Identification of A Glycolysis-Related Seven-lncRNA Signature to Predict Survival in Diffuse Glioma Patients

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Abstract

Background: Glioma, the most common tumor in brain, seriously threaten human's healthy. Glycolysis is a crucial hallmark of malignant tumor which can facilitate cancer progression and deterioration. Long noncoding RNAs (LncRNAs) are increasingly implicated in disease progression. Therefore, our study plans to reveal whether glycolysis-related LncRNAs can independently predict prognosis of glioma patients.

Methods: Firstly, co-expression network between glycolysis-related genes and LncRNAs is constructed using Pearson correlation. Secondly, univariate Cox regression and the Least Absolute Shrinkage and Selection Operator (LASSO) analysis are used to identify key glycolysis-related LncRNAs. Thirdly, based on multivariate Cox regression, a predictive model is built. At last, the Kaplan–Meier survival analysis, receiver operating characteristic (ROC) and gene set enrichment analysis (GSEA) are performed to assess the effect of risk score among glioma patients.

Results: A glycolysis-related LncRNAs risk signature based on nine LncRNAs was identified. The risk score calculation formula is yielded as follows: risk score = (−0.16 × TPM of RP11-294N21.3) + (0.22 × TPM of AC093627.7) + (0.09 × TPM of AC093627.10) + (0.05 × TPM of RP11-359G22.2) +(0.17 × TPM of LINC01272) + (0.05 × TPM of AC092484.1) + (0.01 × TPM of AC026904.1). The risk score is independently associated with prognosis, and each identified LncRNAs is significantly related to the overall survival of patients. Moreover, the results of GSEA analysis indicate that the high-risk score is mainly involved in some vital biologic process.

Conclusion: The risk model based on our LncRNAs signature can significantly predict prognosis and may serve as potential therapeutic targets in the future.

Background

Glioma is the most common primary brain tumor in adult[1] and exhibit a spectrum of aberrantly aggressive phenotype[2]. Every year, approximately 100,000 people worldwide are diagnosed as glioma[3]. The current standard treatments of glioma involve maximal surgical resection, followed by radiotherapy with concomitant and adjuvant chemotherapy[4]. Although the molecular profiling study has made great progress and the diagnosis as well as treatment improved constantly, the prognosis of glioma is still unsatisfactory due to its heterogenous nature. The median overall survival of high-grade glioma is still limited to 14.6 months along with the 2 and 5-year survival rates remaining at 25% and 10%, respectively[5, 6]. Therefore, identification of new tumor related markers, which are able to predict outcome of patients, is urgently required.

In contrast to normal cells, cancer cells primarily utilize the glycolysis pathway for energy metabolism irrespective of oxygen availability[7]. Mounting researches have revealed that elevated tumor glycolysis contributes to the large-scale biosynthesis, uninterrupted cancer growth, proliferation, migration, and distant metastasis[8, 9]. Long noncoding RNA (lncRNA) is a class of no coding RNA, which is 200-

100,000 nucleotides in length lacking protein-coding potential. Existing studies have revealed that LncRNAs can take part in signal pathways regulation and disease progression, such as HOTAIR[10], PVT1[11], and CRNDE[12]. However, the impacts of glycolysis-related LncRNAs exerting on glioma patients are still obscure, as well as whether glycolysis-related LncRNAs can serve as predicted markers in the diagnosis of glioma or not remains unexplored.

In our present study, we screen the glycolysis-related LncRNAs and perform multistep analysis by using the glioma patient data from The Cancer Genome Atlas (TCGA) database. According to Cox regression and the Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis, we identify a 7-lncRNA signature with prognostic value in the training cohort and validate its prognostic value in the validation cohort. Patients can be split into two groups based on the risk score and high-risk scores patients have markedly worse overall survival (OS). In addition, the differences between the two groups are assessed from multiple perspectives. Overall, the established signature of glycolysis-related LncRNAs is demonstrated as an independent prognostic factor and the 7 glycolysis-related -LncRNAs may serve as potential therapeutic targets for glioma patients.

Methods

Patients and Datasets

Transcriptome profiling data and clinical information of glioma patients are downloaded from The Cancer Genome Atlas (TCGA) database. Excluding samples lacking of information, a total of 598 TCGA glioma patients are utilized in our study. By using the random number manner, TCGA glioma patients are evenly divided into a training cohort for identifying prognostic lncRNA signature and a validation cohort for validating its prognostic value. The detailed clinical information of all selected patients is shown in Table 1. Gene expression is normalized and calculated using the TPM (transcripts per kilobase of exon model per million mapped reads) method[13]. The process of this study is presented in Figure 1. The accession and use of the related data are entirely consistent with the rules of the corresponding database. Due to the data are acquired from publicly open database, our study doesn’t have to be accepted by the regional ethical board.

Table 1
Clinical characteristic of diffuse glioma patients

Characteristic	Training cohort (298)	Validation cohort (290)
Age		
≤45	141 (47.3%)	142 (49.0%)
>45	157 (52.7%)	148 (51.0%)
Gender		
Male	163 (54.7%)	178 (61.4%)
Female	135 (45.3%)	112 (38.6%)
Grade		
II	107 (35.9%)	104 (35.9%)
III	120 (40.3%)	114 (39.3%)
IV	71 (23.8%)	72 (24.8%)
Survival Status		
Alive	207 (69.5%)	206 (71.0%)
Dead	91 (30.5%)	84 (29.0%)
IDH mutation statue		
mutation	178 (59.7%)	190 (65.5%)
wildtype	120 (40.3%)	100 (34.5%)
1p19q codeletion		
No-codel	225 (75.5%)	214 (73.8%)
codel	73 (24.5%)	76 (26.2%)

Glycolysis-related LncRNAs Extraction

Firstly, the transcriptome profiling data including protein-coding and long non-coding genes is acquired from TCGA database. Five glycolysis-related gene sets (Hallmark glycolysis, Biocarta glycolysis pathway, KEGG glycolysis gluconeogenesis, Reactome glycolysis, and WP glycolysis and gluconeogenesis) are downloaded from the Gene Set Enrichment Analysis (GSEA) database[14]. Subsequently, the Pearson correlation is applied with R package “corrplot” to build glycolysis-related LncRNA co-expression networks

with glycolysis-related genes (Filter: |r| > 0.8 and P < 0.001). Lastly, 134 glycolysis-related LncRNAs are identified in the training cohort.

Construction of a Prognostic lncRNA Signature by Cox Regression and LASSO Modeling

To identify key glycolysis-related LncRNAs with prognostic values, we firstly perform a univariate Cox proportional hazards analysis using R package “survival”. The statistical significance cutoff of the P-value is considered at <0.001. Based on the above result of univariate Cox analysis, we subsequently apply LASSO analysis with R package “glmnet” to narrow the gene range and constructs a more refined model. The 1-standard error of the minimum criteria is used to tune the regularization parameter (λ), and maxim is set to 1,000[15]. At last, an individual’s risk score for each patient is calculated for predicting prognosis of glioma patients by including expression level of each optimal glycolysis-related lncRNA, weighted by their estimated none-zero regression coefficients of multivariate Cox regression model. The risk score formula is presented as follow:

Risk Score = $\sum_{i=0}^{n} \mathrm{coefficient}(\mathrm{LncRNAi}) \times \mathrm{expression}(\mathrm{LncRNAi})$[16]

Gene set enrichment analysis (GSEA)

GSEA is applied to identify different biological processes and KEGG pathway between the low- and high-risk groups with the GSEA v7.1 software[17]. P <0.05 is regarded as a significant outcome.

