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Research article

Exploring the multifaceted role of key lncRNA in glioma: From genetic expression to clinical implications and immunotherapy potential

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ABSTRACT

Background: Long non-coding RNAs (lncRNAs) are implicated in a variety of regulatory functions within tumors, yet their specific roles in glioma remain underexplored.
Methods: We extracted glioma patient data from The Cancer Genome Atlas and UCSC Xena database for analysis using R, focusing on genomic characterization, biological enrichment, immune evaluation, and the development of a predictive model employing machine learning techniques. Additionally, we conducted cell culture and proliferation assays.
Results: Our analysis revealed that the lncRNA SLC16A1-AS1 plays a pivotal role in glioma pathogenesis and prognosis. We observed that abnormal expression of SLC16A1-AS1 varied with tumor grade, IDH mutation status, and histological type, correlating with worse survival outcomes. Genomically, SLC16A1-AS1 was associated with Tumor Mutational Burden and other prognostic biomarkers. The expression of this lncRNA was also linked to the activation of critical biological pathways and appeared to modulate the immune microenvironment, enhancing the presence of immune cells and checkpoints, which may be predictive of immunotherapy outcomes. Our predictive model, constructed from genes associated with SLC16A1-AS1, accurately forecasted glioma prognosis, strongly correlating with survival and treatment responses. In vitro experiments further demonstrated that SLC16A1-AS1 significantly influences glioma cell proliferation, invasion, and migration, underscoring its role in tumor aggression and its potential as a therapeutic target.
Conclusions: This study underscores the significant influence of SLC16A1-AS1 on glioma progression and prognosis, with its expression correlating with tumor traits and immune responses. The findings highlight the potential of targeting SLC16A1-AS1 in therapeutic strategies aimed at mitigating glioma aggressiveness.

1. Introduction

Glioma, a prevalent malignant tumor in the central nervous system, has consistently been a central focus of neuro-oncology research [1]. The World Health Organization (WHO) classifies gliomas into several subtypes, including astrocytomas, oligodendrogliomas, and oligoastrocytomas [1,2]. The incidence of gliomas increases with age, and their clinical presentations vary considerably, often influenced by the tumor's specific location and size [3]. Despite recent advancements in surgical techniques,

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radiotherapy, and chemotherapy, the survival rates and quality of life for glioma patients remain substantially compromised [4]. Furthermore, the high recurrence rate and post-treatment complications present significant challenges for patients and healthcare teams alike [5]. Consequently, enhancing our understanding of glioma's molecular mechanisms, developing more effective treatments, and improving early diagnosis are essential for improving patient outcomes [6].

Long non-coding RNAs (lncRNAs) are a class of RNA molecules over 200 nucleotides in length that do not encode proteins yet significantly influence various biological processes [7,8]. Recent advances in molecular biology and genomics have highlighted the role of lncRNAs in the pathogenesis and progression of diseases, particularly in oncology [9]. Studies suggest that lncRNAs contribute to tumor development and progression through mechanisms such as gene expression regulation, chromatin remodeling, and mRNA stability and translation [10,11]. For example, certain lncRNAs function as tumor suppressors or oncogenes, affecting cell cycle, apoptosis, invasion, and metastasis by interacting with other molecular entities [12]. Furthermore, lncRNAs are pivotal in tumor drug resistance, tumor microenvironment modulation, and stem cell self-renewal and differentiation [13]. Consequently, lncRNAs not only enhance our understanding of the molecular mechanisms underlying tumors but also provide novel diagnostic and therapeutic targets for cancer.

Our study demonstrated that the lncRNA SLC16A1-AS1 is abnormally expressed in various cancers, with notably low levels in gliomas correlating with advanced grades and poor prognosis. This gene's expression significantly affects survival outcomes, as higher levels are associated with a worse prognosis. Genomically, SLC16A1-AS1 is associated with increased tumor mutational burden (TMB) and homologous recombination deficiency (HRD), along with decreased microsatellite instability (MSI) and mutant-allele tumor heterogeneity (MATH) scores in gliomas. This lncRNA also impacts the immune landscape by notably influencing immune checkpoints such as CD274 and CTLA4, thereby affecting immunotherapy responsiveness. Our analyses further indicate that elevated SLC16A1-AS1 expression increases sensitivity to specific drugs. Incorporating this gene's expression into a clinical model has proven effective in predicting patient outcomes. Moreover, using machine learning techniques, we identified critical SLC16A1-AS1-derived molecules for prognosis, enhancing our predictive model's utility in clinical assessments and treatment planning for gliomas.

