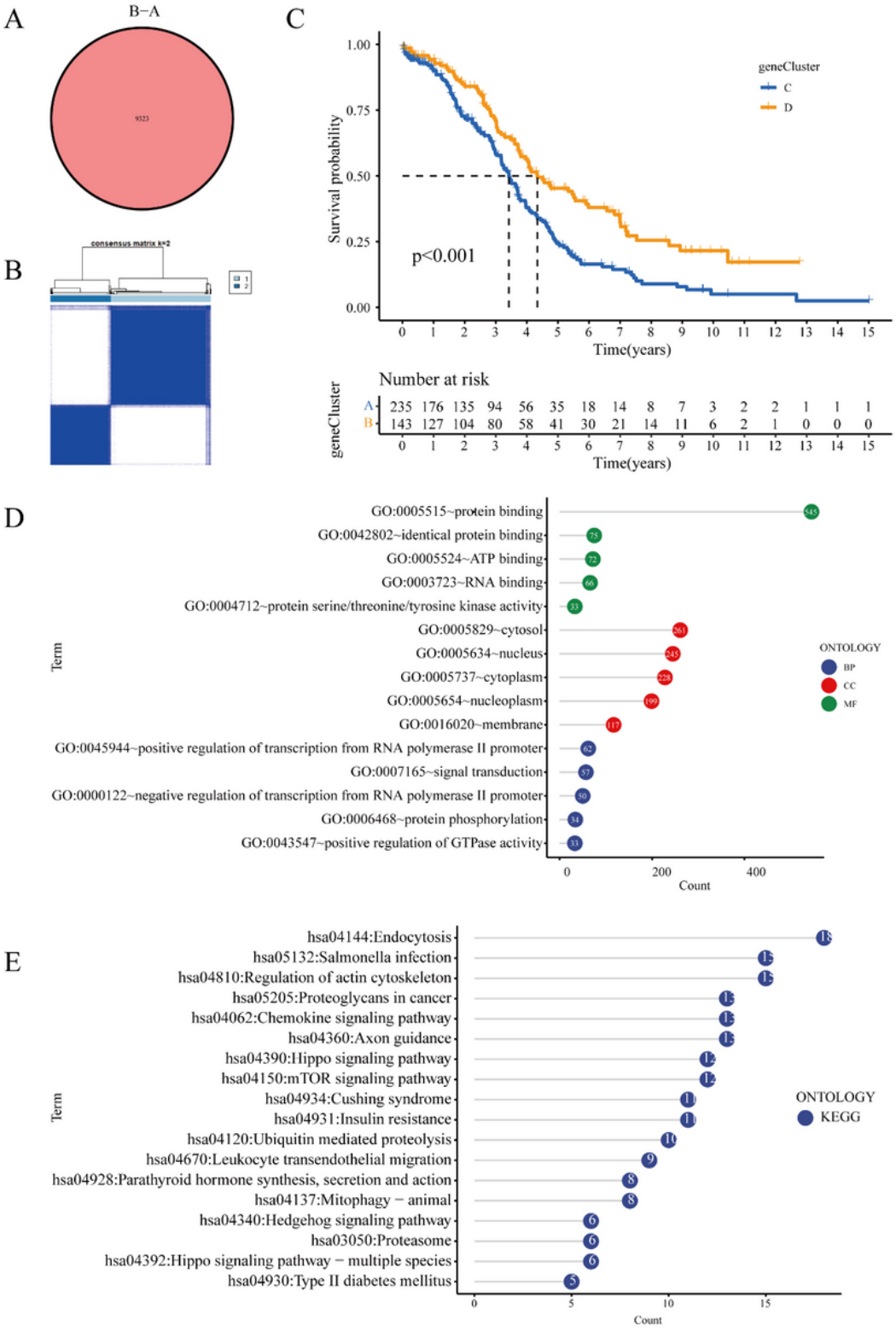

Figure 3

Figure 2 Interfractional prognosis-related differential genes and typing of tumor data in TCGA:A Venn diagram of interfractional differential genes, 9323 interfractional differential genes were screened; B Interfractional prognosis-related differential genes were better divided into two subgroups according to the consensus matrix (k=2); C Inter-typical survival analysis (TCGA patients were divided into two groups based on inter-typical prognosis-related differences in genes, denoted by C and D); D GO functional

annotation analysis of prognosis-related differential genes; E prognosis-related differential genes KEGG enrichment pathway analysis

