



Evaluating the Predictive Value of a Coagulation-Related Gene Model in Glioma

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ABSTRACT

AIM: To evaluate coagulation related gene model as a biomarker for predicting prognosis of gliomas.

MATERIAL and METHODS: The mRNA expression and clinical data of glioma were downloaded from the TCGA and CGGA databases. Coagulation-related genes were downloaded from the KEGG database. The expression model was constructed using LASSO regression. The GBM data were divided into high and low-risk expression groups based on the median risk score, and the differences in overall survival and progression-free survival between them were calculated. The prognostic model was further validated using the TCGA-LGG and CGGA glioma databases, respectively. The accuracy of the risk score was calculated by ROC analysis for 1 year and 3 years.

RESULTS: Four model genes, namely the SERPINA5, PLAUR, BDKRB1, and PTGIR, were identified, and the risk score was calculated as follows: $\text{risk score} = \text{SERPINA5} \times 0.126264111304559 + \text{PLAUR} \times 0.288587629696211 + \text{BDKRB1} \times 0.349215422945011 + \text{PTGIR} \times 0.17334527969703$, respectively. Based on glioma data from three groups, patients were divided into high and low-risk groups according to the median risk score. The overall survival, progression-free survival, and risk scores of the high-risk score group were worse than the low-risk group. The ROC curve analysis showed that the AUC values of the coagulation-related gene model at 1 year, 3 years, and 5 years were more than 0.65, validating the reliability of the prognostic model.

CONCLUSION: This study established the correlation between the coagulation-related gene model and glioma prognosis, providing deeper insight into the mechanism and treatment of glioma.

KEYWORDS: Glioma, Coagulation, Prognostic model, Bioinformatics

ABBREVIATIONS: CNS: Central nervous system, WHO: World Health Organization, GBM: Glioblastoma, LGG: Low-grade glioma, RS: Risk score, ROC: Receiver operating characteristic curve, AUC: Area under the curve, PCA: Principal component analysis, DEG: Differentially expressed coagulation genes, TF: Tissue factor, uPAR: Urokinase-type plasminogen activator receptor

INTRODUCTION

Glioma, originating from glial cells, neural progenitor cells, and cancer stem cells, is the most common malignant tumor with a high recurrence rate in the central nervous system (CNS) (32). According to the 2007 World Health Organization (WHO) classification, gliomas can be divided into grades I, II, III, and IV based on histological characteristics. The overall survival of glioblastoma (GBM)

is usually below 14 months (17,23). In recent years, the key diagnostic genes, molecules, and pathways have been discovered and are getting more attention. The fifth edition of the WHO classification highlights the importance of molecular diagnosis in glioma classification, treatment, and prognosis (18).

Deep vein thrombosis, detected through a vascular ultrasound before and after surgery, often necessitates antico-

agulation therapy. Thrombosis is influenced by three crucial factors: vascular endothelial cell damage, changes in blood flow dynamics, and increased blood coagulability (19, 22). Abnormal growth of blood vessels often occurs in tumor tissues, which leads to inadequate blood and oxygen supply to tumor microenvironments, triggering inflammation and hypoxia. The accumulation of inflammatory cells promotes the aggregation of coagulation factors and alters coagulation function.

Research has shown that the RAS oncogene can influence CXCL8 recruitment through the MAPK and PI3K pathways, initiating tumor-related inflammatory responses and angiogenesis. Inhibition of CXCL8 does not affect tumor proliferation but increases tumor cell death and damages tumor supplying vessels (29). Some studies have demonstrated that glioma patients exhibit increased expression of angiogenic genes and molecules, such as coagulation genes, in tumor tissues compared to normal brain tissues. Glioma patients show significantly lower PT and APTT levels and increased D-dimer and vWF levels compared to meningioma patients, which are associated with higher mortality rates (12,22). Compared to the general population, glioma patients have higher levels of D-dimer, homocysteine, VEGF, tPA, and PAI-1. In contrast, patients with non-neoplastic nervous system diseases do not exhibit significant expression of these indicators compared to the general population. Currently, it is theoretically believed that there is a state of hypoxia in the distal blood vessels of malignant tumors. Hypoxia can lead to an increase in TF expression mediated by ERG1 in mononuclear phagocytes. TF, as a key factor in hemostasis, ultimately leads to thrombosis by binding to VIIa. This implies that hypoxia may contribute to important factors in vascular occlusion and thrombosis (4,21,26). Thus, the angiogenesis and coagulation-related genes play an important role in malignant tumors, but the mechanisms deserve more in-depth research.