2. Methods

2.1. Data acquisition and processing

We obtained the expression profiles and corresponding clinical data of glioma patients from the TCGA (GBM and LGG cohorts, accessible through the TCGA Portal) and Chinese Glioma Genome Atlas (CGGA) databases [14,15]. We also acquired mRNA expression data from tumor samples via the UCSC Xena website (Xena Browser), which we meticulously analyzed. For data preprocessing, we employed the R programming environment, utilizing the 'limma' and 'affy' packages [16]. We constructed a nomogram using the 'survival' and 'RMS' packages, and evaluated its performance using calibration curves and Decision Curve Analysis (DCA).

2.2. Genomic characterization

From the extensive TCGA database, we identified four potential biomarkers critical for immunotherapy: TMB, MSI score, MATH, and HRD. We also used HRD as a predictor for the efficacy of platinum-based chemotherapy drugs and PARP inhibitors. To visualize and analyze the gene mutation characteristics of SLC16A1-AS1 within the TCGA dataset, we utilized the online resource at Home for Researchers.

2.3. Biological enrichment

Using ClueGO within Cytoscape, we effectively mapped and visualized the Gene Ontology (GO) terms related to our target molecules, illustrating them via intricate molecular interaction networks [17]. Furthermore, to explore the signaling pathways associated with central genes and their potential biological variations, we utilized Gene Set Enrichment Analysis (GSEA) based on the GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) gene sets [18].

2.4. Evaluation of immune cells infiltration

The study utilized the CIBERSORT algorithm, to analyze the immune microenvironment [19]. To evaluate the impact of the transcriptional profile on immunotherapy outcomes in glioma patients, we applied the Immunophenoscore (IPS). Additionally, we employed the Tumor Immune Dysfunction and Exclusion (TIDE) algorithm to assess immunotherapy responses in these patients [20].

2.5. Construction of the predictive model using machine learning

To enhance and diversify our patient cohorts, we employed a random allocation strategy, dividing them into two groups: a training cohort and an internal validation cohort. For additional external validation, we used glioma data from CGGA database. Our study conducted a meticulous differential expression analysis of genes (DEGs) to identify differences between patients with high and low expressions of SLC16A1-AS1. The primary goal was to identify molecules significantly associated with clinical outcomes, using univariate Cox regression analysis for this purpose. We refined the variables further using LASSO logistic regression. These optimized variables were then included in a comprehensive multivariate Cox regression analysis. Our study culminated in successfully identifying

