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Construction and evaluation of different glioblastoma prognosis scores based on gene expression databases

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ABSTRACT

Introduction: Glioblastoma (GBM) is the most common malignant brain tumor, and the prognosis of GBM pa-tients is unfavorable. More studies are needed to develop new prognostic tools for predicting GBM patients' prognosis. This study aims to construct gene-risk score (GRS) models based on gene expression databases.

Methods: Genomic data of GBM were downloaded from the CGGA, TCGA, MYO, and CPTAC. Patients were divided into two groups with overall survival (OS) of more or less than 15 months. Top 31 genes from our previous study and clinical data such as age, gender, and IDH wildtype/mutant were used to develop two GRS models. Cox methods in SPSS v26 were applied in this study.

Results: A total of 551 (334 male, mean age 55.5 ± 13.3 years) cases were used. Four-gene (TGFB1, CCL2, CD274, and TNFRSF1A; from the combination of four databases) and eight-gene (EGFR, TGFB1, SPP1, AGT, TNFRSF1A, CDK1, FOXO3, and CEP55; from CGGA) risk scores were developed. Two models could separate OS samples into high and low-risk groups, and AUCs of 0.984 and, 0.998 were achieved that showed excellent discriminating power at the training set (all: $p < 0.0001$). For the 8-GRS model, the OS of cases in the high-risk group was poorer than that in the low-risk group when used on another's datasets at the validation set, however, it was not significant.

Conclusion: Four- and eight-gene prognostic signatures were identified and constructed to predict OS in GBM patients. This study may provide innovative insights into the treatment of GBM.

Keywords:
GBM
Gene expression
Prognostic model
Gene risk score

Introduction

Glioblastoma (GBM) is an aggressive brain tumor in children and adults that arises from the glial cells of the central nervous system (CNS). These tumors are diagnosed in about 48.6% of malignant CNS tumors and are significantly more common in elderly patients (Grochans et al., 2022). At present, the main treatment strategies for GBMs are surgery and chemoradiotherapy, but,

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the median overall survival (OS) of GBM patients was 15 months (Rong et al., 2022). Hence, new therapeutic targets/strategies and precision medicine are highly desired to improve GBM clinical outcomes.

A comparatively short survival time was observed in some GBM patients, while others showed a relatively better outcome. To better understand these patients, the latest fifth edition of the World Health Organization (WHO) classification of the central nervous system (CNS) tumors (WHO CNS 5 classification) was presented to classify GBM patients, however, it could not fully reflect the characteristics and clinical prognosis of GBM (Louis et al., 2021). Further novel molecular markers are still urgently needed to clarify the mechanisms or improve the prognosis of GBM (Micheletti et al., 2023).

It significantly improves the clinical outcome of GBM patients by exploring new predictive markers and models, recognizing high-risk cases, and providing precision medicine approaches to diagnosing and managing these patients. In recent years, based on the gene expression profiles found from the database search, many investigators have created prognostic gene-risk score (GRS) models in GBM through various bioinformatic analysis options (Zhang et al., 2023). Some studies have already assessed the use of gene expression signatures alone or in combination with clinical data as an enhancement for predicting patient survival risk (Prasad et al., 2020; Cao et al., 2019; Cheng et al., 2019; Hsu et al., 2019; Wang et al., 2019; Zuo et al., 2019; Yin et al., 2019). Currently, to predict overall survival in GBM patients, there is no consensus on the best model specification to use in clinical practice yet nor the best gene panel because each study area is unique (Cao et al., 2019).

In this study, we first downloaded gene expression profiles and corresponding clinical data of GBM patients from four public databases. Then, based on 31 genes selected from our previous study (Azimi et al., 2024), two GRS models were established to assess the 15-month survival prediction and validated these in the other GBM cohorts. Our findings will help the understanding of clinical prognostic outcomes of overall survival in GBM patients.