In this study, we analyzed the expression of coagulation-related genes in tumor and normal brain tissues of glioma patients and established a prognostic coagulation-related gene model, which can help us explore the underlying mechanisms of glioma.

■ MATERIAL and METHODS

Data Download and Preprocessing

Transcriptome and clinical data of glioma were downloaded from the TCGA (<https://portal.gdc.cancer.gov/>) and CGGA databases (www.cgga.org.cn), including survival time, survival status, age, sex, etc (35).

The expression and clinical data of TCGA-GBM, TCGA-LGG, and CGGA gliomas were extracted using the Perl program and R software. The coagulation-related genes in hsa04610 and hsa04611 pathways were screened from the KEGG database (<https://www.kegg.jp/kegg/>) (11).

Establishing a Coagulation Gene Prognostic Model for Glioma

The expression of coagulation-related genes and differentially expressed genes between tumor tissues and normal tissues

in TCGA-GBM data were examined by the R-software limma package. Prognostic coagulation-related genes ($p < 0.01$) were calculated by survival package. Finally, model genes were obtained by intersecting the prognostic genes and differential expressed genes with the Venn package (5,25).

In the GBM data, expression of the coagulation gene was combined with survival time and survival state. The coagulation-related gene model was constructed by LASSO regression and the risk score (RS) was calculated as follows: $RS = \sum (Coef1 * Exp \gamma_1 + \dots + Coefi * Exp \gamma_i)$. Coefi and Exp γ_i represented the coefficient and amount of coagulation-related gene expression, respectively. The coagulation genes were divided into high-expression and low-expression groups based on the median risk score. The difference in overall survival and progression-free survival between high and low-risk expression groups was calculated with the survival package. The heatmap package was used to draw survival status and risk score heat maps of high and low-risk groups. The “timeROC” package was used to calculate the receiver operating characteristic curve (ROC) and area under the curve (AUC) to evaluate the diagnostic value of the model to predict 1-year, 3-year, and 5-year survival. The “scatterplot3d” package was used to perform principal component analysis (PCA) of high- and low-risk expression groups and the gsea package was used to plot the differences in immune cells and immune function (1,8).

Model Validation

To validate the model, the TCGA-LGG and CGGA glioma datasets were downloaded and standardized. The high and low-risk groups and the relevant overall survival and progression-free survival were calculated according to the RS. The R software “heatmap” was used to draw the survival status and risk score heatmaps of the two datasets. The “timeROC” package calculated the ROC and AUC values to evaluate the diagnostic value of 1-year, 3-year, and 5-year survival, respectively. The “scatterplot3d” package was used to perform principal component analysis (PCA) of high- and low-risk expression groups and the gsea package was used to plot the differences in immune cells and immune function between the two groups.

■ RESULTS

Identification of Model Genes

The differential expression between GBM and normal tissues was used to screen the differentially expressed coagulation-related genes (DEGs). The prognostic coagulation-related gene expression was identified, and the differentially expressed genes and the prognostic genes were intersected to obtain the model genes (Figure 1).

Prognostic Model and Survival Analysis of Coagulation Genes

The prognostic model was constructed based on LASSO regression, and the risk score was calculated as follows: $RS = (SERPINA5 \text{ expression} * 0.1263) + (PLAUR \text{ expression} * 0.2886) + (BDKRB1 \text{ expression} * 0.3492) + (PTGIR \text{ expression}$