Statistical Analysis

Kaplan–Meier analysis is utilized to evaluate survival with the Log-rank test to assess the differences between the low- and high-risk groups. Independent prognostic variables are performed for survival assessment with multivariate Cox regression models. Receiver operating characteristic (ROC) curve and area under the curve (AUC) at 1-, 3- , and 5-year are calculated to assess the predictive performance of risk score. The ROC curve and AUC of risk-scores, grades, and age are also calculated to compare the predictive performance of risk score with different variables. All data analysis is performed in both training cohort and validation cohort. R studio (version 1.3.1093), and its packages are used for the analysis of all data. P <0.05 is considered to be statistically significant.

Results

Identification of the Prognostic lncRNA from the Training Cohort

In our study, 295 glycolysis-related genes are identified from the Molecular Signatures Database. Subsequently, 134 glycolysis-related LncRNAs are screened out by conducting the correlation analysis

between 295 glycolysis-related genes and LncRNAs in training cohort. To single out the prognostic LncRNAs, expression data of each glycolysis-related LncRNAs are subjected to univariate Cox proportional hazards regression analysis in the training cohort. 28 LncRNAs are found to be significantly associated with the prognosis of glioma patients (p value < 0.05). Furthermore, 28 variables are reduced to seven potential predictors in the training cohort by using LASSO analysis (Figure 2A-B). Among seven prognostic LncRNAs, six LncRNAs (AC093627.7, AC093627.10, RP11-359G22.2, LINC01272, AC092484.1, and AC026904.1) with positive coefficient of univariate regression analysis may be protective factors, whereas the remaining one LncRNAs (RP11-294N21.3) tends to be prognostic risky factors (Figure 2C). The associations between the selected seven glycolysis-related LncRNAs and glycolysis-related genes are presented in Figure 3, which indicated that these LncRNAs may play important role in glycolysis pathway.

Construction of seven-LncRNA prognostic signature for glioma patients

Given the crucial and independent correlations between expression of seven glycolysis-related LncRNAs and overall survival of glioma patients, an individual's risk score model is constructed using the regression coefficients of multivariate Cox regression model to weight the expression level of each LncRNA in the seven-LncRNAs signature. The formula of the seven-LncRNAs signature is as follow: risk score = (−0.16 × TPM of RP11-294N21.3) + (0.22 × TPM of AC093627.7) + (0.09 × TPM of AC093627.10) + (0.05 × TPM of RP11-359G22.2) +(0.17 × TPM of LINC01272) + (0.05 × TPM of AC092484.1) + (0.01 × TPM of AC026904.1). According to the risk score model, the seven-LncRNAs prognostic risk score is calculated for each patient in the training and validation cohorts. All patients of two cohorts are categorize into a high-risk group and a low-risk group according to the median risk score. The Principal Component Analysis (PCA) of the risk score model in training and validation cohorts are presented in the Figure 4A-B.

Association Between Risk Score and Patient Outcome

As presented in the Figure 5A-B, patient's mortality is elevated with the increase in risk score in both the training and validation cohorts. Kaplan–Meier survival curves are applied to verify the effect of the identified glycolysis-related LncRNAs signature both in glioma and . The patients with the low-risk scores survive significantly longer than those with high- risk scores in the training cohort (Figure 5C-E). Kaplan–Meier survival curves of the validation cohort are the same as the training cohort (Figure 5F-H). The Kaplan–Meier survival curves of in training cohort, AUC values of the risk score are 0.811 in the 1st years, 0.833 in the 3rd years, and 0.829 in the 5th years (Figure 6A-B). In validation cohort, AUC values of the risk score are 0.795 in the 1st years, 0.873 in the 3rd years, and 0.840 in the 5th years (Figure 6C-D). The results of the ROC curves indicate that the risk score based on glycolysis-related LncRNAs can act as an effective prognostic indicator for glioma patients. The multivariate Cox regression analysis demonstrates that the risk score is independently associated with OS in the training and validation cohorts. In training

cohort, risk scores are significantly associated with overall survival (OS) (HR=1.184, 95% CI=1.129-1.242, P=0.005) (Figure 6E). In validation cohort, risk scores are also associated with OS ((HR=1.164, 95% CI=1.094-1.238, P<0.044) (Figure 6F). Based on the all the results above, the risk scores are of significance in the prognosis and OS prediction of glioma patients.

Clinic Characteristics of Seven Identified Glycolysis-related LncRNAs in Gliomas

In our study, we examine and analyze the relationships between the expression levels of seven identified LncRNAs and the clinic features (including survival status, grade, IDH mutation, and 1p/19q codeletion status). LncRNAs expression level and clinic features are illustrated in heatmaps (Figures 7A, B), indicating that the expression of every LncRNAs is obviously distinct in different groups. Kaplan–Meier curves analysis demonstrate that the identified LncRNAs is closely associated with survival status in glioma in both training and validation cohorts (Figure 8A–G and S1S1A–G).

GSEA Enrichment Analysis of Seven Identified Glycolysis-related LncRNAs

To interrogate the relationships between risk scores and biological functions across different samples in training cohort, we perform the GSEA enrichment analysis using gene expression profiles corresponding to these samples. The GSEA analysis of GO biological processes unveil that cell cycle regulation (NES=2.00, p-value <0.0001), DNA replication (NES=1.96, P<0.0001), and post-replication repair (NES=1.94, P<0.0001) are significantly enriched between the two groups relying on risk score (Figure 9A-C). The results of the GSEA analysis of KEGG pathway illustrated that high-risk group is significantly associated with the P53 signaling pathway (NES=1.86, P<0.0001), cell cycle regulation (NES=1.86, P=0.0002), and DNA replication (NES=1.85, P<0.0001) (Figure 9D-F).

Discussion

Glioma, the most frequent malignant primary intracranial tumors in adults, seriously threatens human health because of its malignant progression and poor prognosis[18]. Even with the most comprehensive treatments for glioma patients (such as surgery, radiation, chemotherapy and immunotherapy), there still occupies an unsatisfying median survival of 15 months[6, 19]. Although the treatment approaches of gliomas have improved constantly over the past few years, it is still difficult to cure completely, and patients are prone to recurrence after the initial treatment, leading to poor clinical prognosis among glioma patients[20–22]. Therefore, some novel biomarkers need to be discovered as potential therapeutic targets to improve prognosis.