Material and methods

Data preprocessing

Publicly available gene expression for GBM patients were downloaded from four databases: The Cancer Genome Atlas (TCGA) (http://xena.ucsc.edu/), Chinese Glioma Genome Atlas (CGGA) (www.cgga.org.cn), Clinical Proteomic Tumor Analysis Consortium (CPTAC) (https://portal.gdc.cancer.gov/) and Mayo Clinic Brain Tumor Patient-Derived Xenograft National Resource (MAYO-PDX) (Vaubel et al., 2020) cohorts, including 165, 225, 99, and 63 primary GBM samples, respectively. Clinical information in the datasets included age, gender, overall survival, and isocitrate dehydrogenase (IDH) mutation status. Some cases with unavailable or unclear clinical information were removed.

Gene selection for risk score model

In our previous study, a systematic literature search with bioinformatic analysis was executed to find top gene expression for predicting GBM overall survival outcomes (Azimi et al., 2024). All 613 genes (with $P< 0.05$) achieved from this review study were considered in the bioinformatic analysis. The most 31 important genes including IL6, EGFR, STAT3, MMP9, CD44, FN1, CD4, TGFB1, CXCL8, CCL2, IL10, ICAM1, IL1A, CD274, KDR, SPP1, ITGB2, CDKN2A, PARP1, MYD88, AGT, NOTCH1, SERPINE1, TNFRSF1A, CDK1, CAV1, ITGB3, CDK4, FOXO3, MDM2, and PROM1, respectively, were identified. In our other previous study, using bioinformatic analysis and an RT-qPCR approach, we showed the expression of cancer-testis antigens (CTAs) of FBXO39 and CEP55 were significantly higher in GBM patients compared to control. Also, these were significantly related to the survival of GBM patients (Azimi et al., 2024). The combined lists of hub genes from two studies (Azimi et al., 2024, Azimi et al., 2024), 33 genes (IL6, EGFR, STAT3, MMP9, CD44, FN1, CD4, TGFB1, CXCL8, CCL2, IL10, ICAM1, IL1A, CD274, KDR, SPP1, ITGB2, CDKN2A, PARP1, MYD88, AGT, NOTCH1, SERPINE1, TNFRSF1A, CDK1, CAV1, ITGB3, CDK4, FOXO3, MDM2, PROM1, FBXO39 and CEP55) were considered to gene-risk score model. Two genes (CXCL8 and ITGB3) were not included in the final analysis because they were not reported in all databases such as the CGGA.

Cox regression analysis and risk score models construction

15-month GBM-specific survival was the outcome of interest. The prognostic prediction ability of 31 gene ex-

TABLE 1: Cox analysis from TCGA, CGGA, MYO, and CPTAC databases. The list of independent prognostic feature genes.

Gene	β	P value	Hazard Ratio	95%CI
TGFB1	-1.626	0.005	0.197	0.063 - 0.618
CCL2	1.743	0.011	5.712	1.479 - 22.067
CD274	1.977	0.006	7.223	1.754 - 29.741
TNFRSF1A	1.149	0.034	3.154	1.089 - 9.140

TABLE 2: Cox analysis from CGGA database. The list of independent prognostic feature genes.

Gene	β	P value	Hazard Ratio	95%CI
EGFR	2.838	0.004	17.075	2.461-118.486
TGFB1	-2.906	0.020	0.055	0.005- 0.631
SPP1	2.702	0.044	14.908	1.070- 207.686
AGT	1.533	0.008	4.632	1.481- 14.488
TNFRSF1A	4.190	0.002	65.995	4.561-954.820
CDK1	2.658	0.011	14.274	1.832-111.219
FOXO3	-3.661	0.002	0.026	0.002-0.269
CEP55	-3.540	0.007	0.029	0.002-0.384

pression, age, gender, and IDH1 status was examined using multivariate Cox regression based on samples from the CGGA, TCGA, MYO, and CPTAC databases. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated accordingly. Then, factors with significant prognostic values were obtained and the risk scoring formula was established for the combination of four databases, and the CGGA database, separately. The calculation formula is as follows: Risk score = Σ (Coefi × Exp). In this formula, Coefi indicates the risk coefficient, and Exp indicates the expression level. The risk score formulas for the combination of all databases and the CGGA database were established and compared. In each model, cases were categorized into high-risk and low-risk groups based on the median risk score level. Then a Kaplan-Meier survival analysis was performed to compare the 15-month overall survival difference between the high-risk and low-risk groups. Finally, two GRS formulas were assessed.