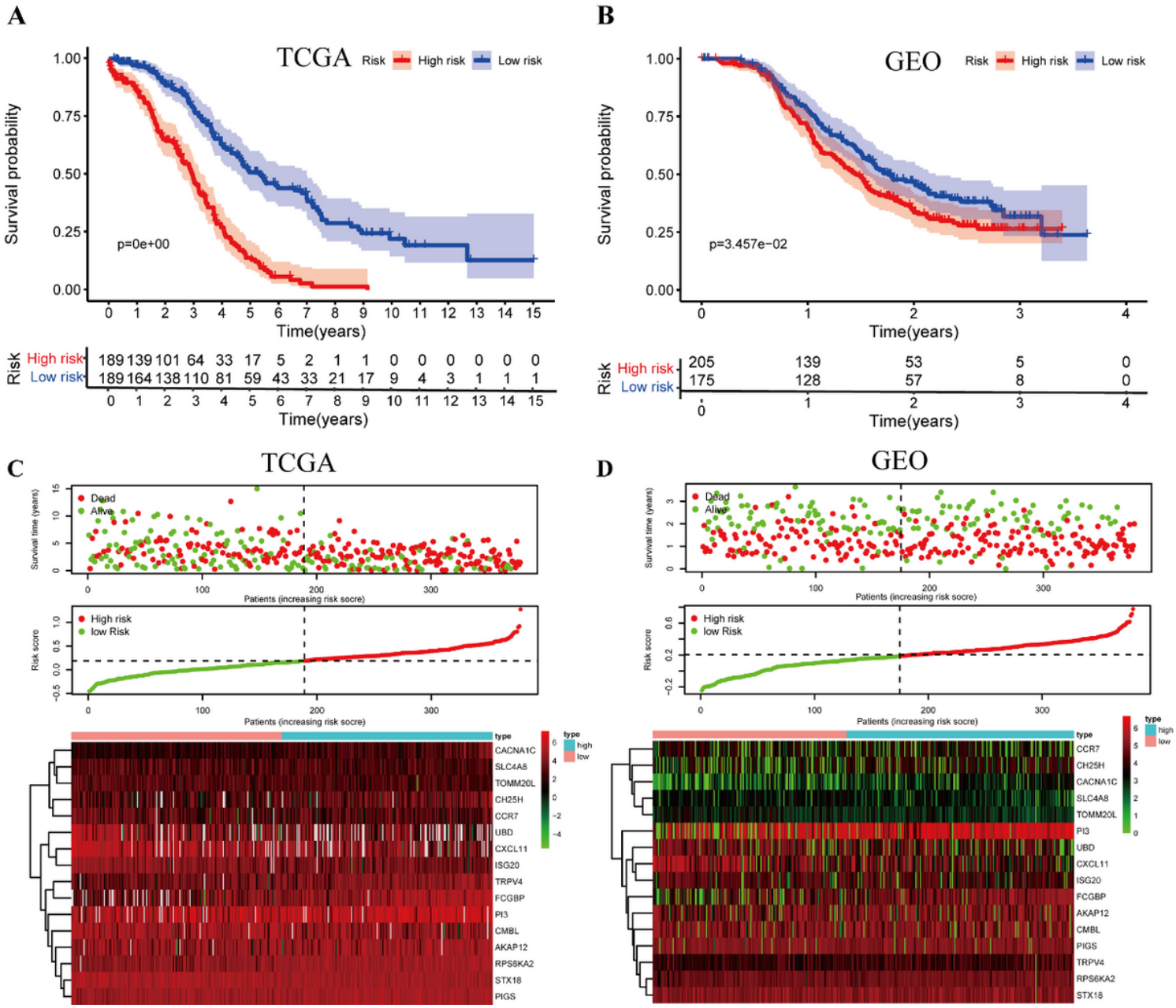

Figure 4

Figure 3 Risk model construction: A Training set (TCGA tumor data) survival analysis; B Validation set (GEO tumor data) survival analysis; C Training set (TCGA tumor data) risk heat map; D Validation set (GEO tumor data) risk heat map