Reprogramming of energy metabolism is considered as one of the cancer hallmarks[23, 24]. Tumor cells primarily utilize the glycolysis pathway for energy supply and glycolysis rate is 100 times higher compared to the normal cells[25, 26]. Thus, this trait of tumor has attracted prodigious attention from researchers in recent years. Mounting studies have revealed that glycolysis pathway exhibits a high prognostic value in glioma patients[27, 28]. Multiple well-known biomarkers of glioma are associated with the glycolysis pathway. For example, compared to the IDH1 wild-type, the intermediate products of glycolysis pathway are obviously reduced in the glioma tissues with IDH1 mutation[29]. Ras inhibition can cause glycolysis pathway shutdown and might therefore block tumor cell invasiveness, survival in glioma[30]. Down-regulation of EGFR, a significant oncogenic signature in glioma, can trigger regression of the glioblastoma through reversing the Warburg effect[31]. At the same time, LncRNAs have been proven to be implicated in considerable human diseases including cancers[32]. Numerous studies have evidenced that some signaling transduction and function related LncRNAs, such as immune-related[33] and autophagy-related LncRNAs[34], can affect the development and progression of the glioma.

In 2007, Chen et al. constructed a five gene prognostic signature for NSCLC[35]. Since then, gene signature, also known as classifier, has been regularly utilized to predict prognosis of various cancers including glioma. For example, an immune-related six-LncRNAs was developed to predict the prognosis of glioma[36]. Considering the significance of the glycolysis pathway in cancer, we construct a glycolysis-related LncRNAs signature through various methods such as LASSO regression, Cox regression and this signature is independently associated with the glioma prognosis. In addition, two groups based on risk score are analyzed by Kaplan–Meier survival curves analysis, ROC curve analysis, multivariate Cox regression analysis, and GSEA. All the above results prove that our signature is significantly related to OS and can be further considered to be a novel potential molecular therapeutic target.

In our signature, we screen and identify seven LncRNAs (AC093627.7, AC093627.10, RP11-359G22.2, LINC01272, AC092484.1, AC026904.1, and RP11-294N21.3). LINC01272 is considered as a new predicter biomarkers of gastric cancer and is closely related to the cancer cell proliferation and cell migration[37]. Li et al. has reported that LncRNAs AC026904.1 could regulate SLUG expression at both transcriptional and post-transcriptional levels, exerting critical roles in epithelial-mesenchymal transition in breast cancer[38]. AC093627.7, AC093627.10, RP11-359G22.2, AC092484.1, RP11-294N21.3 have been reported for the first time in our present study. These LncRNAs may play an unknown biological role in glioma. According to the results of Kaplan–Meier survival curves analysis in our study, all the identified seven LncRNAs are associated with the survival status of glioma patients. The patients with high expression of RP11-294N21.3 can live longer time. On the contrary, the patients with low expression of AC093627.7, AC093627.10, RP11-359G22.2, LINC01272, AC092484.1, AC026904.1 live longer time.

The results of GSEA enrichment analysis demonstrate that several pathways and biology functions are positively associated with risk scores such as p53 signaling pathway, cell cycle pathway, DNA replication pathway, DNA post-replication repair pathway. The p53 is a famous tumor suppressed factor which is significantly associated with some important roles such as DNA damage and oncogenic signaling, and its dysfunction can promote cancer development and deterioration[39, 40]. Deviant cell cycle is the most

common variation during tumor onset and development[41]. Abnormal DNA replication and DNA post-replication repair process may induce the accumulation of genetic aberrations that promote diseases such as cancer[42]. Thus, it is speculated that the identified seven LncRNAs might impact cell cycle, cell proliferation, DNA replication, and p53 signaling pathway through glycolytic biologic processes.

Although the seven glycolysis-related LncRNAs prognostic signature identified in our study is robust, there are still several limitations. Firstly, we need to validate functional features of this seven LncRNAs signature through basic biological experiments (in vivo or in vitro) and clinical researches. Secondly, the whole seven glycolysis-related LncRNAs, identified in our study using TCGA database are not completely comprised in other databases such as Chinese Glioma Genome Atlas (CGGA) or Gene Expression Omnibus (GEO), so we have to divide the total TCGA glioma data into a training cohort and a validation cohort by using random number manner, which limited the generalizability of our conclusions to some extent.

Conclusions

In conclusion, we identify a glycolysis-related LncRNAs signature comprising seven LncRNAs (AC093627.7, AC093627.10, RP11-359G22.2, LINC01272, AC092484.1, AC026904.1, and RP11-294N21.3), which can be used as an independent prognostic marker in stratifying risk subgroups in terms of survival for patients with glioma. The risk model based on our LncRNAs signature can significantly predict prognosis and may serve as potential therapeutic targets in the future.

Abbreviations

GSEA: Gene Set Enrichment Analysis; LncRNAs: long noncoding RNAs; LASSO: Least Absolute Shrinkage and Selection Operator; PCA: Principal Component Analysis; ROC: Receiver Operating Characteristic; TCGA: The Cancer Genome Atlas; TPM: Transcripts Per Kilobase of Exon Model Per Million Mapped Reads;

Declarations

Ethics approval and consent to participate

Data obtained from the TCGA open-access database was collected from tumors of patients who provided informed consent based on the guidelines from the TCGA Ethics, Law and Policy Group[43].

Consent for publication

Not applicable.

Availability of data and materials

All data obtained and/or analyzed in this study were available from the TCGA database. (Data Category: transcriptome profiling, Project: TCGA-LGG and TCGA-GBM, https://portal.gdc.cancer.gov/repository). Glycolysis-related gene sets were downloaded from GSEA database. (Keywords: glycolysis, http://www.gsea-msigdb.org/gsea/msigdb/search.jsp).

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Authors' contributions

CD and HJ designed the study. LS, XB, CS, and ZL collected, analyzed, and interpreted the data. LS wrote and edited the manuscript, and all authors read and approved the manuscript.