Statistical analysis

All statistical analyses were performed using the SPSS, Version 26 (SPSS Inc., Chicago, IL, USA). Row data were normalized to maximum (1) and minimum (0) for each gene and each database. The multivariate Cox regression analyses were employed to recognize the independent clinical prognostic factors using the Cox regression in SPSS with log-rank p-value < 0.05 as the threshold for significance. GBM cases were divided into high and low-risk score expression groups based on the median risk score level. Kaplan–Meier survival analysis was applied to assess the difference in overall survival time between the two groups using the log-rank test. The area under the curve (AUC) was calculated from the receiver operating characteristic (ROC) analysis to evaluate the discrimination capability. AUC is interpreted as follows: fail (0.50 to 0.60), poor (0.60 to 0.70), fair (0.70 to 0.80), good (0.80 to 0.90), and excellent (0.9 to 1.0).

Results

The demographics of the primary GBM patients from the four databases and their gene expression (n=31) are shown in the Supplementary file. A total of 551 (334 male, mean age 55.5 ± 13.3 years; ranging from 11 to 89 years) cases from the four databases were used in this study.

In two GRS models, the multivariate Cox regression analysis was performed to obtain the independent prognostic feature genes. As shown in Table 1-2, genes were

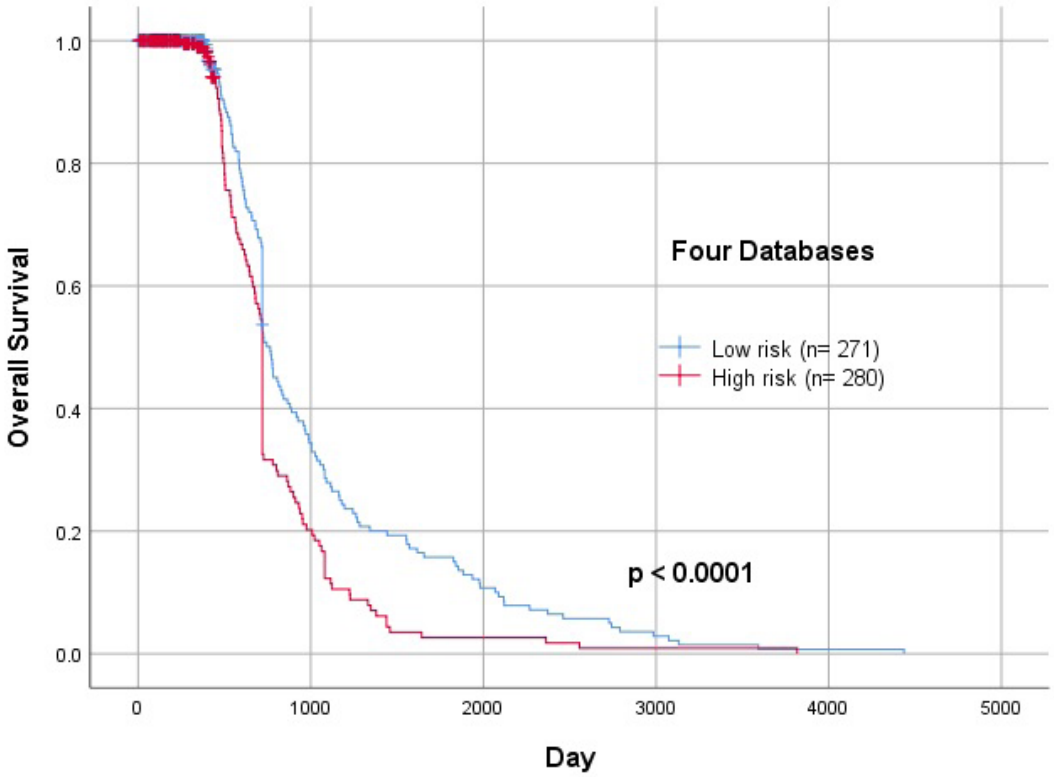

FIGURE 1. Kaplan-Meier analysis of the four-gene risk score model form the combination of TCGA, CGGA, MYO, and CPTAC databases to predict 15-month survival for the high- and low-risk group in GBM patients at training set (log-rank test, $P < 0.0001$).

