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Original Article

A super-enhancer-related gene signature predicts prognosis and immune microenvironment features in glioma

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Abstract

Glioma is the most frequent malignant tumor in the brain. Super-enhancer (SE) is a class of transcriptional activator, which drives gene expression. SE-related genes (SERGs) affect occurrence and development of several tumors. We explored the predictive role of SERGs in the prognosis and immune features of glioma. A total of 1557 glioma patients were collected from four data sets, including The Cancer Genomic Atlas (TCGA, n = 691), the Chinese Glioma Genomic Atlas (CGGA) array (n = 286), the CGGA sequencing (n = 316), and GSE16011 (n = 264) from Gene Expression Omnibus (GEO) database. SERGs were selected from SEdb (http://www.licpathway.net/sedb), a comprehensive human SE database. Survival analysis and visualization were performed using the R packages survival (v3.3-1) and survminer (v0.4.9). Immune subtype classification was conducted with the ImmuneSubtypeClassifier (v0.1.0) R package. A nomogram was generated using the rms (v6.7-1) package. A risk score model based on 13 super-enhancer-related genes (SERGs) was constructed, demonstrating that patients in the low-risk group had significantly better prognosis. The SERGs signature significantly correlated with age, molecular and immune subtypes, IDH mutation, MTMG promoter methylation, 1p19q co-deletion, and expression of immune checkpoint genes in glioma patients. The SERGs signature could predict the prognosis and immune features of glioma, and SERGs might serve as novel immunotherapy options for glioma.

Keywords: Glioma, Super-enhancer, Prognosis, Immune feature, Methylation.

1. Introduction

Glioma is the most frequent and aggressive primary malignancy in the brain[1]. Approximately 49% of primary malignancies in the central nervous system (CNS) are glioblastoma (GBM), and 30% are lower-grade glioma (LGG)[2]. GBM has the worst prognosis with overall survival (OS) of 15 months, and most patients die from progressive disease[1]. Isocitrate dehydrogenase (IDH) mutation, methylguanine-DNA methyltransferase (MGMT) promoter methylation, and 1p/19q-codeletion are protective factors for the prognosis of glioma patients[3, 4]. Diagnosis of glioma requires tumor biopsy with consideration of histologic and genetic characteristics. Early diagnosis and precise prognosis are essential for the management of glioma patients. Therefore, it is crucial to identify accurate and predictive prognostic biomarkers for gliomas.

Super-enhancer (SE) was first proposed in 2013 as a set of cis-regulatory elements with super transcriptional activation potential to drive the expression of genes that define cell identity[5]. Moreover, SEs can promote the expression of oncogenes in numerous tumors, thereby regulating tumorigenesis and progression[6]. Shang-Xin Liu et al reported that the expression of SOX2 was driven by SE. SOX2 was highly expressed in nasopharyngeal carcinoma and was correlated with poor prognosis. Silencing of SOX2 suppressed tumor growth[7]. SE-driven lncRNA TMEM44-AS1 aggravated glioma progression through binding to SerpinB3 and activating Myc and EGR1/IL-6 signaling pathways [8]. Moreover, subtype-specific SEs have been revealed in neuroblastoma, which were able to define regulatory subtypes and cell identity[9]. SE-related genes (SERGs) may serve as prognostic markers, and have been widely used to construct prognostic models in some tumors, such as breast cancer, hepatocellular carcinoma, and pancreatic cancer[10-12].

In the study, we comprehensively explore the role of SERGs in the prognosis, tumor microenvironment (TME), and immune features in glioma. We constructed and validated a SERGs risk model in predicting prognosis and immune features of 1,557 glioma patients from four data sets, including The Cancer Genomic Atlas (TCGA), the Chinese Glioma Genomic Atlas (CGGA) array, the CGGA sequencing, and GSE16011 from Gene Expression Omnibus (GEO) database.

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2. Materials and methods

2.1. Data collection

A total of 1557 glioma patients were collected from four data sets, including TCGA (n = 691), CGGA array (n = 286), the CGGA sequencing (n = 316), and GSE16011 (n = 264) from GEO database. TCGA GBM data set was downloaded from UCSC Xena (https://xenabrowser.net/datapages/?cohort=GDC%20TCGA%20Glioblastoma%20(GBM)&removeHub=https%3A%2F%2Fxena.treehouse.gi.ucsc.edu%3A443). TCGA LGG data set was downloaded from UCSC Xena (https://xenabrowser.net/datapages/?cohort=GDC%20TCGA%20Lower%20Grade%20Glioma%20(LGG)&removeHub=https%3A%2F%2Fxena.treehouse.gi.ucsc.edu%3A443). CGGA_array (DataSet ID: mRNA-array_301) and CGGA sequencing (DataSet ID: mRNAseq_325) data sets were downloaded from CGGA (http://www.cgga.org.cn/download.jsp). GSE16011 expression matrix was downloaded from GEO database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE16011), and its survival data was achieved from their previously published study[13]. The expression and survival data were cleaned and preprocessed by the tinyarray (v2.3.1) R package.