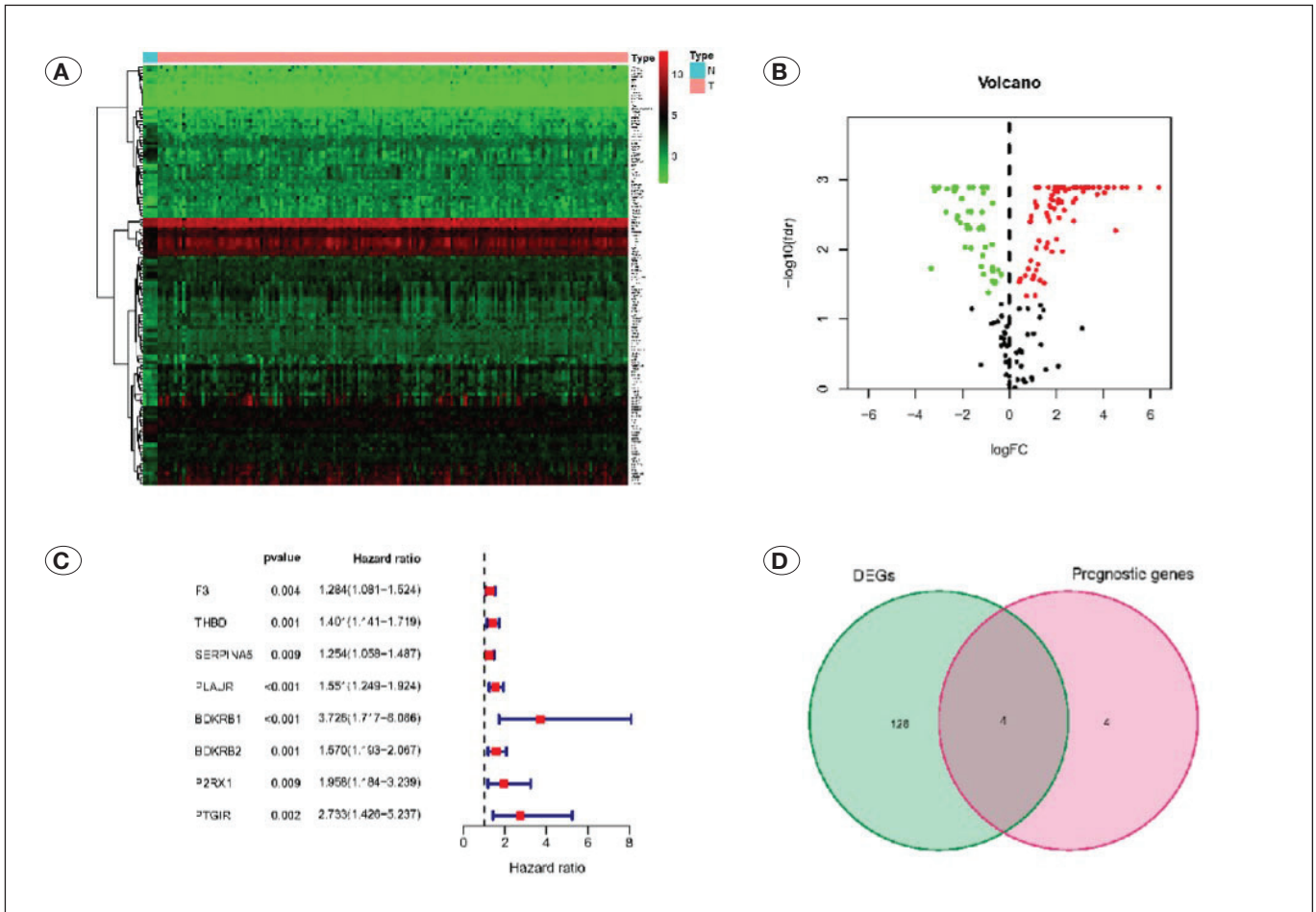


Figure 1: **A)** Heatmap of the expression of coagulation genes between tumor tissues and normal tissues; **B)** Volcano plot of differentially expressed coagulation genes; **C)** Coagulation genes related to prognosis; **D)** Intersection genes.

* 0.1733). The survival analysis showed that the overall survival and progression-free survival of the high-risk group were significantly lower than those of the low-risk group. The ROC curve showed that the AUC values predicted by the coagulation-related model at 1 year, 3 years, and 5 years were 0.730, 0.684, and 0.724, respectively (Figure 2).

Validation of the Coagulation Gene Model

To explore the applicability of the coagulation-related gene model in glioma, TCGA-LGG, and CGGA data were divided into high and low-risk expression groups based on the RS. The total survival, survival state map, and risk score heatmap of the two groups were calculated. Results indicated significantly lower overall survival in the high-risk group, accompanied by a higher mortality rate compared to the low-risk group. The ROC curve showed that the AUC values at 1 year, 3 years, and 5 years in TCGA-LGG data were 0.812, 0.756, and 0.760, respectively. The AUC values predicted by the model at 1 year, 3 years, and 5 years in CGGA data were 0.696, 0.747, and 0.730, respectively. These results suggested the reliability of the gene model (Figure 3, 4).

Immune-related Assessments

PCA was performed on three datasets using the R software package “tsne”. The results showed that the high and low-risk groups were significantly separated. Furthermore, immunoassay data indicated significantly higher levels of immune cells and immune function in the high-risk group compared to the low-risk group. This implied that immunotherapy may have some benefits for GBM (Figure 5, 6).