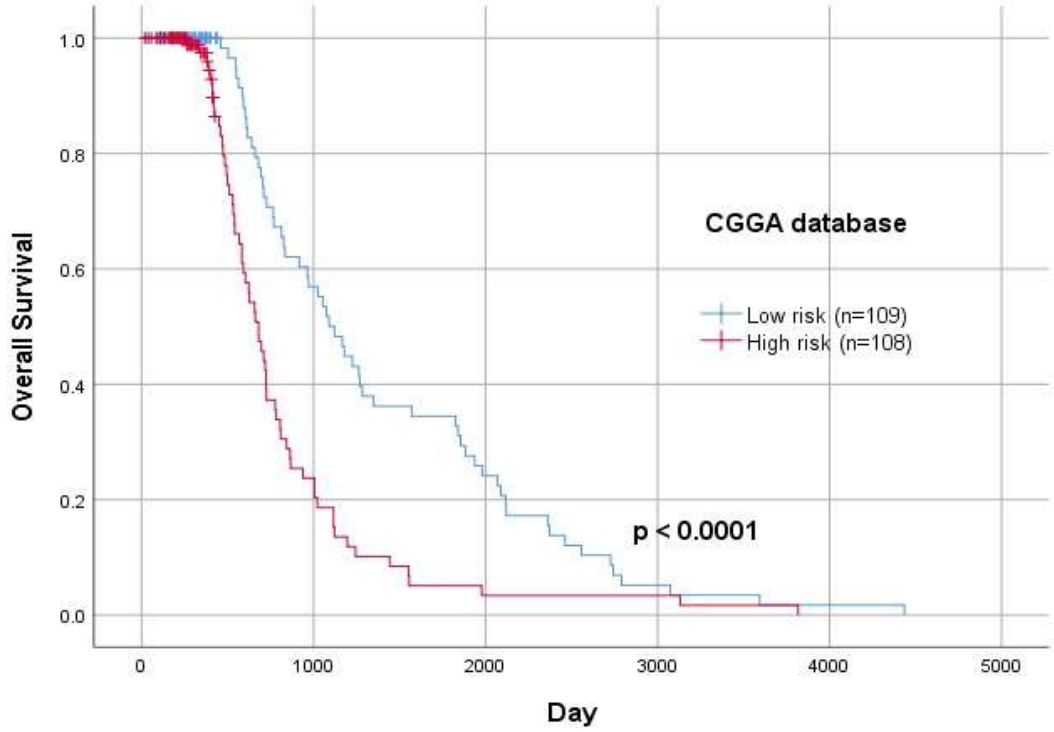

FIGURE 2. Kaplan-Meier analysis of the eight-gene risk score model from CGGA database to predict 15-month survival for the high- and low-risk group in GBM patients at training set (log-rank test, $p < 0.0001$).