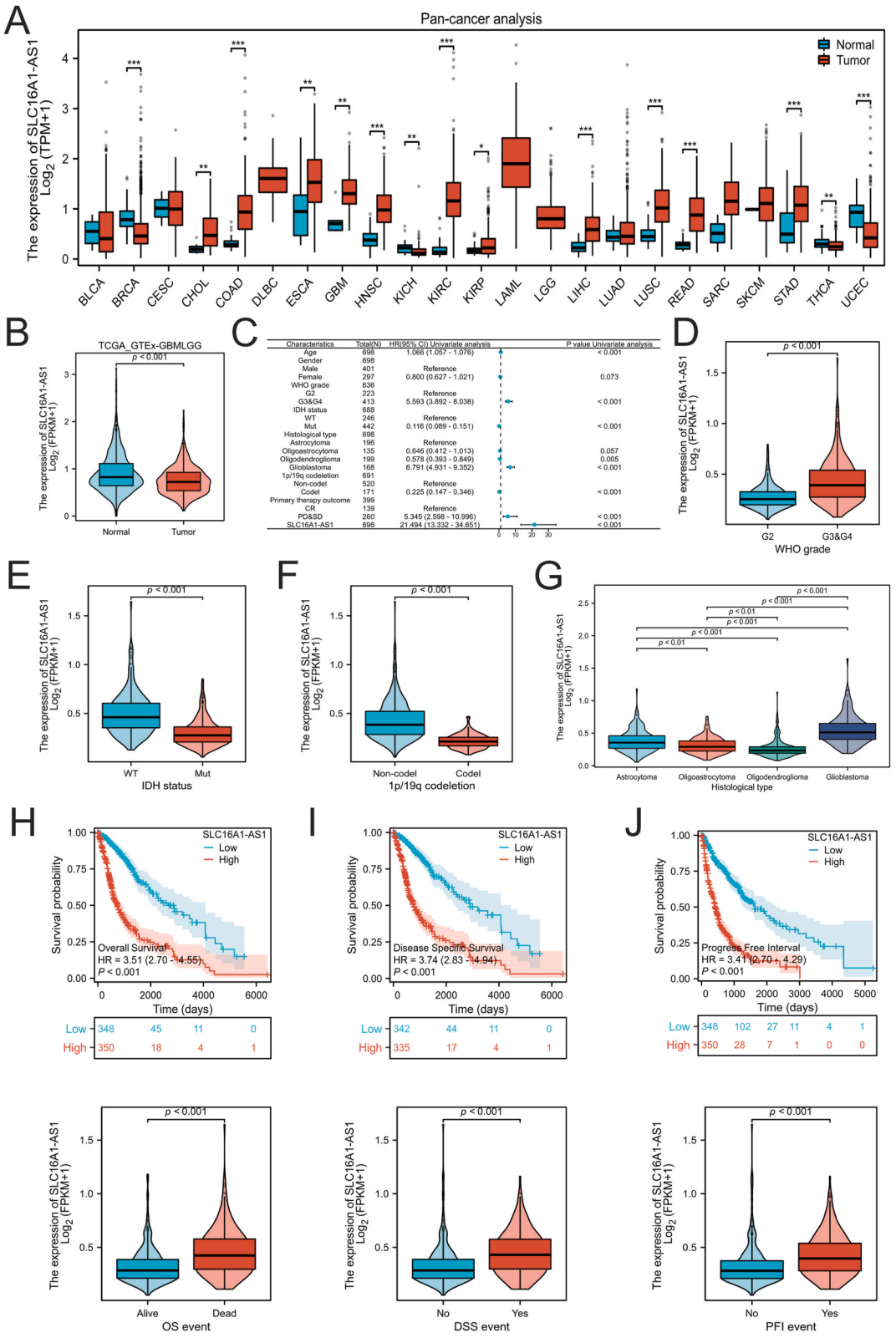

Fig. 1. Gene expression and clinical significance of SLC16A1-AS1 in gliomas
(A): Expression of SLC16A1-AS1 in pan-cancer; (B): Expression level of SLC16A1-AS1 in TCGA_GTEx gliomas; (C): Univariate analysis of different clinical features; (D–G): Clinical characteristics analysis of SLC16A1-AS1; (H–J): Survival data analysis of SLC16A1-AS1 expression in TCGA.

a prognostic signature, formulated as follows: 'Risk score = A's expression * A's coefficient + B's expression * B's coefficient + … + X's expression * X's coefficient'.

2.6. Cell culture

The HA, U251, T98G, U87 and 293T cell lines were obtained from the Cell Bank of the Chinese Academy of Sciences. We strictly adhered to sterile techniques in all cell culture procedures to effectively minimize contamination risks. The cells were meticulously cultured in a controlled environment, maintaining a constant temperature of 37 °C and 5 % CO2 concentration. Upon reaching approximately 80 % confluency, we performed cell passaging.

2.7. Plasmid transfection and lentiviral packaging

For targeting the SLC16A1-AS1 gene, the specific shRNA was cloned into the pLKO.1 lentiviral vector, and the construct was verified via DNA sequencing to ensure specificity and accuracy of insertion. HEK293T cells, utilized for lentiviral production. For transfection, cells at 70–80 % confluency were transfected using Lipofectamine 2000 with the pLKO.1 construct alongside the packaging plasmids, pMD2.G and psPAX2, to produce lentiviral particles. The medium was replaced 6 h post-transfection, and viral particles were harvested 48 h later, followed by filtration through a 0.45 μm pore size filter to remove cellular debris. The virus was concentrated using ultracentrifugation at 100,000 g for 2 h at 4 °C. The resulting lentiviral preparation was aliquoted and stored at −80 °C for further transduction process.

2.8. Cell proliferation assay

In our study, we conducted CCK-8 and colony formation assays on T98G and U251 glioma cell lines to evaluate their proliferative characteristics. For the CCK-8 assay, we seeded T98G and U251 cells in 96-well plates at 1000 cells per well. After incubating at 37 °C with 5 % CO2, we added CCK-8 solution to each well and returned the plates to the incubator for 2 h. In the colony formation assay, we plated T98G and U251 cells at 500 cells per well in 6-well plates and cultured them under standard conditions until visible colonies formed. We then fixed and stained the colonies with crystal violet for subsequent counting and analysis. We compared the number and size of colonies from both cell lines to assess their proliferative capabilities and growth kinetics.