DISCUSSION

Glioma, as the most common intracranial malignant tumor, exhibits high aggressiveness and recurrence rates. The routine treatments involve surgery combined with postoperative chemoradiotherapy and targeted therapy. However, some patients experience venous thrombosis before and after surgery, which affects the standard treatment process and prolongs the overall treatment duration. Notably, the coagulation process is a systemic mobilization process, and the abnormal activation of intracranial coagulation genes also influences patient prognosis. Glioma cells often exhibit elevated levels of tissue factor (TF), and inhibiting TF through protease activa-

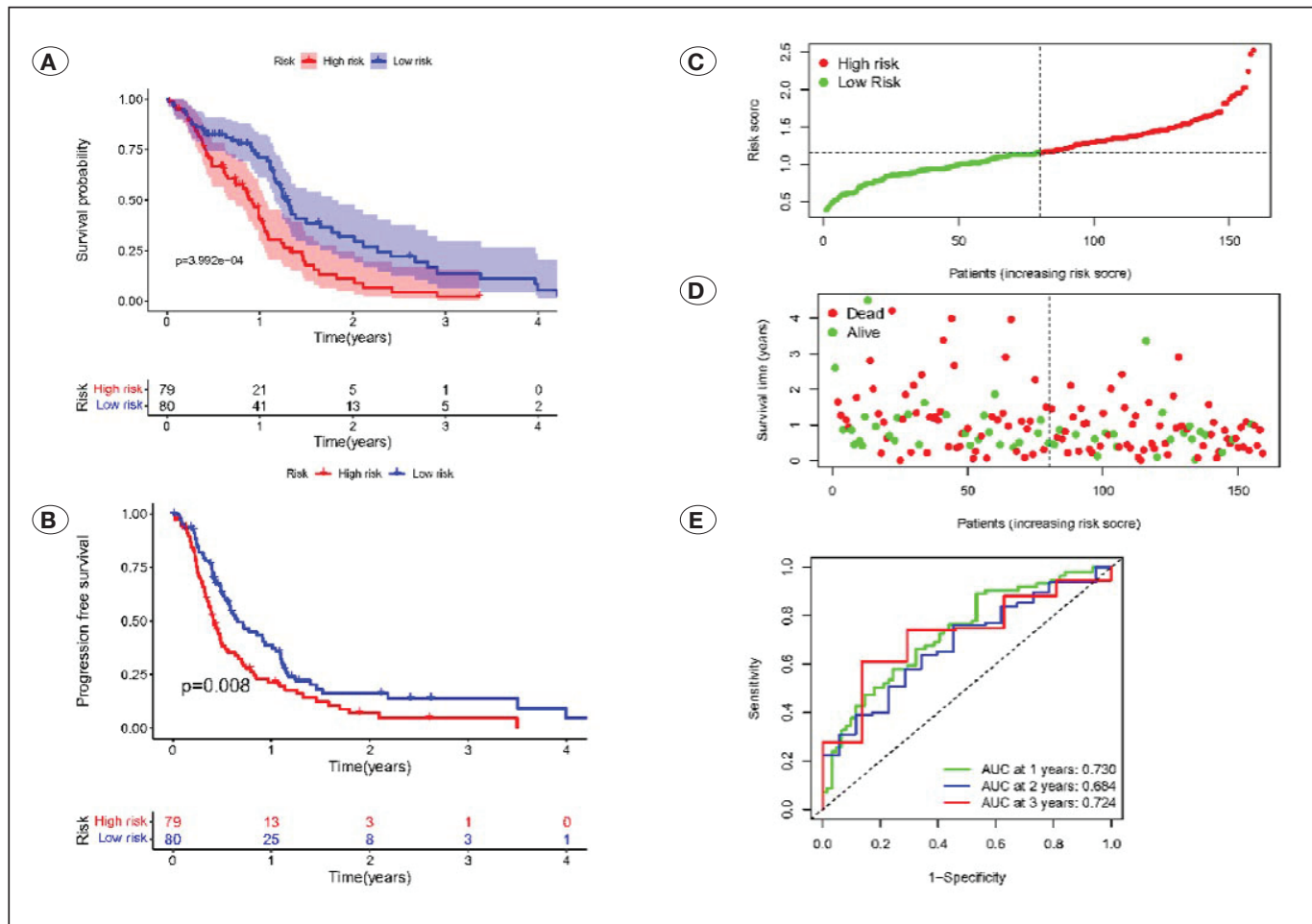


Figure 2: GBM group: **A)** Overall survival between high and low risk expression groups; **B)** Progression-free survival between high and low risk expression groups; **C)** Heatmap of risk score between high and low risk groups; **D)** Survival status between high and low risk groups; **E)** The ROC curves of the coagulation gene model.

tion of the receptor-2 (PAR-2)/ERK axis can effectively hinder tumor cell invasion and infiltration (10).