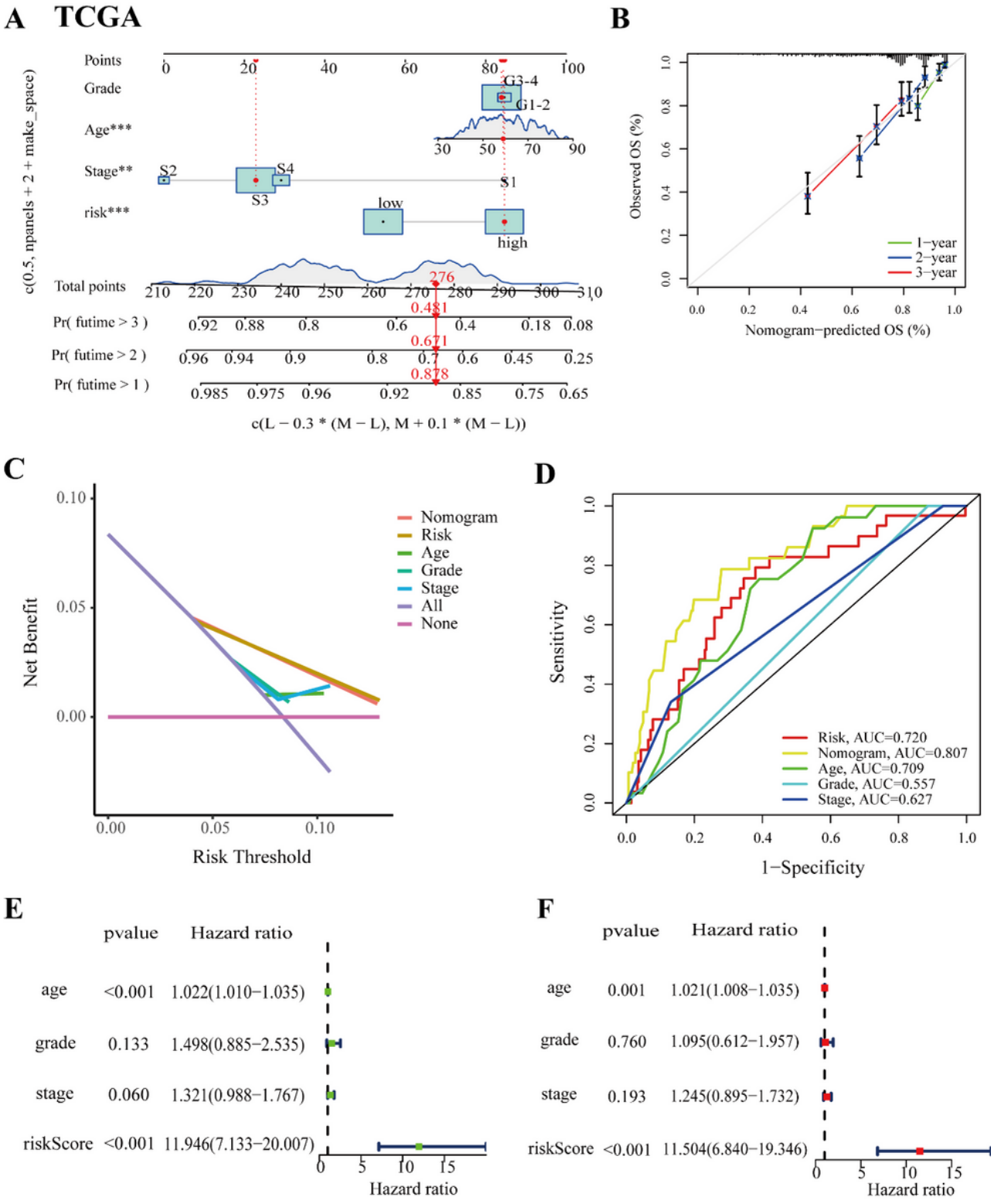

Figure 5

Figure 4 Model validation by applying the training set (TCGA tumor data): A column line plot; B correction curve; C DCA curve; D column line plot ROC curve; E single-factor independent prognosis; G multi-factor independent prognosis