2.9. Transwell assay

In our study, we performed Transwell assays to evaluate both cell migration and invasion capabilities. The assay was conducted using Transwell chambers with 8.0 μm pore polycarbonate membrane inserts (Corning Inc.). For migration assays, we seeded 200 μL of the cell suspension (4 × 10^4) into the upper chamber. For invasion assays, the upper chamber membranes were pre-coated with 100 μL of Matrigel to simulate extracellular matrix conditions, and allowed to polymerize at 37 °C for 2 h before cell seeding. In both assays, we added 600 μL of medium supplemented with 20 % FBS to the lower chamber to serve as a chemoattractant. The chambers were then incubated at 37 °C in a 5 % CO2 atmosphere for 24 h. Following incubation, non-migrating or non-invading cells were gently removed from the upper surface of the membranes using a cotton swab. The cells that had migrated or invaded through the membrane were fixed with 4 % formaldehyde, stained with 0.1 % crystal violet, and quantified under a microscope by counting the stained cells.

2.10. Statistical analysis

In this study, we performed all analytical procedures using the R software platform. We set a threshold for statistical significance at P values below 0.05. Given the diverse distribution of data encountered, we carefully selected the most appropriate statistical methods for each type, ensuring rigorous and accurate data analysis.

3. Results

The flowchart of our study is shown in Figure S1.

3.1. Pan-cancer analysis and clinical significance of SLC16A1-AS1

Our pan-cancer analysis indicated notable abnormalities in SLC16A1-AS1 expression across various tumor tissues, highlighting its potential role in cancer development (Fig. 1A). Specifically, in gliomas, SLC16A1-AS1 expression was lower than in normal tissue (Fig. 1B). Fig. 1C shows a univariate analysis of various clinical characteristics. Additionally, increased SLC16A1-AS1 expression correlated with a higher WHO grade (Fig. 1D). Conversely, in cases of IDH mutation or 1p/19q codeletion, a decrease in SLC16A1-AS1 expression was noted (Fig. 1E and F). The expression levels also varied across different histological types (Fig. 1G). Furthermore, our analysis of Overall Survival (OS), Disease-Specific Survival (DSS), and Progression-Free Interval (PFI) suggested that higher SLC16A1-AS1 expression might be associated with poorer prognosis in gliomas (Fig. 1H–J).

3.2. Role of SLC16A1-AS1 in genomic characteristics of gliomas

TMB has been identified as a potential predictor of immunotherapy outcomes. Our findings reveal a positive correlation between SLC16A1-AS1 and both TMB and HRD, as well as a negative correlation with MSI and MATH scores (Fig. 2A–D). Additionally, Fig. 2E displays a ranking of genomic mutations associated with SLC16A1-AS1, identifying IDH1, TP53, CIC, TTN, and EGFR as the top five mutated genes.

3.3. Functional clustering of DEGs based on SLC16A1-AS1 expression

In our study, we identified 384 genes with increased expression and 327 genes with decreased expression associated with varying levels of SLC16A1-AS1 (Fig. 3A). These DEGs were primarily involved in biological processes such as rhombomere and cartilage development in endochondral bone morphogenesis, regulation of postsynaptic membrane potential via transmitter-gated ion channels, endocytic vesicle lumen, and embryonic skeletal system development and morphogenesis (Fig. 3B). GO analysis indicated that the top three enriched cellular components (CC) included ion channel complex, synaptic membrane, and transporter complex. For molecular function (MF), enriched processes comprised neurotransmitter receptor activity, gated channel activity, and ion channel activity. In the KEGG pathways, the most enriched included neuroactive ligand-receptor interaction, nicotine addiction, and calcium signaling pathway (Fig. 3C). Additionally, GSEA revealed significant enrichment in areas such as Potassium channels, immunoregulatory interactions between lymphoid and non-lymphoid cells, Mir5093p alteration of the Yap1ecm Axis, and GABA Receptor Signaling (Fig. 3D–G).

3.4. SLC16A1-AS1 affects immune microenvironment of gliomas

Our study identified a positive correlation between SLC16A1-AS1 expression and various immune-related scores, including the immune, stromal, and ESTIMATE scores (Fig. 4A–C). By employing CIBERSORT algorithms, we observed distinct patterns of immune cell infiltration in GBMLGG patients with different levels of SLC16A1-AS1 expression. Our correlation analysis showed that SLC16A1-AS1 expression correlates with an increase in several immune cells, including $CD8^+$ T cells, neutrophils, dendritic cells, macrophages, NK cells, myeloid dendritic cells, and fibroblasts, and a decrease in B cells and $CD4^+$ T cells (Fig. 4D–L). Additionally, we found a