In this study, the LASSO model was used to calculate the expression of four coagulation-related genes, including SERPINA5, PLAUR, BDKRB1, and PTGIR. SERPINA5, a member of the SERPIN family A5, is a potent inhibitor of serine proteases (such as factor V/VIII) and may cause deficiency of these factors and vWF disease. Moreover, SERPINA5 inactivates other proteases involved in hemostasis and fibrinolysis. Elevated plasma levels of SERPINA5 are a risk factor for venous thrombosis (6,9,20). High expression of SERPINA5 has been reported in gastric cancer, where SERPINA5 inhibits apoptosis and promotes cell cycle progression through the PI3K/AKT/mTOR pathway (7). Furthermore, patients with low-grade gliomas with high expression of SERPINA5 have been associated with shorter overall survival and recurrence-free survival rates (33).

PLAUR, also known as uPAR (urokinase-type plasminogen activator receptor), facilitates the binding of urokinase-type plasminogen activator complex, leading to the conversion of extracellular plasminogen to active plasmin. This process pro-

motes the degradation of the basement membrane, extracellular matrix proteins, and activation of matrix metalloproteinases, thereby contributing to matrix remodelling, invasion, and metastasis of tumor cells (14,24). Meanwhile, PLAUR is highly expressed in many malignant tumors including glioma and plays a critical role in tumor invasion and metastasis. In vitro experiments have demonstrated that inhibiting uPA/PLAUR could reduce the spread of tumor cells (3,13,34).

BDKRB1, the bradykinin receptor B1, binds to bradykinins and plays an important role in the inflammatory response by promoting the release of inflammatory cytokines. Under normal physiological conditions, BDKRB1 is rarely detected in peripheral tissues but can be found in the cerebral cortex (27). Research has demonstrated that bradykinin activates the MEK1-ERK1/2 and NF- κ B pathways by increasing BDKRB1-mediated calcium influx. This activation promotes glioma cell migration and invasion while silencing BDKRB1 shows the opposite effect (31). Additionally, bradykinin has been shown to promote the expression of interleukin-8 through BDKRB1, facilitating glioma cell migration and invasion (16).

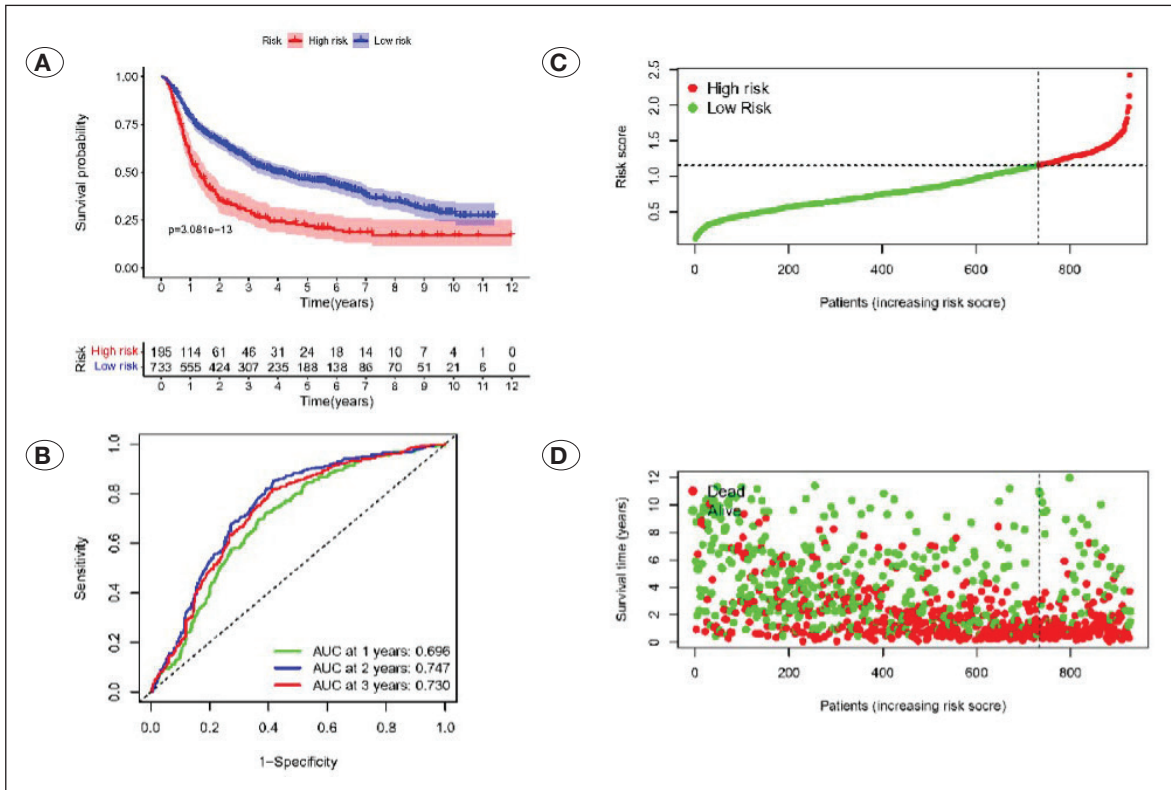


Figure 3: CGGA group: **A)** Overall survival analysis; **B)** The ROC curve; **C)** Heatmap of risk score; **D)** Survival status chart.