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Figures

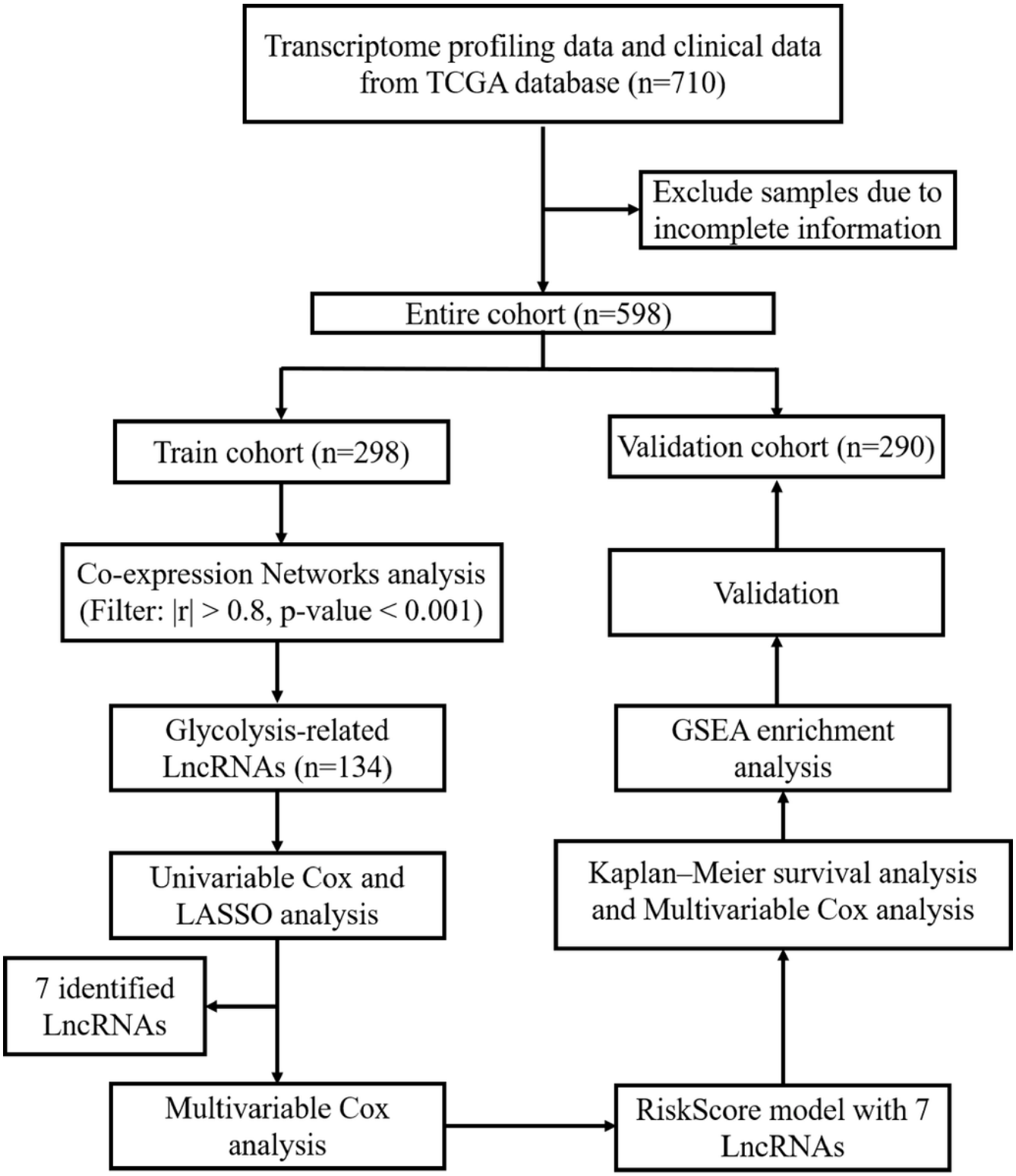

Figure 1

Flow chart of data collection and analysis.

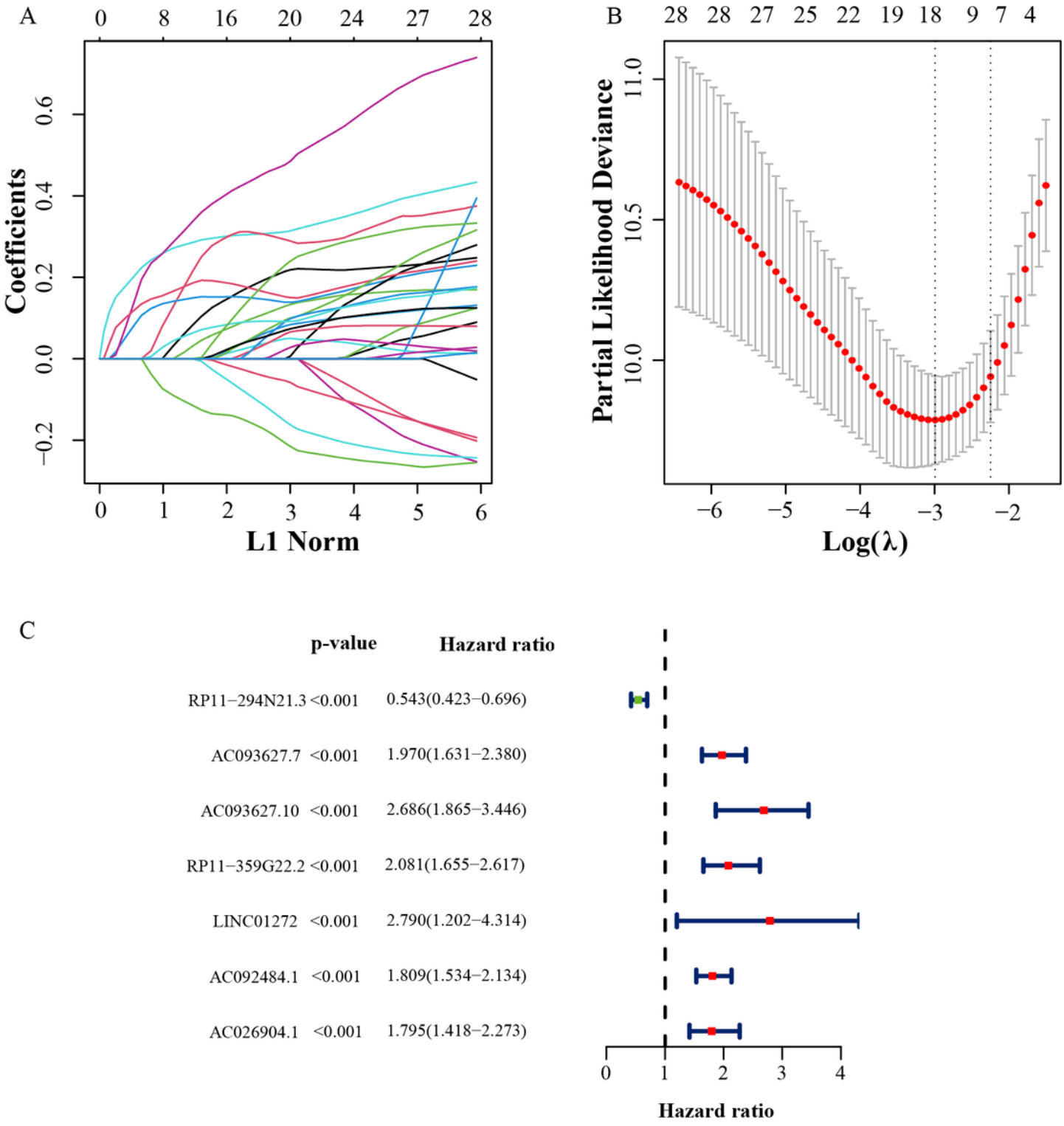

Figure 2

Identification of key glycolysis-related LncRNAs. (A, B) 7 key glycolysis-related LncRNAs was identified by LASSO regression analysis, where optimal λ resulted in seven non-zero coefficients in the training cohort. (C) The univariate regression analysis of the 7 key glycolysis-related LncRNAs.