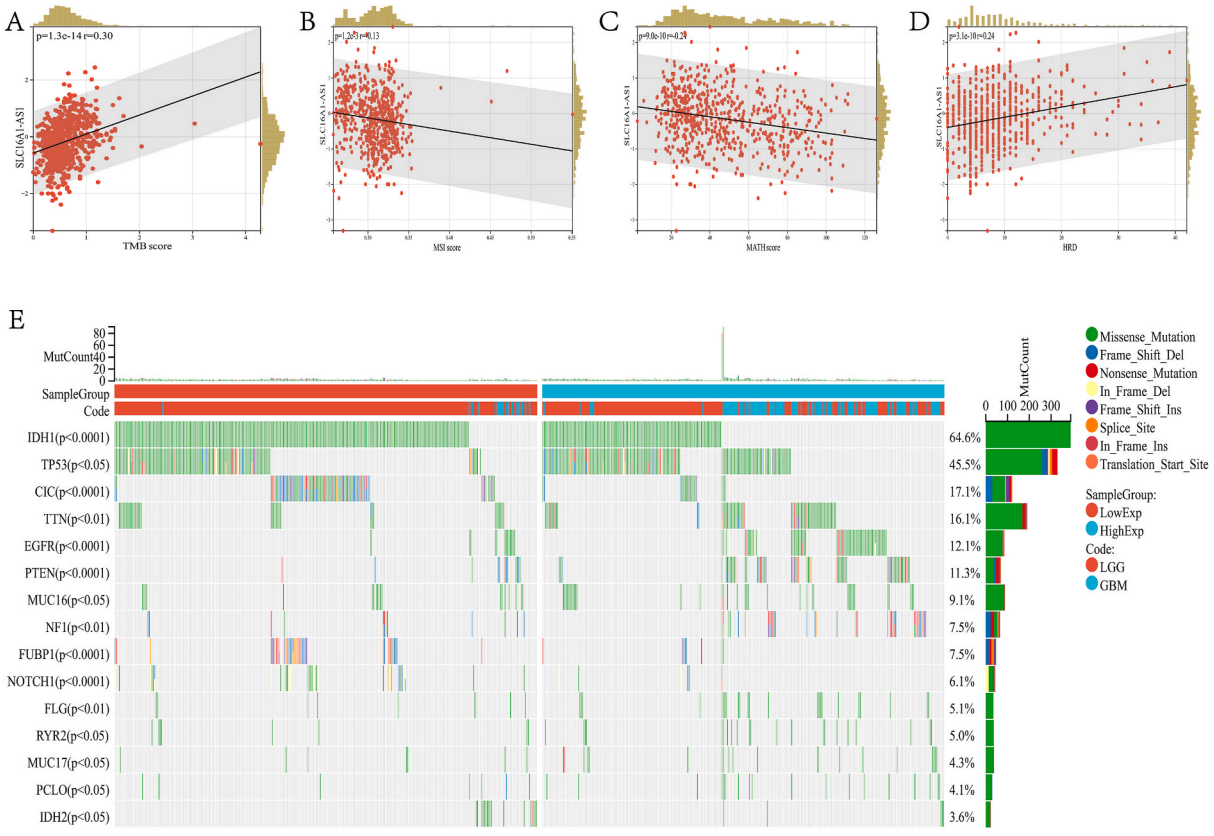

Fig. 2. Genomic characteristics of gliomas
(A-D): Correlation of SLC16A1-AS1 with TMB, MSI, MATH score and HRD; (D): The mutation characteristics of SLC16A1-AS1.