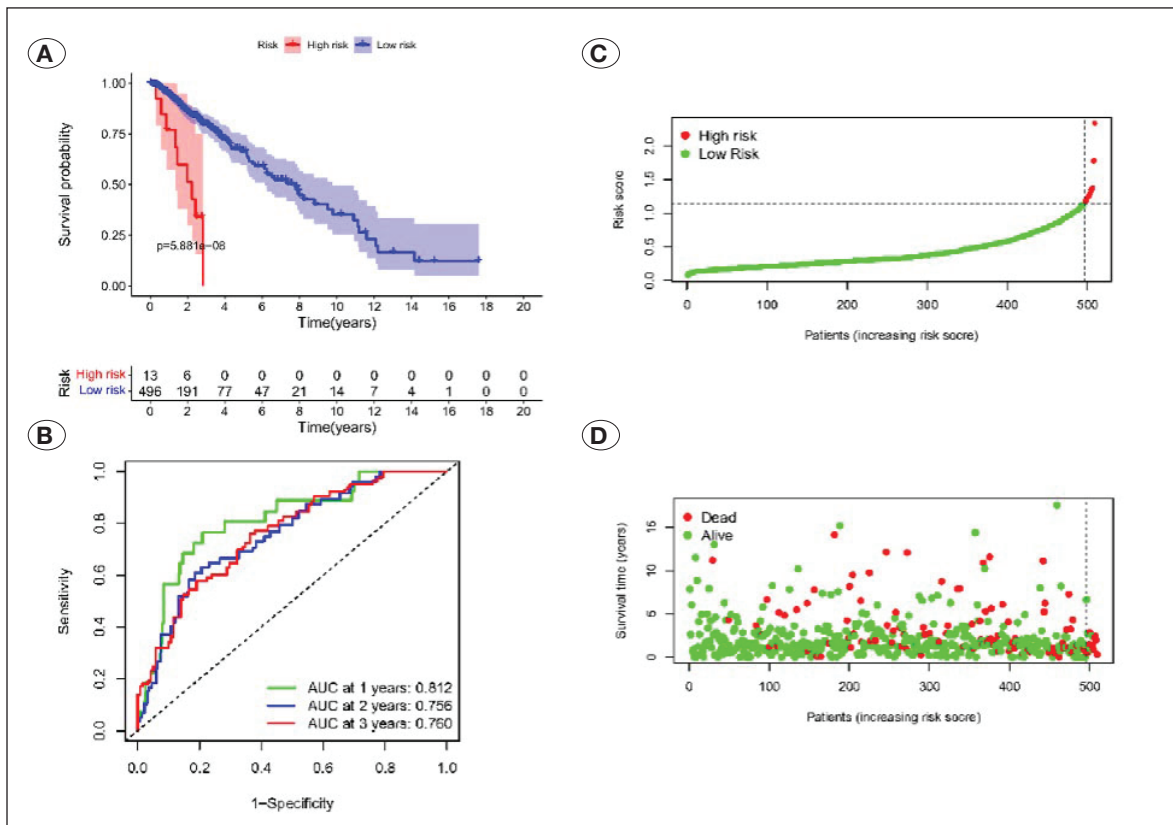


Figure 4: LGG group: **A)** Overall survival analysis; **B)** The ROC curve; **C)** heatmap of risk score; **D)** survival status chart.