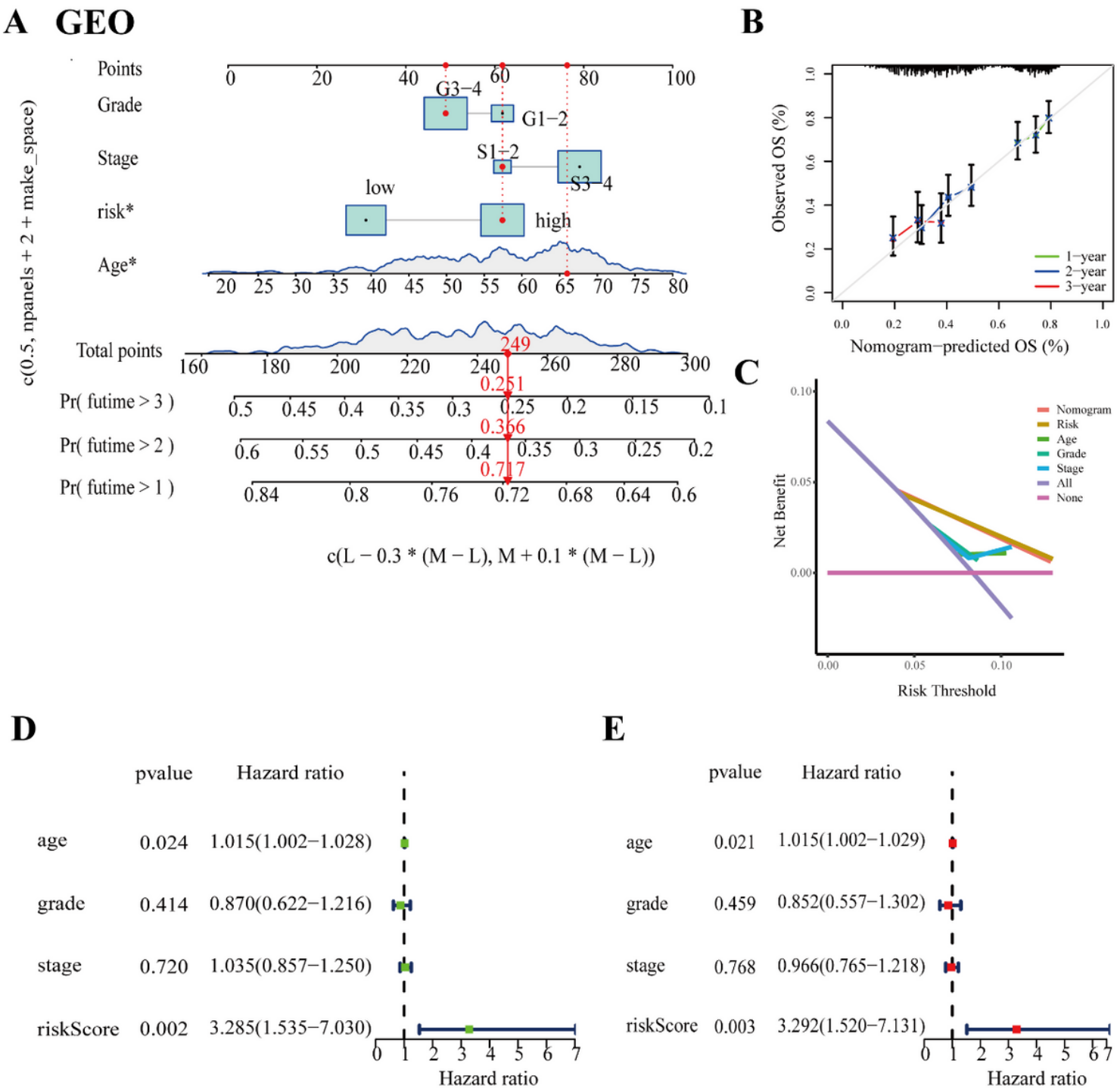

Figure 6

Figure 5 Model validation by applying the validation set (GEO tumor data): A column line plot; B correction curve; C DCA curve; D single-factor independent prognosis; E multi-factor independent prognosis