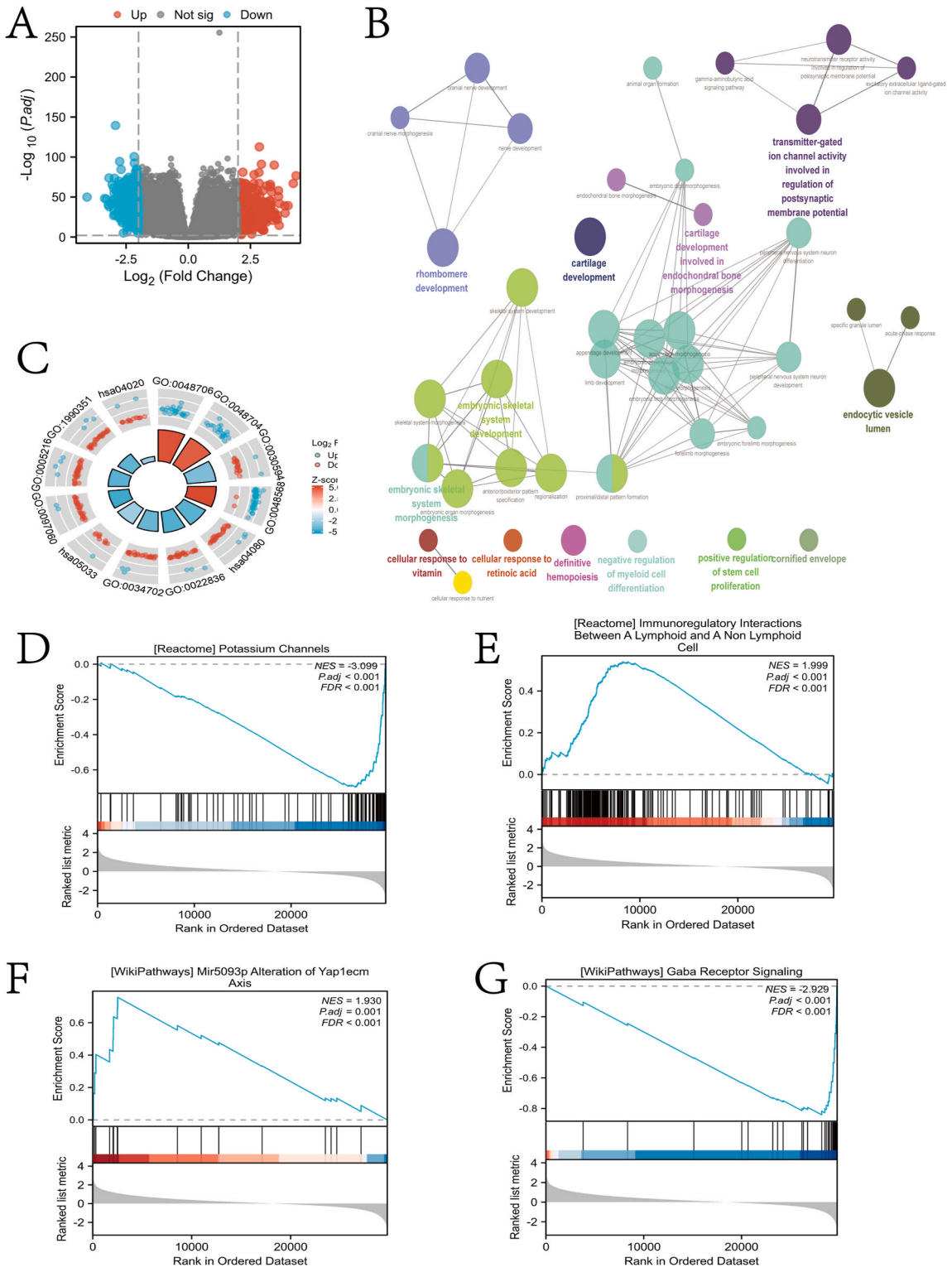

Fig. 3. Biological enrichment analysis of SLC16A1-AS1
(A): DEGs between different expression level of SLC16A1-AS1; (B): clueGO analysis based on DEGs; (C): GO analysis of the DEGs; (D–G): GSEA enrichment analysis.