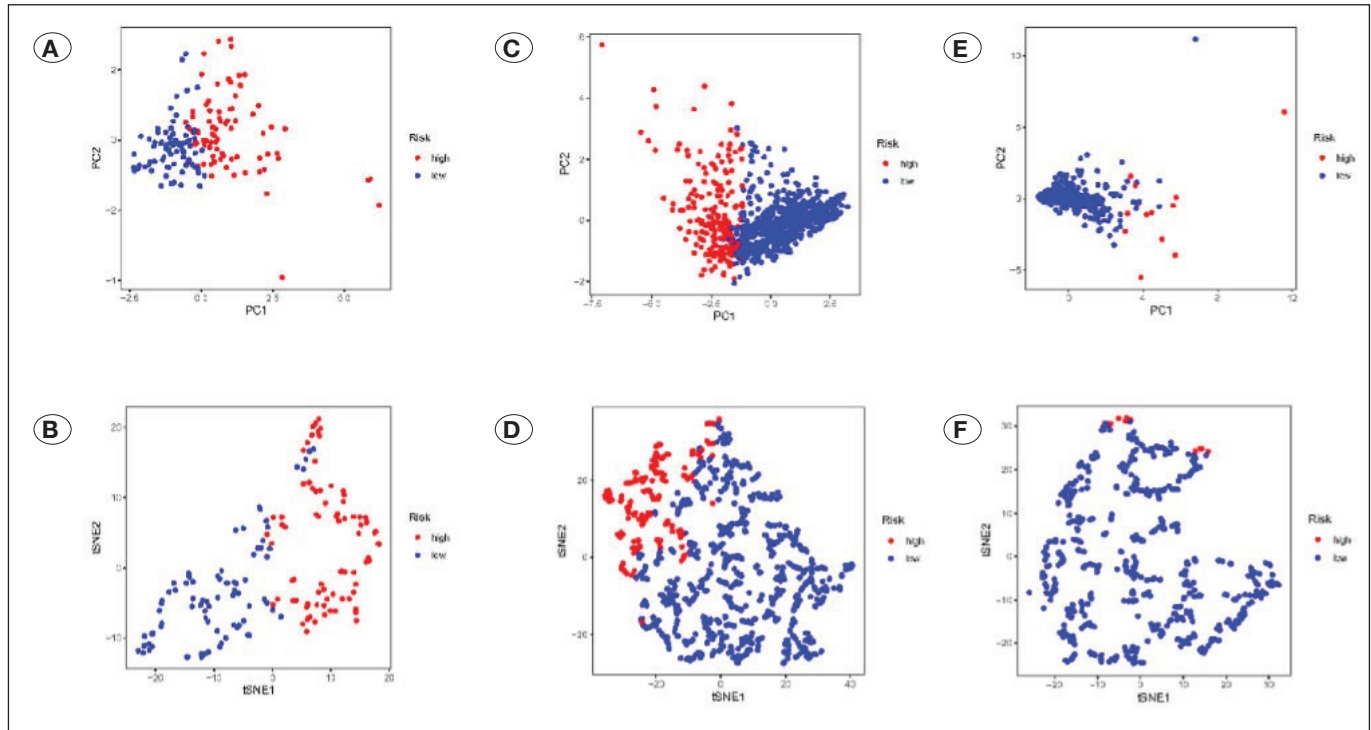


Figure 5: The PCA plots between the three groups. **A, B)** GBM group; **C, D)** CGGA group; **E, F)** LGG group.