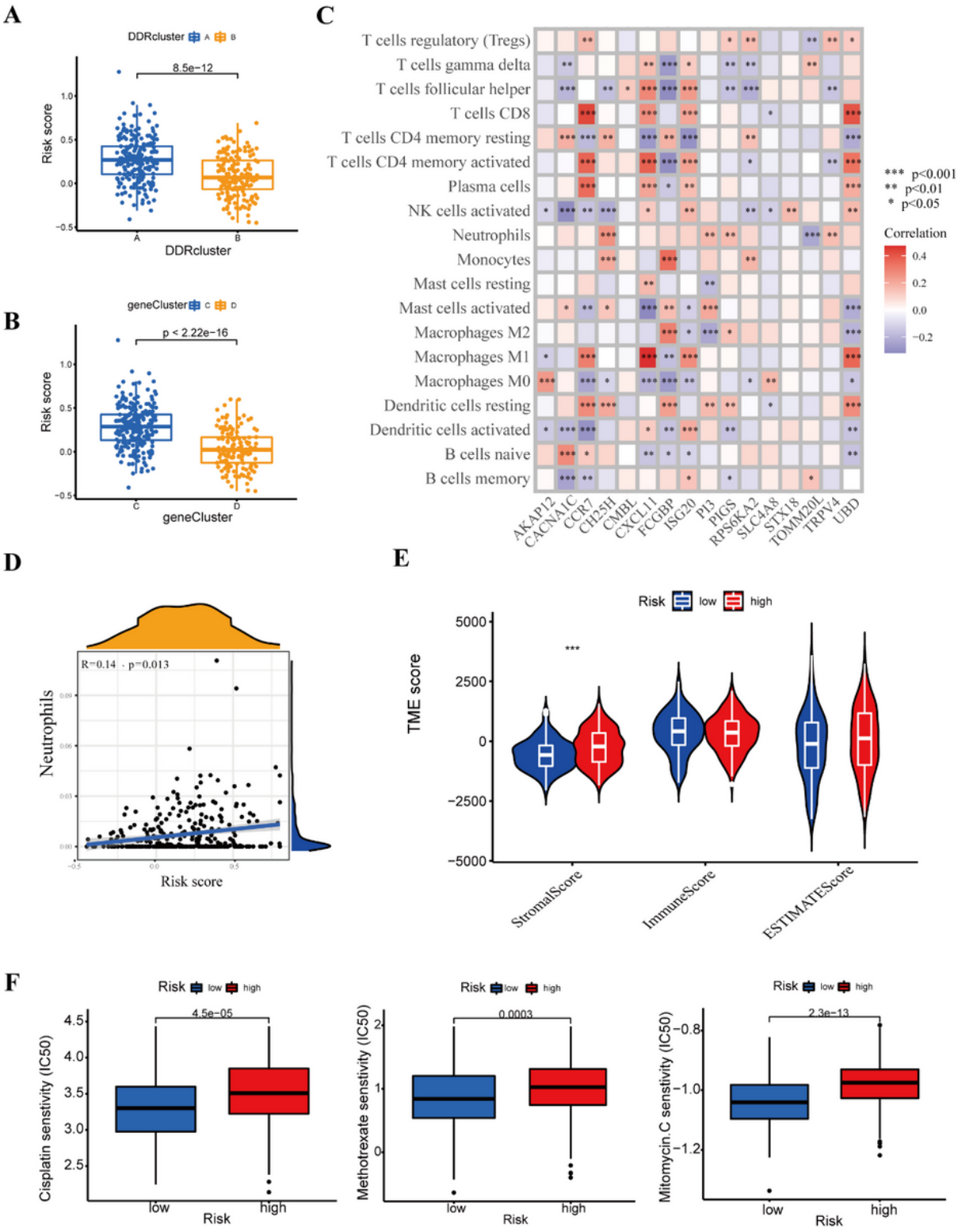

Figure 7

Figure 6 A Risk model applicability analysis: A Differential correlation between high and low risk groups in DDR-related genes on staging of TCGA tumors; B Differential correlation between high and low risk groups in prognosis-related differential genes between staging on staging of TCGA tumors; C Risk model correlation with immune cells; D Risk model correlation with stem cells; E Correlation between high and low risk groups and tumor microenvironment; F Risk model application to drug sensitivity analysis