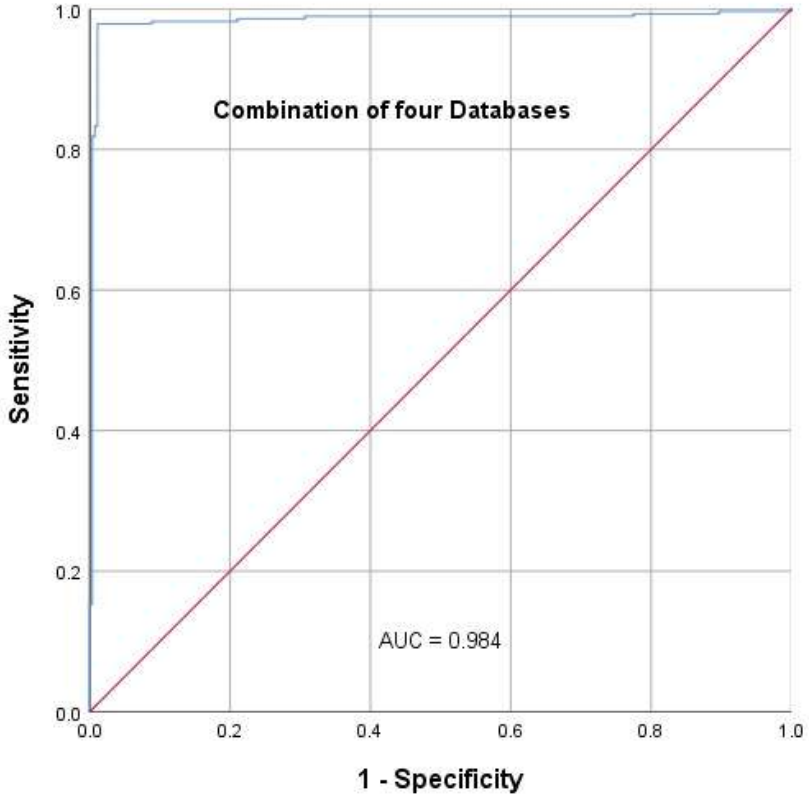

FIGURE 3. Valuation of the predictive ability of the GRS model from the combination of TCGA, CGGA, MYO, and CPTAC databases by time-dependent ROC analysis at the training set.

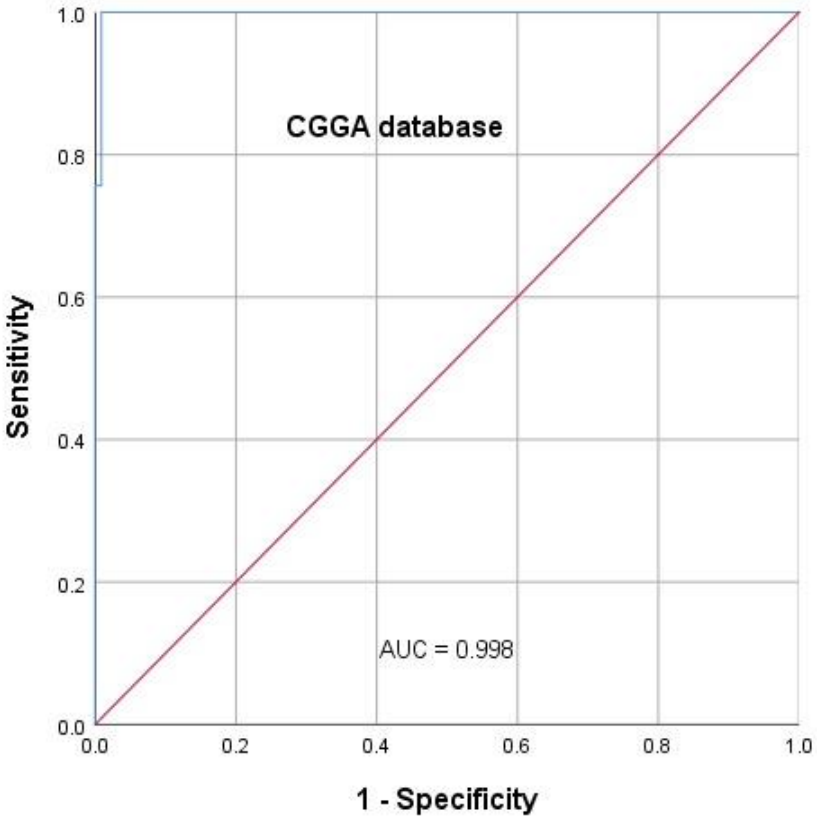

FIGURE 4. Valuation of the predictive ability of the GRS model from CGGA by time-dependent ROC analysis at the training set.

found to be independently correlated to OS prognosis in the combination of four datasets and the CGGA dataset, respectively. Afterwards, the expression levels of these genes in each training dataset were computed and the GRS prediction model was constructed as follows:

Combination of four datasets, 4-GRS model = (1.149) × ExpTNFRSF1A + (1.977) × ExpCD274 + (1.743) × ExpCCL2 + (− 1.626) × ExpTGFB1.