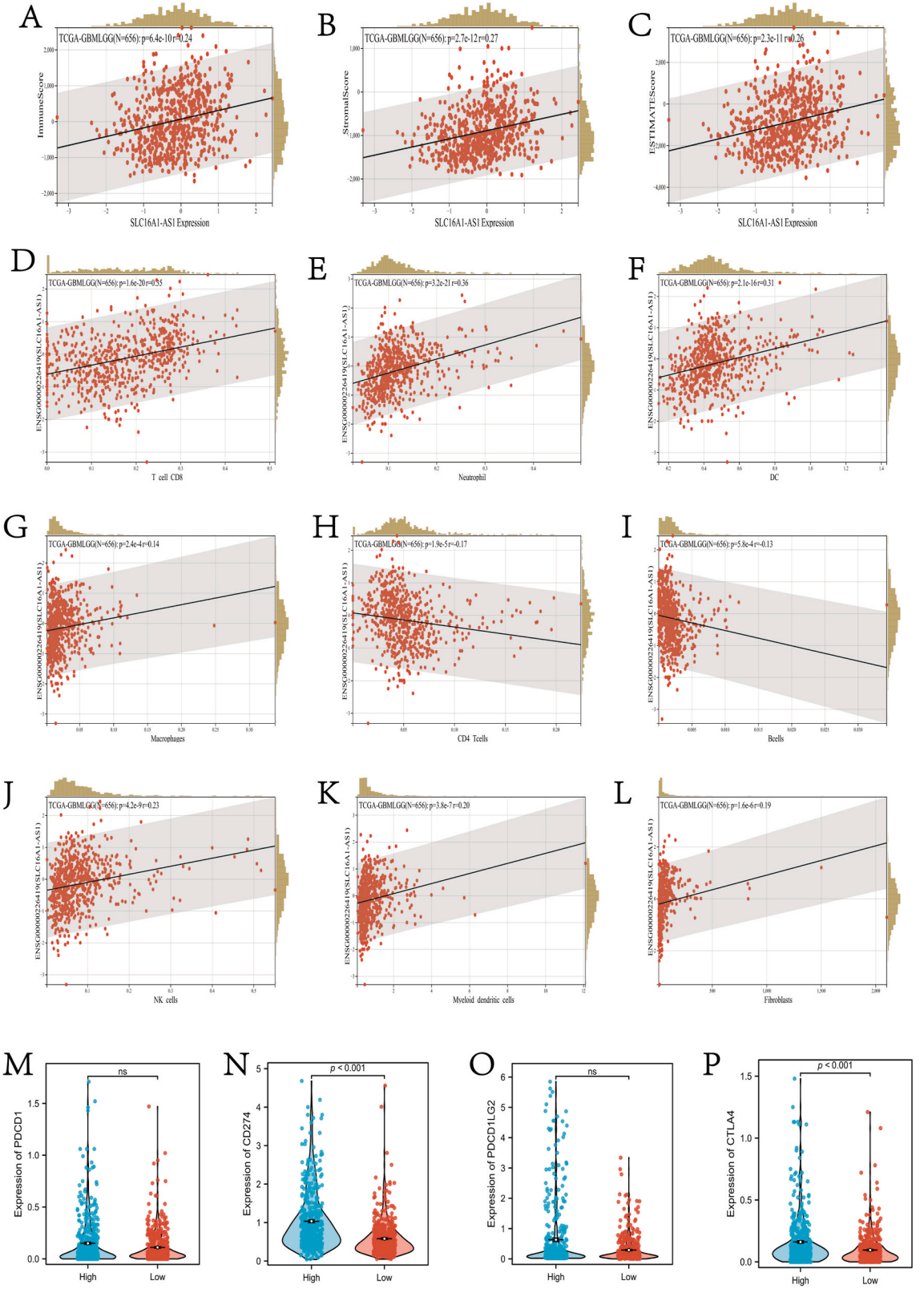

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Fig. 4. Immune cells and immune infiltration analysis of SLC16A1-AS1
(A–C): Correlation analysis between SLC16A1-AS1 and three scores; (D–L): Correlation analysis between SLC16A1-AS1 and immune cells; (M–P): Expression level of common immune checkpoints in different SLC16A1-AS1 expression group.

significant correlation between SLC16A1-AS1 expression and the presence of immune checkpoints such as CD274 and CTLA4, suggesting a potential role for SLC16A1-AS1 in predicting the efficacy of immunotherapy in gliomas (Fig. 4M–P).

3.5. *Immunotherapy evaluation and clinical model of SLC16A1-AS1 in glioma*

The TIDE analysis revealed a positive association of SLC16A1-AS1 with the TIDE and exclusion scores, but a negative correlation with the dysfunction score (Fig. 5A–C). Analysis of the immune response indicated that individuals responding to treatment generally exhibited lower SLC16A1-AS1 expression levels (Fig. 5D). Notably, an inverse relationship was observed between SLC16A1-AS1 and