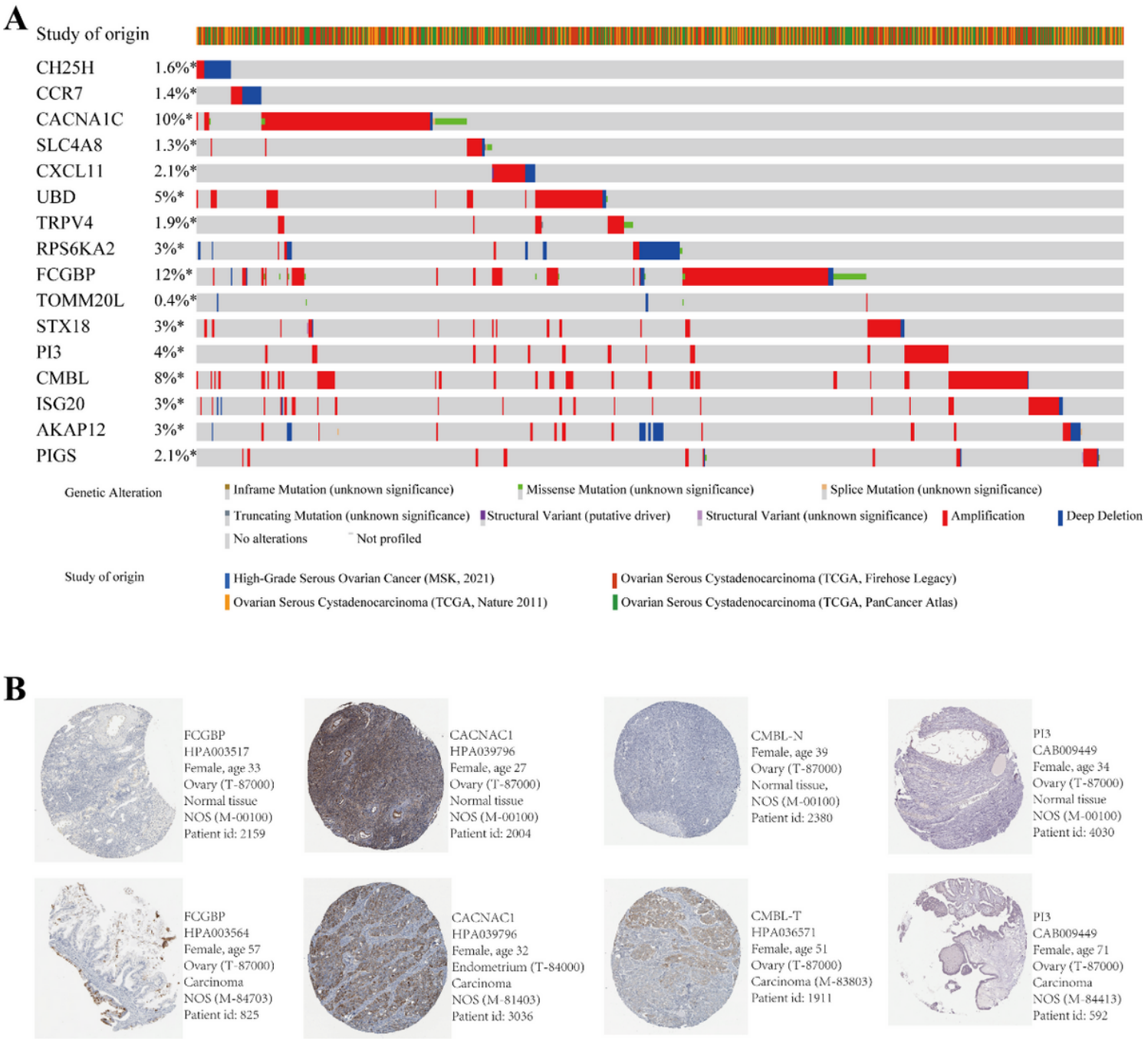

Figure 8

Figure 7 Risk model gene expression: A Mutation frequency of risk model genes; B Protein level expression of risk model genes in OC tissues

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 1.txt