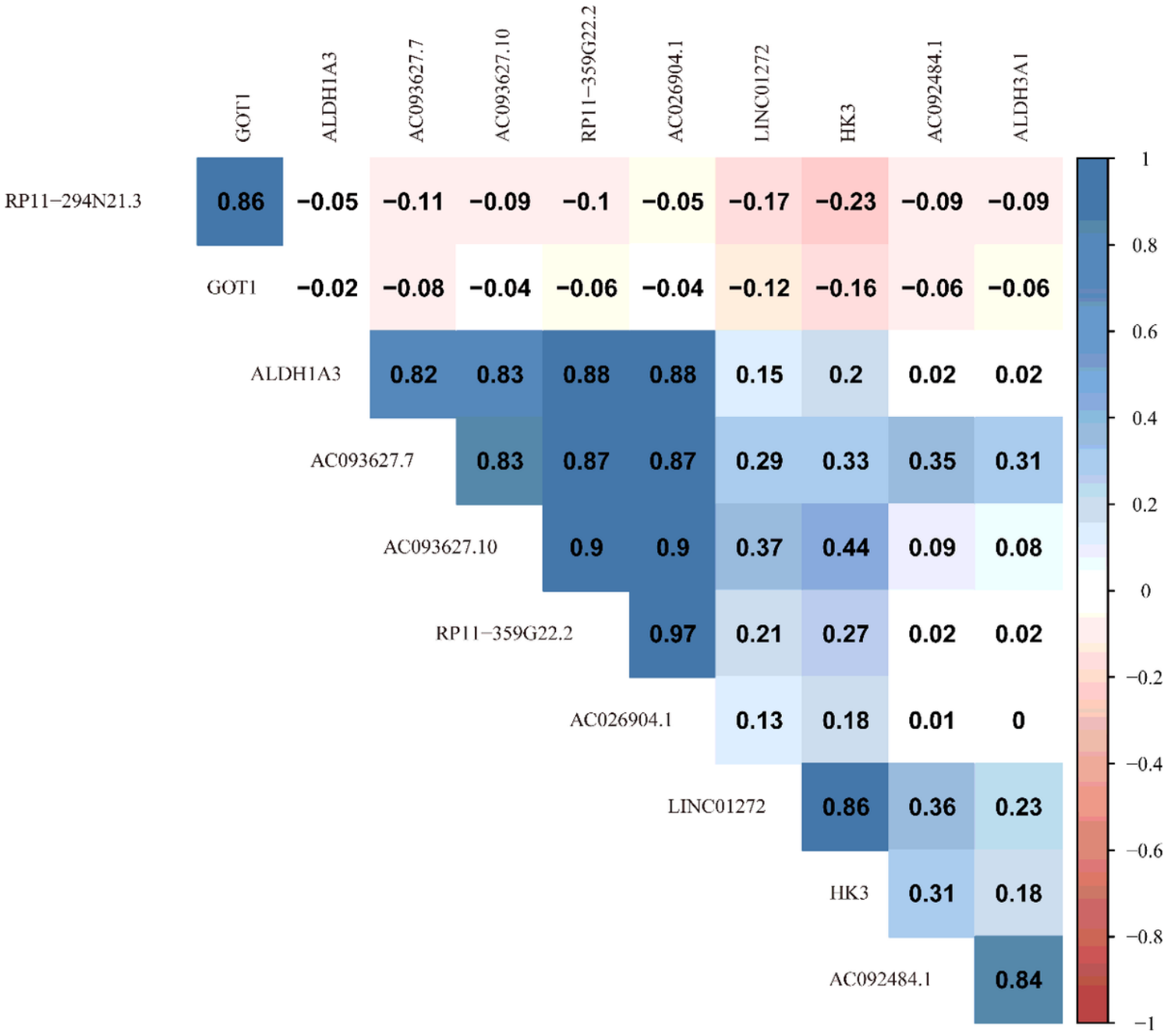

Figure 3

Association between the identified seven glycolysis-related LncRNAs and glycolysis-related genes.

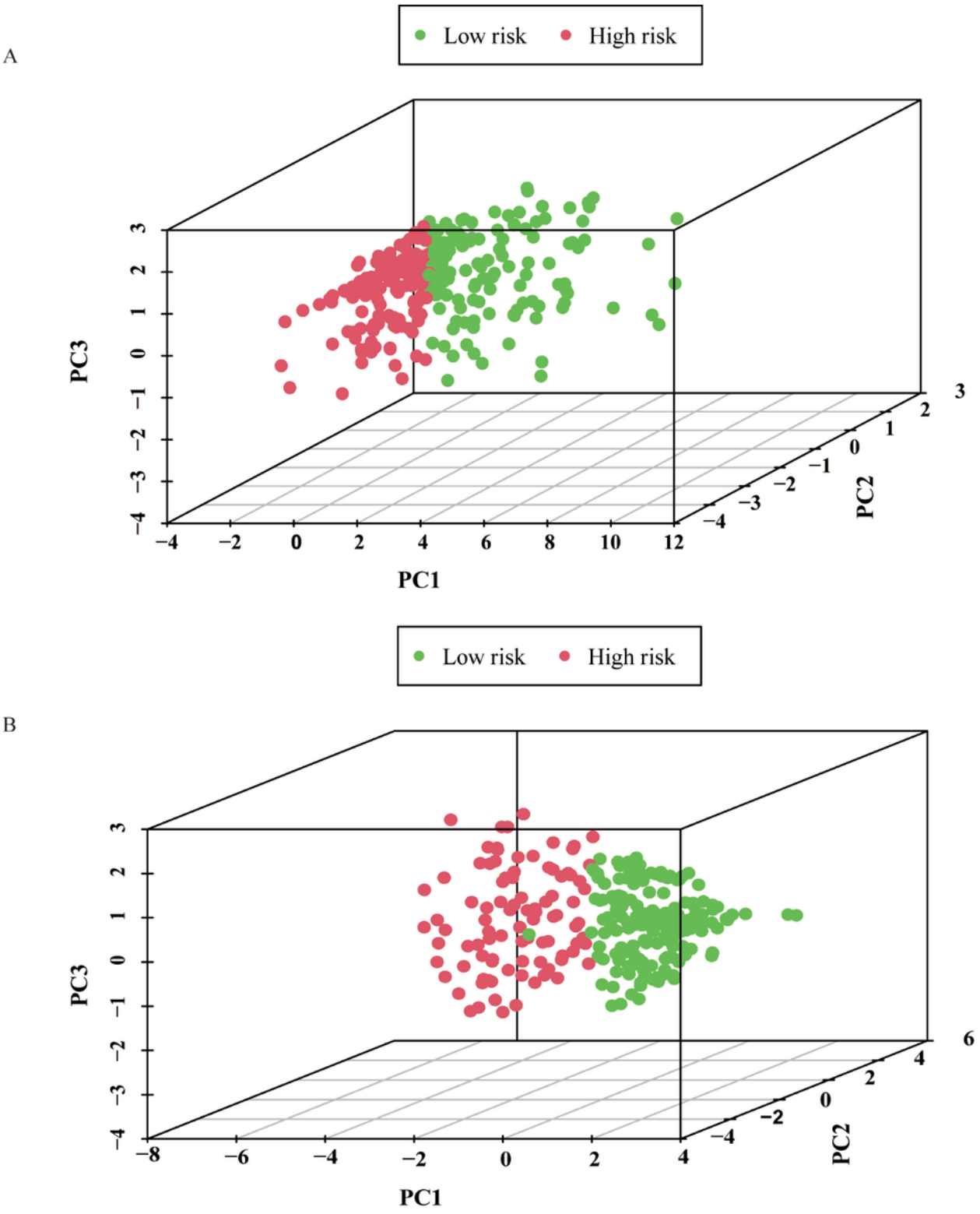

Figure 4

The Principal Component Analysis (PCA) of the glycolysis-related LncRNAs signature. (A) PCA of the training cohort. (B) PCA of the validation cohort.