2.2. SERGs signature construction and validation

A total of 1,126 SERGs were downloaded from SERGs database SEdb (http://www.licpathway.net/sedb) using data from GBM_Sample_02_1175 and GBM_Sample_02_1176 samples. These genes were intersected with the expression matrix of the four cohorts, followed by Kaplan-Meier (KM) analysis and Univariate Cox regression analysis with survival (v3.3-1) and survminer (v0.4.9) R packages to screen SERGs correlated with OS. A cutoff p-value of 0.001 was used. The least absolute shrinkage and selection operator (LASSO) Cox regression analysis and stepwise variable selection procedure were conducted using glmnet (v4.1-8) and My.stepwise (v0.1.0) R packages respectively. Finally, the multivariate Cox regression analysis was used to construct the SERGs risk model using TCGA data set, and the remaining three cohorts were used as validation data sets.

2.3. Time-dependent receiver operating characteristic (ROC)

The timeROC (v0.4) R package was utilized to estimate the 1-, 3-, and 5-year outcome of patients by using the timeROC function to calculate the area under curve (AUC) and draw time-dependent ROC curves.

2.4. Gene set enrichment analysis

The Gene Ontology (GO) biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were downloaded from C2: curated gene sets of the Molecular Signatures Database (MSigDB) by using the msigdbr (v7.5.1) R package, and scored using the GSVA (v1.46.0) R package. Remarkably different GO terms and KEGG pathways between high- and low-risk glioma patients were shown in heat map with pheatmap (v1.0.12) R package.

2.5. Immune subtype analysis

According to previously published study, tumor samples were sub-grouped into six subtypes: C1~C6 (Wound Healing, IFN-γ Dominant, Inflammatory, Lymphocyte Depleted, Immunologically Quiet, and TGF-β Dominant respectively)[14]. The ImmuneSubtypeClassifier (v0.1.0) R package was applied to divide tumor samples into immune subgroups.

2.6. Nomogram and Decline Curve Analysis (DCA)

The rms (v6.6-0) R package was used to assess the total risk considering risk score, IDH mutation, age, gender, grade, MTMG promoter methylation, and 1p/19q-codeletion status. The ggDCA (v1.2) R package was used to assess the benefit of nomogram compared with other risk factors via DCA.

2.7. Figure and plot generation

jvenn (http://jvenn.toulouse.inra.fr/app/example.html), an interactive Venn diagram viewer, was used to drawn the venn plot[15]. The survminer (v0.4.9) R package was used for forest plot and survival KM plot. The ggbeeswarm (v0.7.2) R package was used for beeswarm plot. The other plots were drawn by pheatmap (v1.0.12) and ggplot2 (v3.4.3) R packages.

3. Results

3.1. Construction of SERGs risk model

The work workflow of this study is shown in Figure 1. A total of 1,126 SERGs were extracted from the data sets of two glioma patients in the SE database SEdb. These SERGs were intersected with the expression matrix of four independent cohorts, and the correlation between intersected SERGs and survival of glioma patients was analyzed using KM analysis and Univariate Cox regression analysis to screen SERGs correlated with OS. A total of 109 prognosis-related SERGs were further processed by LASSO Cox regression analysis and stepwise variable selection procedure (Figure 2A-C), and 13 SERGs were eventually selected to construct risk model using multivariate Cox regression analysis (Figure 2D).

3.2. Evaluation of SERGs risk signature

The SERGs risk score was calculated as following: risk score = (0.5346596 × CD58) + (-1.0720239 × ARHGAP12) + (0.2988874 × EPHB2) + (0.2807450 × P2RX7) + (-0.5792164 × HDDC2) + (0.8381438 × TGIF1) + (-0.4469411 × MKNK2) + (-0.3374566 × NOL4) + (0.3447619 × RNF112) + (0.2395863 × CTSB) + (0.6181895 × ATP6V0A1) + (-0.3495064 × MYH9) + (0.4345116 × FNDC3B). The time-dependent ROC curves

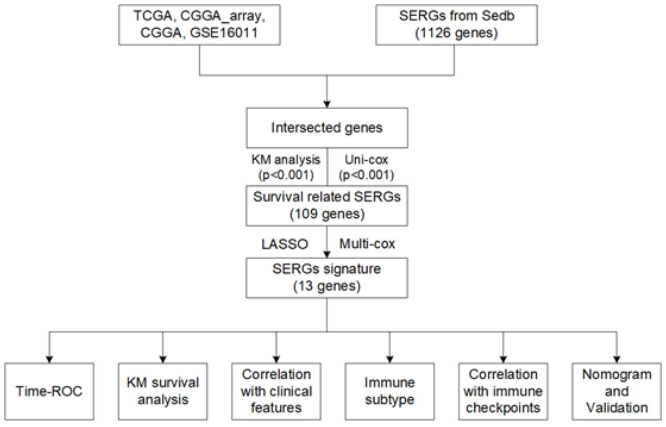

Fig. 1. Workflow of this study.