CGGA, 8-GRS model= (2.838) × ExpEGFR + (− 2.906) × ExpTGFB1 + (2.702) × ExpSPP1+(1.533) × ExpAGT + (4.190) × ExpTNFRSF1A+(2.658) × ExpCDK1 + (−3.661) × ExpFOXO3 + (−3.540) × ExpCEP55.

The GRS for each sample of datasets was then calculated in the training set. All samples of each of the datasets were classified into high-risk group and low-risk group in the light of the median value of GRS models. The survival analysis showed that there was a significant correlation between two different risk groups and survival outcomes for two 4- and 8-GRS models in the training set (log-rank $p < 0.000\,1$; Figure 1 and 2). At the validation set for the 8-GRS model, the samples of other datasets were also stratified into a high-risk group and low-risk group using the same method and found that the survival of the high-risk group was lower than the survival of the low-risk group. However, a significant relationship was not observed between these risk groups and clinical survival.

The time-dependent ROC analysis was applied to evaluate the predictive ability of the two models at the training set, the AUC values for 15-month survival were 0.984, and 0.998, in the combination of datasets and the CGGA,respectively (Figure 3 and 4). Hence, these models demonstrated excellent discriminating power.

Discussion

Patients suffering from GBM disease often demonstrate varied clinical outcomes, and GBM remains a challenge in oncology to effectively treat, due to the complexity of the multicellular structures and genetic heterogeneity. Hence, it is important to understand the mechanisms of GBM progression and identify potential biomarkers for effective treatment strategy development. In the current study, using data obtained from multiple platforms (CGGA, TCGA, MYO, and CPTAC) containing 551 GBMs, we identified a novel 4-GRS model, which may predict their relative survival. Meanwhile, the 8-GRS model was created to be an independent prognostic factor, which needs further validation to effectively predict the prognostic risk of GBM patients. In this regard, more studies on interactions between these genes and their biological mechanisms are required. To evaluate and validate the conflicts described in this study, it is noted that these conflicts seem to depend on the GBM sample size, the heterogeneity of GBM, the datasets used, and the methodologies employed. All the above-mentioned may explain why the validation step did not yield significant results. Also, more work is required to clarify their validity in clinical settings for these patients. In the future, we can improve our models by mixing clinical demographics from the analysis of GBM patients with more comprehensive clinical information.

The 4- and 8-GRS models created in this study included the following four genes: TGFB1, CCL2, CD274, and TNFRSF1A; and eight genes: EGFR, TGFB1, SPP1, AGT, TNFRSF1A, CDK1, FOXO3and CEP55, respectively. In our systematic review, we found that all ten genes in two models were significantly associated with survival in patients with GBM (Azimi et al., 2024). These ten genes play a role in cancer-related biological processes including apoptosis (EGFR, FOXO3, CDK1, AGT, CEP55), proliferation (EGFR, AGT, TNFRSF1A, CDK1), regulation of cell differentiation (AGT, TGFB1), angiogenesis (TGFB1, AGT), invasion (CEP55, TGFB1, EGFR, TNFRSF1A, SPP1, CDK1), and migration (EGFR, FOXO3, TGFB1, CEP55) (Arimappamagan et al., 2013; Azimi et al., 2024; Kijewska et al., 2017; Li et al., 2019; Li et al., 2018; Sunayama et al., 2011; Yang et al., 2020; Zhang et al., 2018). Also, the overexpression of CCL2 and CD274 induces an immune-suppressive GBM microenvironment and affects the prognosis of patients with GBM (DiDomenico et al., 2018; Yoon et al., 2023). Based on the negative and positive risk coefficient values of each gene in our GRS models, the biological functions of genes are consistent with those reported previously, reflecting our results' reliability. Albeit, functional and mechanism studies on all genes alone and in combination should be performed to support their clinical use. Two genes of TGFB1 and TNFRSF1A were common between the two GRS models. The above-mentioned researchers reported that both genes contributed to the invasion. Various pathways such as phosphatidylinositol 3-kinase (PI3K) have been