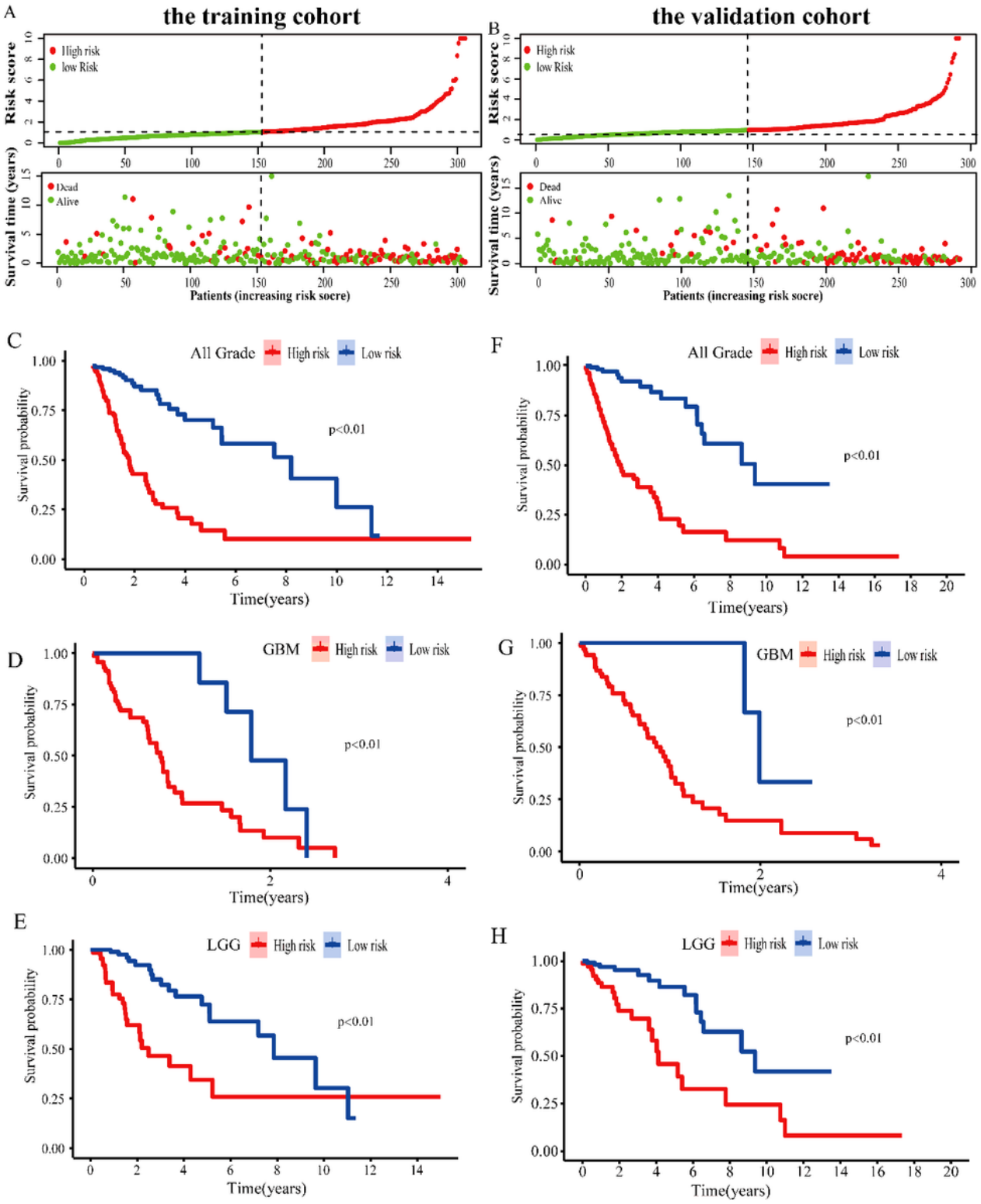

Figure 5

Survival prediction of the glycolysis-related LncRNAs signature. (A, B) Risk score distribution, survival statue for patients in low- and high-risk groups by the LncRNA signature. (C, D, E) Kaplan–Meier survival curves of the risk score in the training cohort. (F, G, H) Kaplan–Meier survival curves of the risk score in the validation cohort.