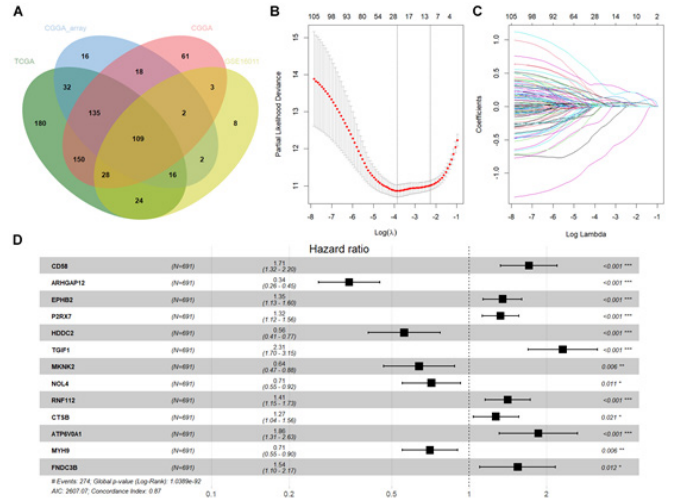

Fig. 2. Construction of risk model using thirteen SERGs. (A) Intersected SERGs correlated with OS of glioma patients analyzed using KM survival analysis and univariable Cox regression analysis from four independent cohorts. (B, C) The LASSO coefficient profiles were generated by 109 prognostic SERGs. A total of 24 SERGs were selected using the log(λ).min as cutoff value, for stepwise variable selection process with My.stepwise (v0.1.0) R package to achieve the best candidates. (D) Multivariate Cox regression analysis of the thirteen SERGs of glioma patients in TCGA cohort.

were drawn for all four cohorts, and the results showed that the SERGs risk model had good performance in the prediction of 3-year survival across all four cohorts with AUC >0.8 (Figure 3A). According to the median risk score, glioma patients were grouped into high- and low-risk groups. The KM plots showed that low-risk patients had better prognosis than high-risk patients across all four cohorts (Fig. 3B).

The risk score and outcome distribution of glioma patients showed that alive patients were mainly enriched in low-risk group, and the expression of the selected thirteen SERGs was consistent across all four cohorts (Figure 4), indicating an accurate prediction potential of SERGs risk signature for glioma.

3.3. Correlation between SERGs signature and clinical features

Since the SERGs signature had remarkable correlation with prognosis of glioma patients and showed accurate prediction potential, we further investigated the association between the SERGs signature and clinical features. GBM patients had higher risk scores than LGG patients (Figure 5A), indicating that SERGs score correlated with grade of glioma. Low-risk LGG patients had better prognosis than high-risk LGG patients in most cohorts, while this was not significant in GBM patients (Figure 5B), suggesting that the SERGs signature may have more accurate prediction potential in LGG than GBM patients.

However, the SERGs risk score showed no significant difference between males and females (Figure 6A). Patients aged less than 60 years old had lower risk scores than patients older than 60 years old (Figure 6B). We further explored the prognostic potential of the SERGs signature in glioma patients aged less than 60 years old, and the results showed that low-risk glioma patients had better prognosis than high-risk glioma patients in patients aged less than 60 years old across all four cohorts (Figure 6C).

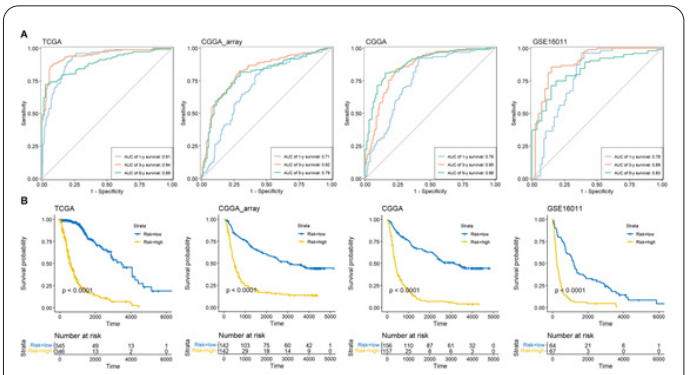

Fig. 3. Evaluation of SERGs risk signature. (A) The time-dependent ROC curves of SERGs risk signature were drawn with the timeROC R package. (B) The KM plots of glioma patients were grouped into high- and low-risk groups.

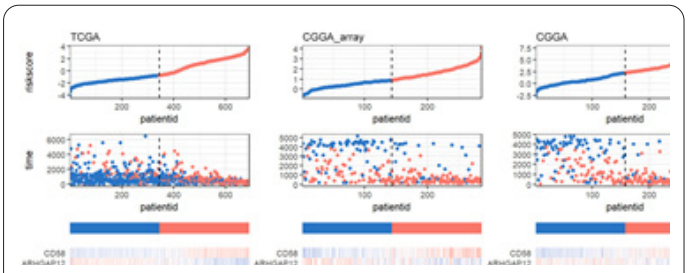

Fig. 4. Risk score and outcome distribution of glioma patients.