revealed to contribute to GBM invasion. Also, GBM invasion starts from the migration of tumor cells situated at the border, and typically, there is a leader cell (Li et al., 2022). Therefore, targeting TGFB1 and TNFRSF1A to prevent GBM invasion and recurrence might be feasible, although many studies are needed to confirm it.

Due to incurability, it is imperative to develop new prognostic tools or markers for differentiating between high and low-risk GBM patients or survival prediction. In this regard, researchers have identified some of the GRS models associated with survival prediction, which might be critical in the choice of treating patients with GBM (Prasad et al., 2020; Cheng et al., 2019; Hsu et al., 2019; Wang et al., 2019; Zuo et al., 2019; Yin et al., 2019). At present, various GRS models with different types and numbers of genes were reported in the literature including Prasad et al. (Prasad et al., 2020), (AUC = 0.766 for 1-year prediction), Wang et al. (Wang et al., 2019), (AUC = 0.720 for 1-year prediction),Yin et al. (Yin et al., 2019) (AUC = 0.708), Zuo et al. (Zuo et al., 2019) (AUC = 0.699 and 0.718 for CGGA and TCGA for 1-year prediction), Cheng et al. (Cheng et al., 2019), (AUC = 0.734 for TCGA, GEO, and ArrayExpress for 1-year prediction), andHsu et al. (Hsu et al., 2019), (the mean AUC = 0.7 for TCGA,and GEO). At the training set, our 4 and 8-gene risk score models in this study show better results (AUC = 0.984 andAUC = 0.998 for 15-month prediction) compared to other studies (Prasad et al., 2020; Cheng et al., 2019; Hsu et al., 2019; Wang et al., 2019; Zuo et al., 2019; Yin et al., 2019). One might inquire about the GRS models obtained from our and other studies. Are these GRS models reliable and clinically relevant? Certainly, there is limited evidence as to whether these GRS models perform equally across diverse databases and their objects. It is noted that each GRS model has its discrimination power and efficiency and there is no best one for all cases. Moreover, the best GRS model in clinical practice is uncertain, and may be obtained by combining clinical data with molecular mechanisms, and research in this field continues. Finally, apart from the GRS model, various computer modeling algorithms and prediction methods such as machine learning have been and are being developed and used to predict outcomes in medical research (Azimi et al., 2024).

In this research, there are some limitations. First, despite our use of data for large patient cohorts attained from four databases supporting the reliability of our 4-GRS model, invivo and invitro studies are required before applying the risk model in clinical practice. Second, we used four datasets, but there are biases between different methods which may cause differences in results. Third, this is a retrospective study. In the future, prospective clinical research should be performed for the stability of the 4 and8-gene prognostic models. Fourth, the efficiency of the two GRS models should be established in more GBM patients from different regions.

Conclusions

Four- and eight-gene risk scores were constructed by associated algorithms, which may be the independent prognostic factor for patients with GBM. The prognostic value of the two models may be valuable for guiding therapeutic strategies to improve the clinical management of patients with GBM. This finding merits further prospective study in multicenter clinical trials to confirm successful of the two GRS models, and further large cohorts in the future are required for validation.

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Conflict of interest

The authors declare that they have no competing interests.

Availability of data and materials

Datasets associated with this article are from the public database. All data generated or analyzed during this study are included in this article/Additional files.

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None.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.REC.1398.023, Tehran, Iran).

Consent for publication

Not applicable.

Electronic supplementary material

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