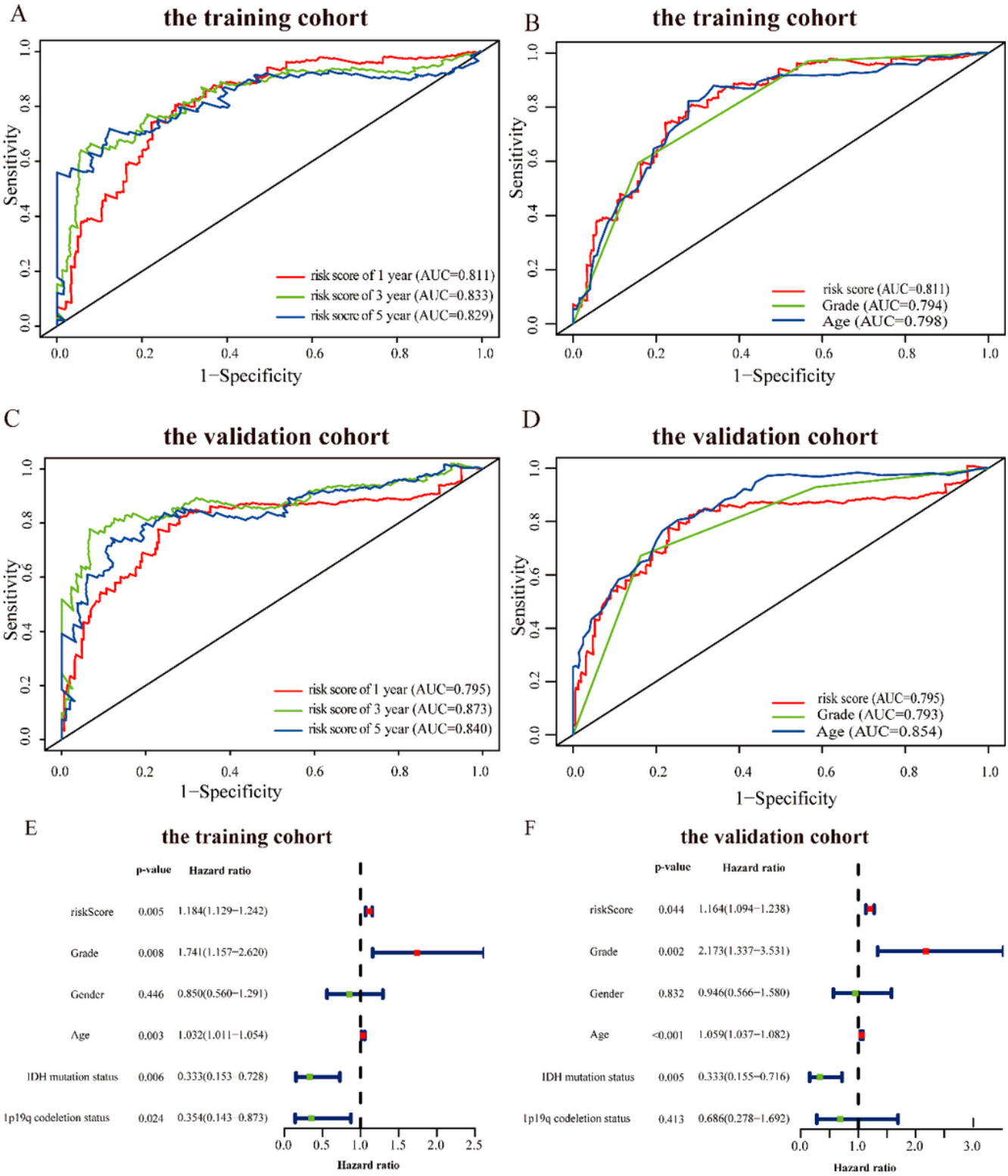

Figure 6

Prognostic prediction of the glycolysis-related LncRNAs signature. (A, B) ROC curves of the training cohort. (C, D) ROC curves of the validation cohort. (E) multivariate Cox regression analysis of the risk score in training cohort. (F) multivariate Cox regression analysis of the risk score in validation cohort.

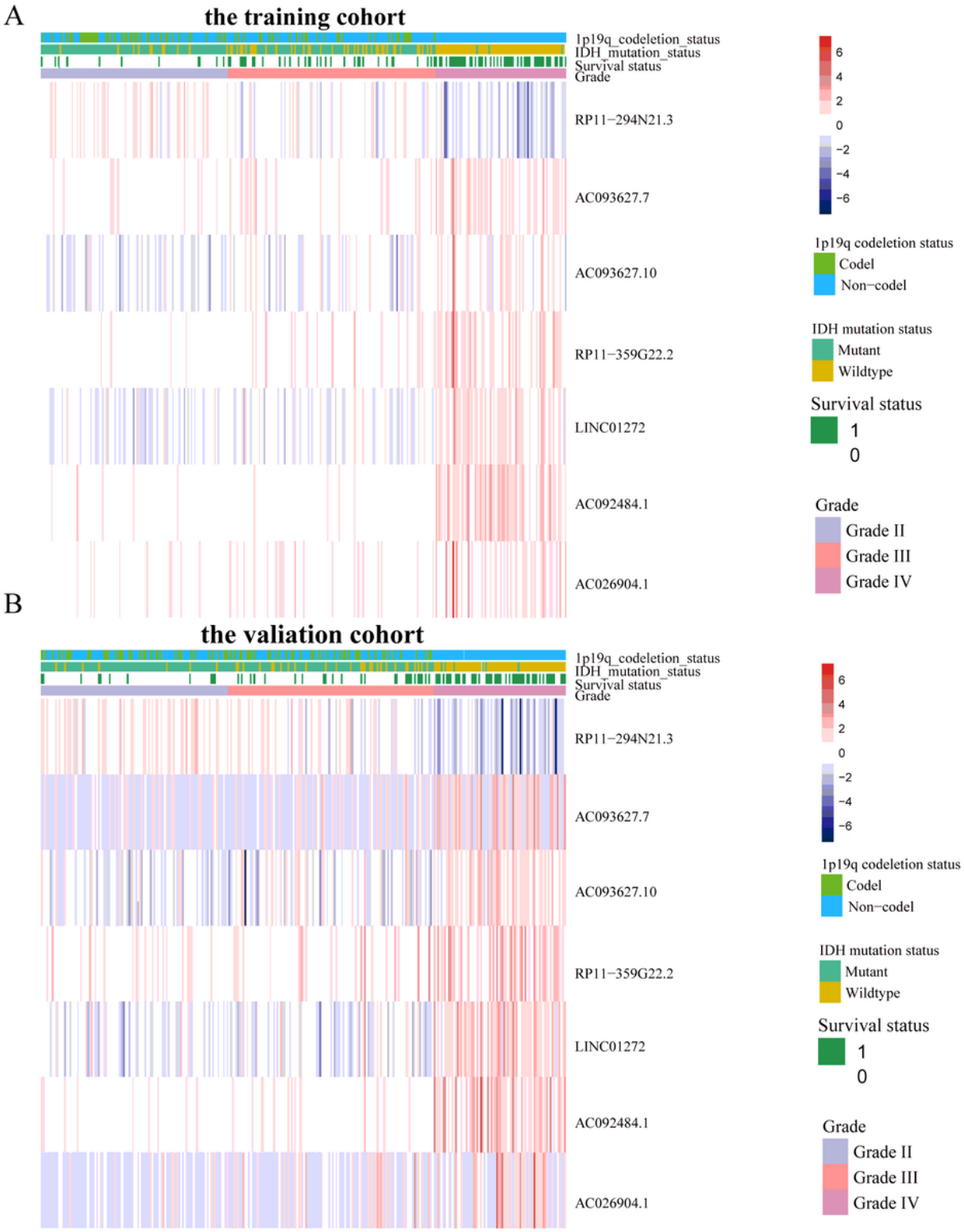

Figure 7

Expression of the identified seven glycolysis-related LncRNAs is related to clinicopathological features. (A, B) Heatmaps showing the expression levels of seven LncRNAs in gliomas with different groups.