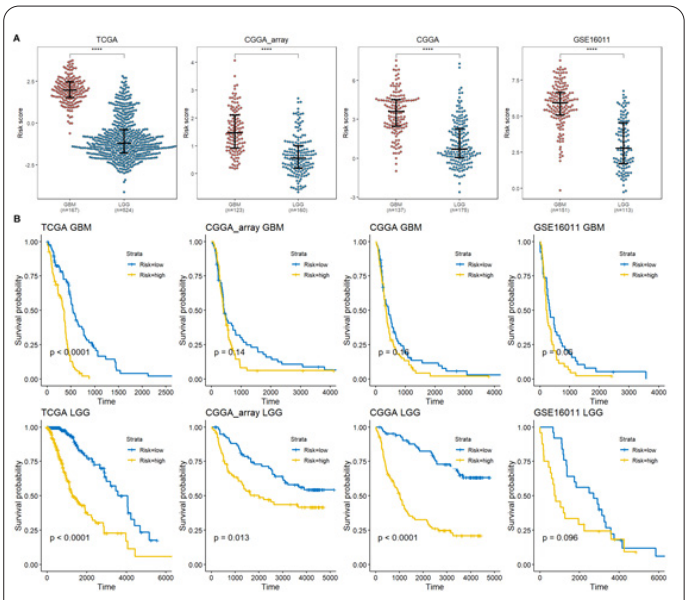

Fig. 5. Correlation between the SERGs signature and grade. (A) The beeswarm plot showed GMB patients had higher risk score than LGG patients. (B) The KM survival plots showed that low-risk LGG patients had better prognosis than high-risk LGG patients.

Since IDH mutation, MGMT promoter methylation, and 1p/19q-codeletion are correlated with the prognosis of glioma patients, we also explored their correlation with SERGs risk scores. Wild-type IDH, unmethylated MGMT promoter, and 1p19q non-codeletion patients had higher SERGs risk scores in TCGA cohort (Figure 7A), and similar results were observed in CGGA cohort (Figure 7B). These results suggest that the SERGs signature was remarkably associated with the clinicopathological features of glioma patients.

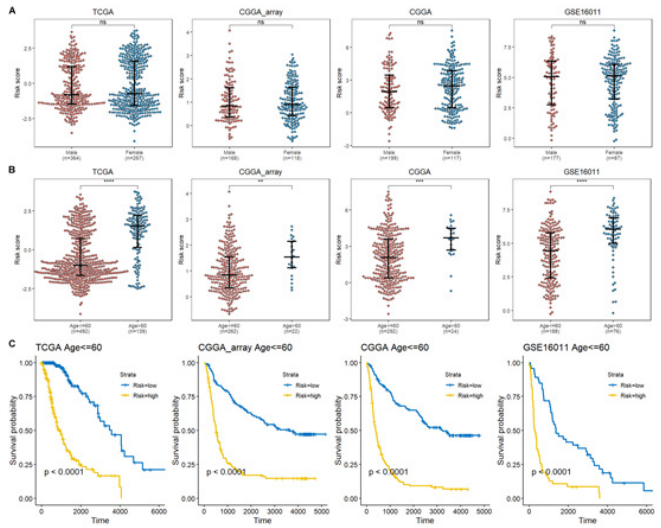

Fig. 6. Correlation between the SERGs signature and gender and age. (A) The beeswarm plot showed no significant difference in risk score between male and female glioma patients. (B) The beeswarm plot showed that patients aged less than 60 years old had lower risk scores than those aged over 60 years old. (C) The KM plots showed that low-risk patients had better prognoses than high-risk patients in patients aged less than 60 years old.

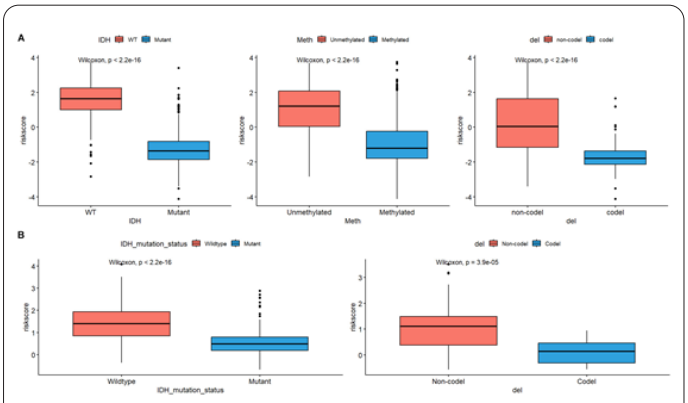

Fig. 7. Correlation between SERGs risk scores and IDH mutation, MGMT promoter methylation, and 1p/19q-codeletion. (A) The boxplot revealed the difference of the SERGs risk scores between wildtype IDH (WT) and mutant, unmethylated and methylated MGMT promoter, 1p19q codeletion and non-codeletion glioma patients in TCGA cohort. (D) The boxplot revealed the difference of the SERGs risk scores between wildtype IDH and mutant, 1p19q codeletion and non-codeletion glioma patients in CGGA cohort.