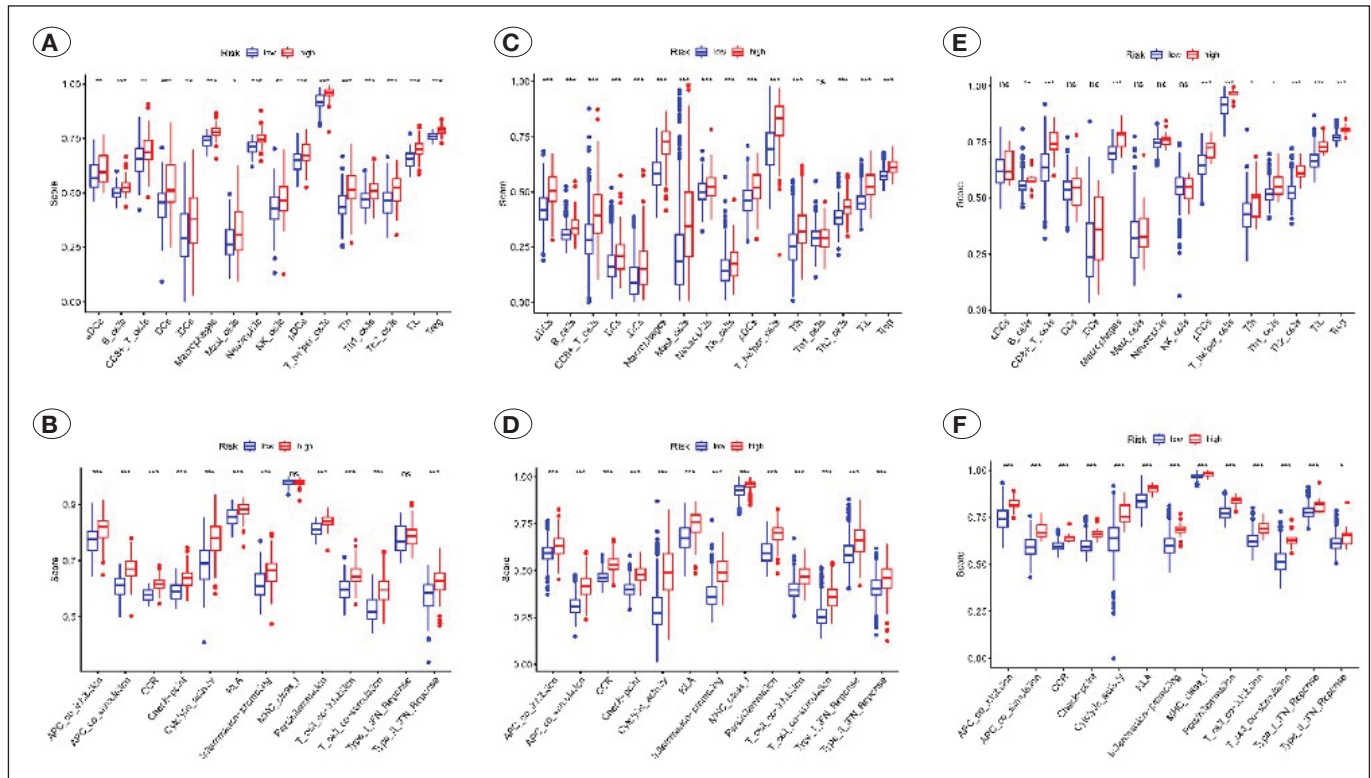


Figure 6: Analysis of immune cells and immune function among the three groups. **A, B)** GBM group; **C, D)** CGGA group; **E, F)** LGG group.

PTGIR, a seven-transmembrane G protein-coupled receptor, is a prostacyclin (PGI₂) binding receptor. This PTGIR and PGI₂ combination activates adenylate cyclase, leading to cyclic adenylate production and influencing the inflammatory response (30). PGI₂-PTGIR contributes to anti-vasodilation, regulation of vascular homeostasis, and enhanced vascular production and cellular protection (2,15). Additionally, the study has shown that PGI₂ facilitates phenotypic switching of tumor-associated macrophages via the PTGIR-cAMP axis, reducing tumor cell adhesion, and increasing tumor cell migration (28).

In this study, an analysis of coagulation-related genes and a prognostic model were conducted in GBM. Survival differences were calculated between the high- and low-risk groups based on the model parameters. The results demonstrated that the high-risk group exhibited higher mortality, shorter overall survival, and shorter progression-free survival. To examine the potential applicability of this gene model in gliomas, the TCGA-LGG and CGGA data were used for verification, and the findings revealed that the high-risk group had shorter overall survival and higher mortality.

Furthermore, PCA demonstrated notable distinctions between the high and low-risk groups. Immune cell analysis revealed the predominance of CD8⁺ T cells, macrophages, neutrophils, and T-helper cells in the high-risk group. Immune function analysis demonstrated significant differences in lower cell function associated with increased inflammatory response, para-inflammation, and checkpoints in the high-risk group. These findings suggested the potential benefits of immunotherapy for glioma patients.

Nonetheless, this study has some limitations. The glioma guidelines (2021) consider molecular typing as an important factor for determining the degree of glioma malignancy. This study, focusing solely on histopathological perspectives for glioma grouping, did not carefully consider IDH, MGMT, and other related genes for classification. Meanwhile, theoretical studies may be limited, and the prognostic model built in this study is based on database analysis, which lacks verification of gene expression and biological effects on glioma through cell and tissue experiments. Lastly, the clinical data is not comprehensive enough to allow for further survival predictions. We hope, in the future, further experimental studies and many clinical cases are put into support the model.

CONCLUSION

This study identified the significant prognostic coagulation-related genes and constructed the four-gene model to distinguish the high and low-risk groups in glioma. The most of AUC values were above 0.70 in 1 year, 3 years, and 5 years, respectively. We highlighted the value of the coagulation-related gene model, providing new insights into the comprehensive mechanisms of glioma. In any case, our current work was forecasting characteristics of coagulation genes in the prognosis and treatment of glioma.

AUTHORSHIP CONTRIBUTION

Study conception and design: MC, JC

Data collection: MC

Analysis and interpretation of results: MC

Draft manuscript preparation: MC

Critical revision of the article: RZG

Other (study supervision, fundings, materials, etc...): MC, JC, RZG

All authors (MC, JC, RZG) reviewed the results and approved the final version of the manuscript.

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