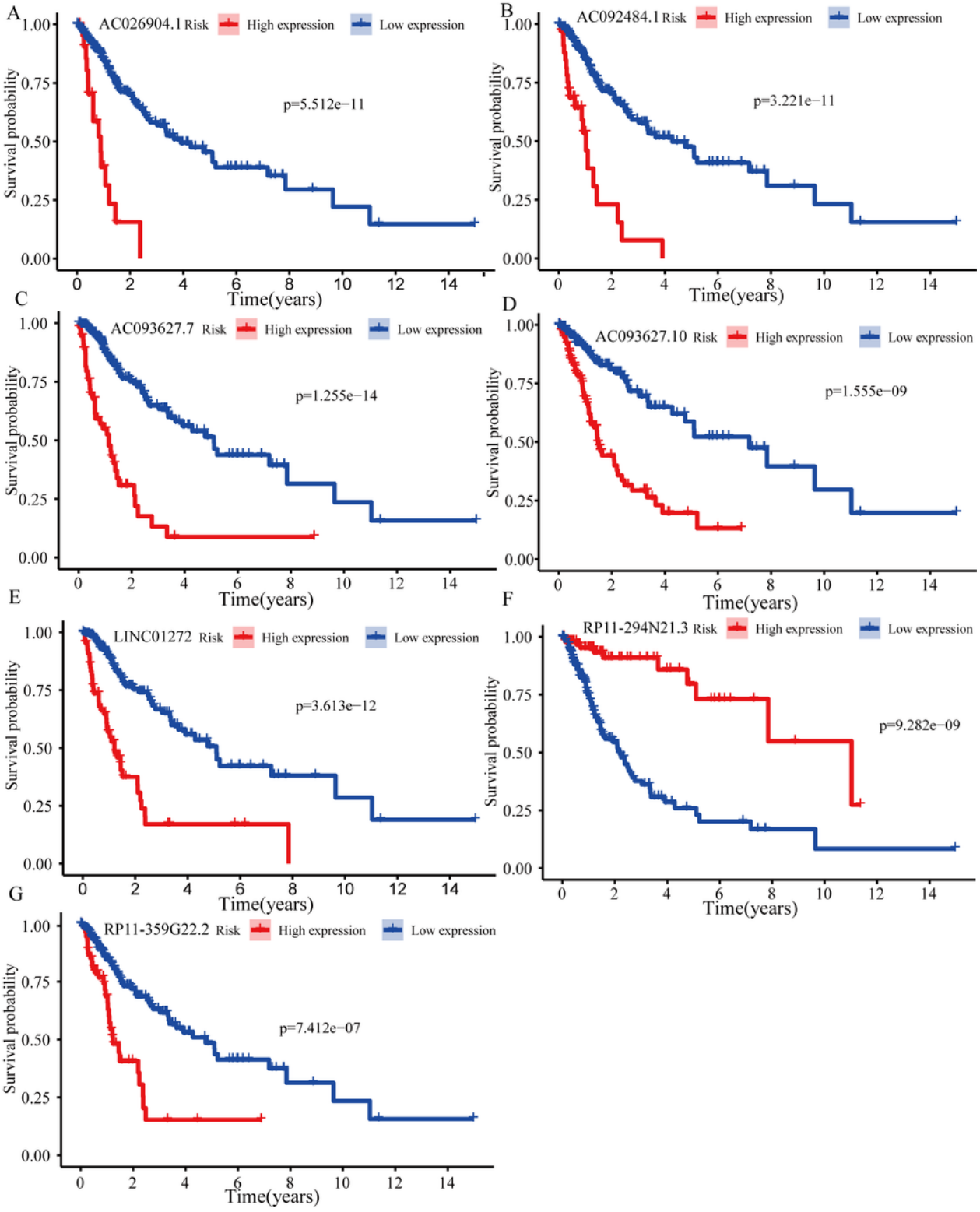

Figure 8

(A-G) Kaplan–Meier survival curves of every single identified LncRNAs in the training cohort.

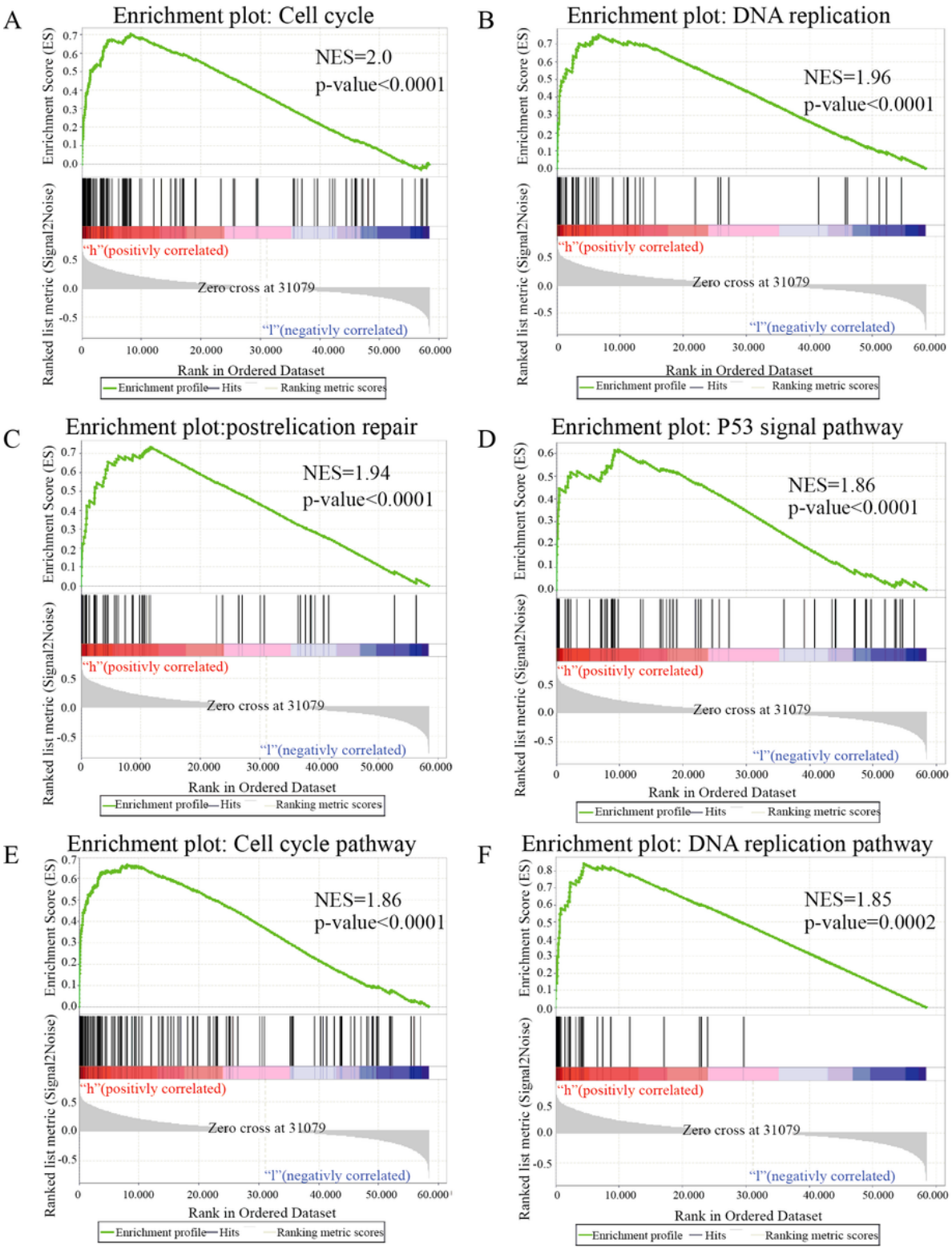

Figure 9

GSEA enrichment analysis (A-C) GSEA analysis of GO biological processes. (D-F) GSEA analysis of KEGG pathway.

Supplementary Files

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

- FigureS1.pdf