3.4. Gene set variation in different patients grouped by SERGs risk score

Gene set variation sometimes provides more comprehensive information than single gene differences. GSVA was utilized to compare the functional differences between low- and high-risk glioma patients concerning the KEGG and GO terms from the Msigdb database. The high-risk patients enriched KEGG pathways included base excision repair, mismatch repair, DNA replication, and cell cycle (Figure 8A). The high-risk patients enriched GO terms included mitotic spindle midzone assembly, chromatin organization, programmed cell death, and dTMP metabolic process (Figure 8B). These results suggest that the SERGs signature may correlated with the expression of genes involved in cell cycle.

3.5. Correlation between the SERGs signature and immune features

We further explored the correlation between the SERGs signature and immune features in glioma patients. The immune subtype distribution in all four cohorts as analyzed using the ImmuneSubtypeClassifier (v0.1.0) R package. The lymphocyte-depleted C4 subtype which represented a high M2 response, made the majority in high-risk group, while the immunologically quiet C5 subtype accounted for the majority in low-risk group in three out of four cohorts (Figure 9). These data indicate that high SERGs risk score represents immunosuppressive status in glioma patients.

The expression of immune checkpoints was widely used as indicator of the response to immunotherapy. We further explored the expression of these genes in the two risk groups. Most immune checkpoints showed signifi-

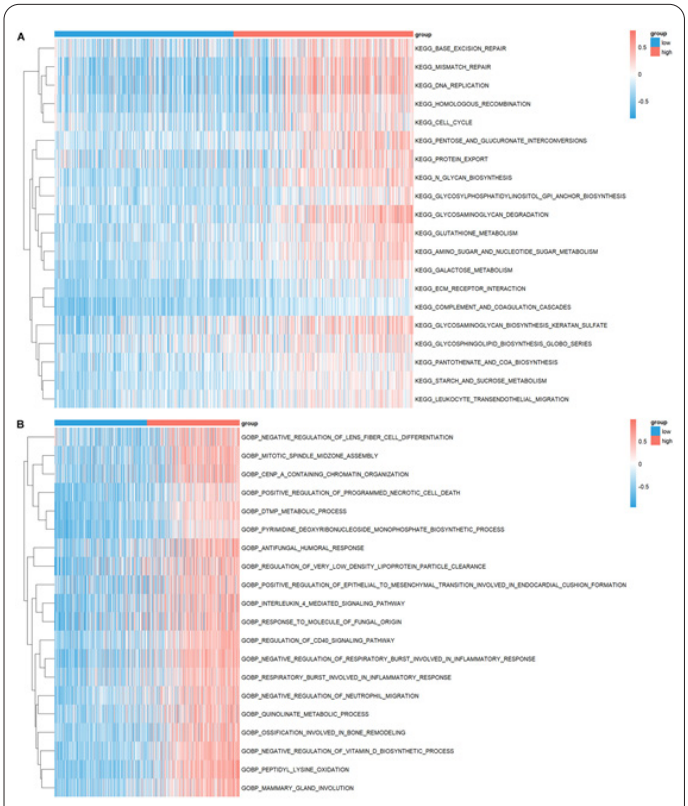

Fig. 8. Functional annotation of the SERGs signature. (A) The top 20 KEGG pathways enriched in high-risk glioma patients in TCGA cohort. (B) The top 20 GO terms enriched in high-risk glioma patients in TCGA cohort.

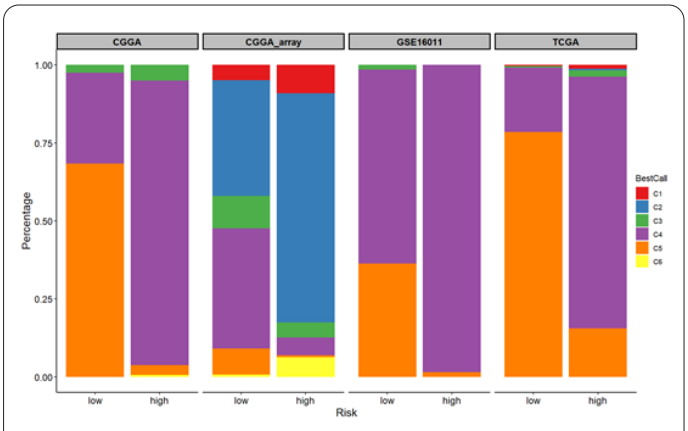

Fig. 9. Correlation between the SERGs signature and immune features. Distribution of immune subtypes across all four cohorts.

cantly different expressions between the two risk groups (Figure 10A). The SERGs risk score was positively correlated with PDCD1 (PD-1) and CD274 (PD-L1) in three out of the four cohorts (Figure 10B). These results suggest that the SERGs risk signature may predict the immunotherapy response of glioma patients.

3.6. Establishment of a predictive nomogram

Univariate and multivariate Cox regression analyses were used to select potential risk factors correlated with OS (Figure 11A, B). The SERGs risk score was remarkably correlated with OS in both univariate and multivariate Cox regression analyses. To make the SERGs risk model useful in clinic, a nomogram was established including risk score, IDH mutation, age, gender, grade, MGMT methylation, and 1p19q co-deletion in the TCGA cohort (Figure 11C). The SERGs risk score had the most weight as depicted in the nomogram, followed by age. The calibration plot showed consensus between predicted 1-, 3-, and 5-year OS and actual survival (Figure 11D). The DCA curves clarified that the nomogram predicted the OS with more sensitivity compared with other clinical factors (Figure 11E).

4. Discussion

SEs are cis-regulatory elements with strong transcriptional activation capacity and play vital roles in defining cell identity. SEs have indispensable impact on tumorigenesis and progression by up-regulating the expression level of oncogenes. An increasing number of studies suggested that SERGs signature could be able to predict prognosis of numerous tumors, including breast cancer, hepatocellular carcinoma, and pancreatic cancer[10-12]. Therefore, we conjectured that SERGs might be a predicting factor for glioma. Furthermore, we also investigated the correlation between SERGs and immune features of glioma patients. In this study, a novel 13-gene risk model was constructed to explore the predicting performance of SERGs in the prognosis, TME, and immune features in glioma. We comprehensively investigated the prediction potential of this risk model and highlighted the prospect of SEGGs for immunotherapy in glioma patients.

We extracted a total of 1126 SERGs from Sedb database. Then, KM analysis and Univariate Cox regression analysis were applied to select 109 OS-related coexisting genes among TCGA, CGGA, CGGA-array and GSE16011 date sets. Finally, we identified 13 SERGs according to Multivariate Cox regression analysis for the purpose of establishing a prognostic model. The SERGs signature was consisted of CD58, ARHGAP12, EPHB2, P2RX7, HDDC2, TGIF1, MKNK2, NOL4, RNF112, CTSB, ATP6V0A1, MYH9, and FNDC3B. Among them, CD58, EPHB2, P2RX7, TGIF1, RNF112, CTSB, ATP6V0A1, and FNDC3B were risky genes, which are relevant to adverse prognosis for glioma patients in our study. Whereas ARHGAP12, HDDC2, MKNK2, NOL4, and MYH9 are associated with promising prognoses as protective factors.

Wu et al. demonstrated that CD58 was one of the survival-related immunosuppressive factors in LGG patients, significantly correlated with inhibitory checkpoint genes responsible for the immune escape in LGG[16]. EPHB2 was an oncogenic receptor, and overexpressing EPHB2 promoted the invasion potential of glioma cells, while EPHB2 antibody significantly declined the migration and invasion of glioblastomas[17]. P2RX7 contributed to glucose metabolism, thereby facilitating the cell proliferation, migration, invasion and development of tumors, such as osteosarcoma[18]. However, the biological functions of P2RX7 in glioma progression were seldom reported. The expression level of TGIF1 was positively correlated with proliferation and invasion of glioma cells, and TGIF1

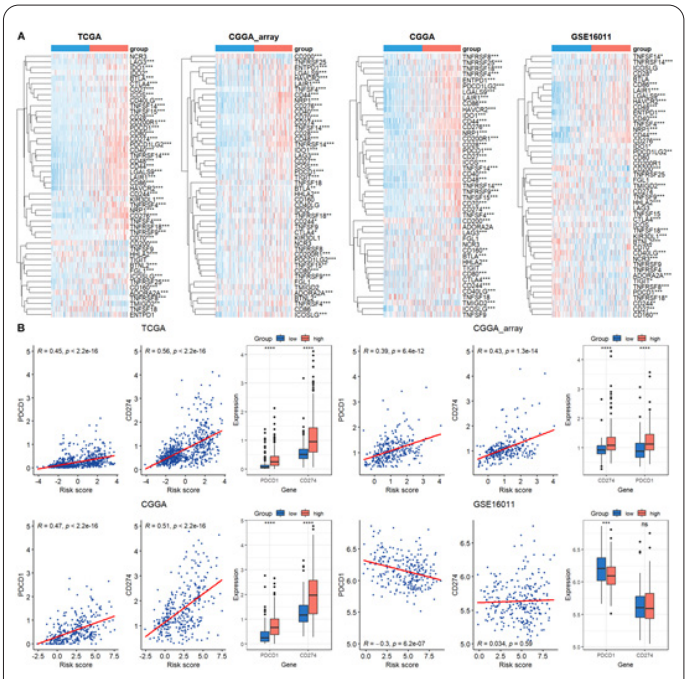

Fig. 10. Correlation between the SERGs signature and immune checkpoints. (A) Heat map showed the expression of immune checkpoints between two groups. (B) Correlation between SERGs risk score and expression of PDCD1 and CD274. ***p<0.001, ****p<0.0001.

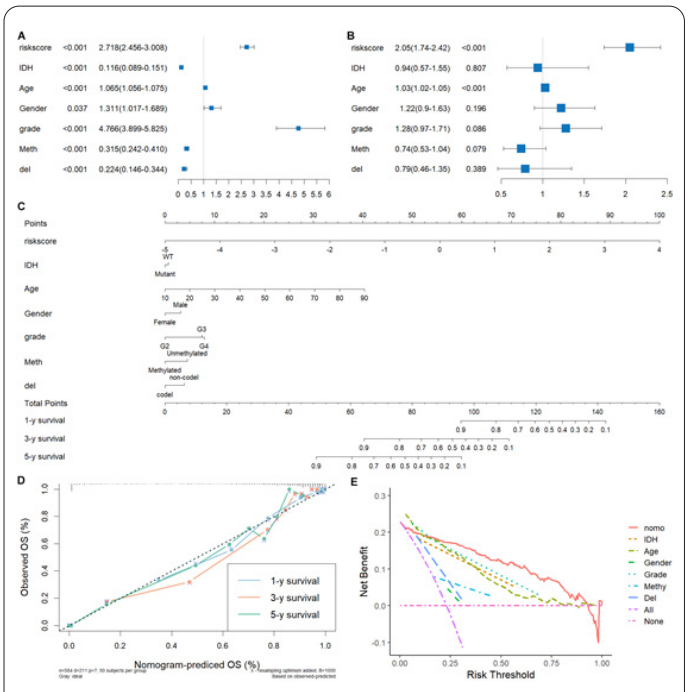

Fig. 11. Establishment of a predictive nomogram. (A, B) Univariate and multivariate Cox regression analyses of the SERGs risk score and clinical factors in predicting the prognosis of glioma patients. (C) A nomogram was constructed based on the SERGs risk scores and clinical factors in TCGA cohort. (D) Calibration plot of the nomogram in TCGA cohort. (E) DCA curve of the nomogram, IDH, age, gender, grade, MGMT methylation, and 1p19q co-deletion for glioma patients in TCGA cohort.

overexpression indicated shorter OS time in glioma patients[19]. RNF112 was a member of RING finger protein family and enriched in brain. RNF112 not only sustained the structure and functions of brain, but also decreased the brain injury which was derived from intracerebral hemorrhage[20, 21]. CTSB was remarkably upregulated in HGG and positively related to the levels of glioma-infiltrating immune cells (tumor-associated macrophages, myeloid-derived suppressor cells, regulatory T cells), leading to immunosuppression and therapeutic resistance of gliomas, revealing CTSB may be a promising biomarker and potential target for gliomas[22]. ATP6V0A1 was a subunit in the V-ATPase and controlled the pathway of proton translocation. ATP6V0A1 mutations caused lysosomal and autophagic dysfunction in neurodevelopmental disorders, suggesting the essential role of ATP6V0A1 in brain development[23]. The FNDC3B expression was significantly correlated with immune checkpoint genes, especially B7-H3, which acted as a suppressive factor for T-cell activities. Down-regulating the expression of FNDC3B may be served as an immune-related treatment for gliomas[24]. Although ARHGAP12 was a protective factor in our research, it was over-expressed and stimulated the tumor migration in Gastric Cancer[25] and Nasopharyngeal carcinoma[26]. HDDC2 was related to the maintenance of pluripotency in human cells and interfered with the process of neural differentiation[27]. MKNK2 was one of the downstream effectors in MAPK-signaling pathway and regulated the protein synthesis process. The higher MKNK2 expression was reported in glioblastoma multiforme compared with other subtypes of glioma, and MKNK2 inhibition presented an antiproliferative effect in glioblastoma cells[28]. NOL4 has played tumor suppressive function and signaled a favourable prognosis in hepatocellular carcinoma according to a recent study[29]. By contrast, NOL4 exhibited positive correlation with poor prognosis of Endometrial cancer as an immune-infiltrating related gene[30]. Several studies argued that MYH9 was a risk gene, increasing the proliferation and chemoradiotherapy resistance of glioma cells, leading to an unfavorable prognosis for patients with glioma[31]. This was contrary to our exploration, and further research was required to verify the role of MYH9 in glioma.

The above-mentioned studies supported that majority of 13 genes may affect the occurrence, progression and immunological condition of tumor cells. Subsequently, we established a SERGs risk model using the 13 genes, which successfully differentiated the immune subtypes and molecular subtypes of glioma. The time-dependent ROC analysis indicated that SERGs signature had the best performance in 3-year survival prediction for glioma patients in TCGA cohort with the largest AUC value of 0.94. Additionally, the glioma patients in four databases were divided into two risk groups on the basis of median risk score, and KM analysis illustrated that the risk score was negatively correlated with favorable OS.

Immune subtypes were closely linked to prognosis, immune-modulatory, and tumor immune environment in malignant tumors. We conducted immune analysis in different groups and found that the largest proportion of glioma samples were C4 subtypes in high-risk group. In the meanwhile, the most of samples in low-risk group were C5 subtypes. The C4 subtype means the unfavorable prognosis in glioma[32]. This confirmed the prediction potential of SERGs signature in immune features and prognosis for glioma patients. Moreover, we also found that immune checkpoint genes were differentially expressed in two risk groups. PDCD1 and CD274 were up-regulated in high-risk group and exhibited positive correlation with SERGs risk score. These results suggest that SERGs might serve as novel immunotherapy targets for glioma.

We further constructed a predictive nomogram in combination of risk score, IDH mutation, age, gender, grade, MTMG promoter methylation, and 1p/19q-codeletion status. The results demonstrated that SERGs risk score was the most sensitive factor relating to OS. Therefore, the SERGs signature could accurately predict the prognosis of glioma patients.

Our current work provided evidence for targeting SERGs in immunotherapy and prognosis for gliomas. However, several limitations still needed to be resolved in this study. Firstly, we analyzed the functions of SERGs signature utilizing publicly available databases, subsequent validation experiments based on silencing the 13-gene should be conducted to confirm the specific mechanism of SERGs in gliomas. Secondly, the correlations of 13 genes with each other need further investigation. Thirdly, the accuracy of this risk model in GBM patients remains to be improved.

In this study, we systematically identified and validated a novel super-enhancer-related gene (SERGs) signature that robustly predicts prognosis and immune microenvironment features in glioma patients. By integrating transcriptomic and clinical data from four large, independent cohorts encompassing 1,557 glioma patients, we constructed a 13-gene SERGs-based risk model with high predictive accuracy for overall survival. The model was consistently validated across all cohorts, demonstrating its reliability and generalizability. Our findings reveal that the SERGs signature is significantly associated with key clinicopathological features, including tumor grade, age, IDH mutation status, MGMT promoter methylation, and 1p/19q co-deletion. Importantly, the risk score derived from the SERGs model stratified patients into high- and low-risk groups with distinct survival outcomes, particularly among lower-grade glioma patients. Functional enrichment analyses indicated that high-risk patients exhibit upregulation of cell cycle and DNA repair pathways, suggesting a link between super-enhancer activity and proliferative tumor phenotypes. Furthermore, the SERGs signature was closely correlated with immune subtypes and the expression of immune checkpoint genes, implying a role in shaping the tumor immune microenvironment and potentially influencing immunotherapy responses. We also developed a clinically applicable nomogram incorporating the SERGs risk score and established prognostic factors, which outperformed traditional clinical variables in predicting patient outcomes. Collectively, our study highlights the prognostic and immunological relevance of SERGs in glioma and provides a robust molecular tool for risk stratification and personalized clinical management. These results also suggest that SERGs may serve as promising biomarkers and therapeutic targets, paving the way for improved prognostic assessment and the development of novel immunotherapeutic strategies in glioma.

Abbreviations

CNS (central nervous system); GBM (glioblastoma);

LGG (lower-grade glioma); OS (overall survival); IDH (isocitrate dehydrogenase); MGMT (methylguanine-DNA methyltransferase); SE (super-enhancer); SERGs (SE related genes); TME (tumor microenvironment); TCGA (The Cancer Genomic Atlas); CGGA (The Chinese Glioma Genome Atlas); GEO (Gene Expression Omnibus); KM analysis (Kaplan-Meier analysis); LASSO (the least absolute shrinkage and selection operator); ROC (receiver operating characteristic); AUC (the area under curve); GO (Gene Ontology); KEGG (Kyoto Encyclopedia of Genes and Genomes); DCA (Decline Curve Analysis).

Availability of data and materials

The datasets used during this study can be downloaded from public databases including TCGA, CGGA, and GEO.
TCGA-LGG: https://portal.gdc.cancer.gov/projects/TCGA-LGG
TCGA-GBM: https://portal.gdc.cancer.gov/projects/TCGA-GBM
CGGA (mRNAseq_325): http://www.cgga.org.cn/download?file=download/20220620/CGGA.mRNAseq_325.Read_Counts-genes.20220620.txt.zip&type=mRNAseq_325_counts&time=20220620
CGGA_array (mRNA-array_301): http://www.cgga.org.cn/download?file=download/20200506/CGGA.mRNA_array_301_gene_level.20200506.txt.zip&type=mRNA_array_301_gene_level&time=20200506
GSE16011: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE16011

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Contributions

Daoyuan Yue: Investigation. **Xiong Wang:** Writing – original draft, Visualization, Validation, Investigation. **Bin Luo:** Investigation, Conceptualization. **Huijun Li:** Data curation, Methodology. **Yibadaiti Tulufu:** Data curation, Methodology.

Ethics declarations

Ethics approval and consent to participate
Not applicable.

Competing interests

The authors declare no competing interests.

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