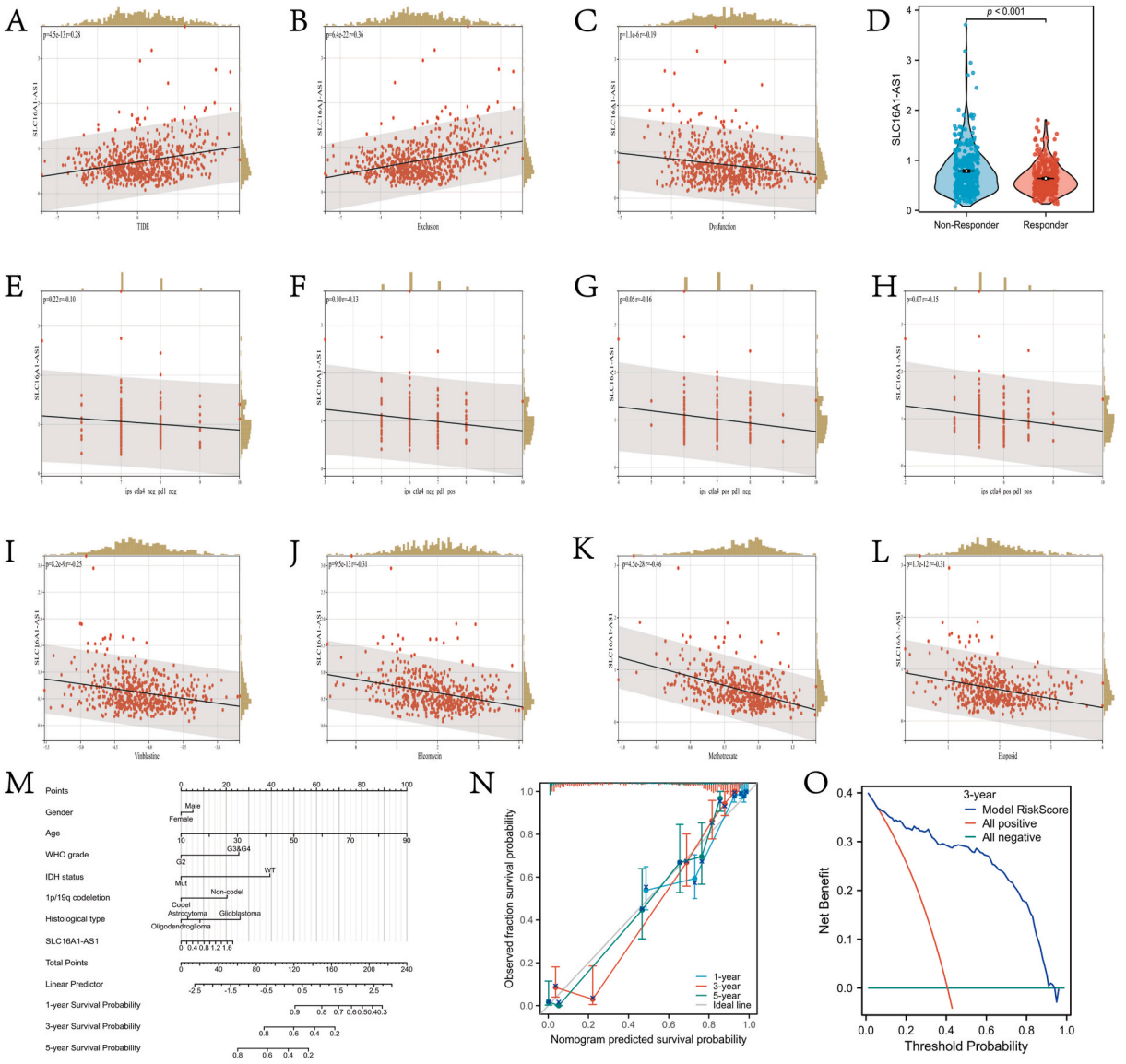

Fig. 5. Immunotherapy and drug sensitivity of SLC16A1-AS1
(A–C): Correlation of SLC16A1-AS1 with TIDE, immune exclusion and dysfunction; (D): SLC16A1-AS1 expression in different immunotherapy response groups; (E–H): IPS score and SLC16A1-AS1 expression; (I–L): Relation of SLC16A1-AS1 expression and commonly used immunotherapy or chemotherapy drug sensitivity; (M): Nomogram plot built on SLC16A1-AS1 expression and related clinical characteristics; (N): The calibration prediction curve; (O): The DCA prognosis curve.

four different types of IPS, indicating potential new methods to predict immunotherapy effectiveness in glioma patients (Fig. 5E–H). Drug sensitivity analysis showed that higher SLC16A1-AS1 expression correlated with increased sensitivity to drugs such as Vinblastine, Bleomycin, Methotrexate, and Etoposide (Fig. 5I–L). Additionally, we developed a nomogram that integrates SLC16A1-AS1 expression and key clinical characteristics (Fig. 5M). The calibration curve confirmed a strong alignment between our model and actual clinical outcomes (Fig. 5N). Finally, the DCA suggested that our model could improve prognosis assessment in patients with gliomas (Fig. 5O).

3.6. SLC16A1-AS1-derived molecules can predict prognosis of glioma on the basis of machine learning

In our study, we applied univariate Cox regression to assess prognostic molecules related to SLC16A1-AS1, identifying the top 50 genes as shown in Fig. 6A. We then used LASSO logistic regression to determine the most suitable candidates, depicted in Fig. 6B and C. From these analyses, we derived a new prognostic signature using Cox regression analysis, expressed as: Risk score = −0.6833 + SAA10.1850 + H190.2606 + MMP130.2558 + HOXB30.3412 + SCNN1B0.2137 - HMGA20.1418 (Fig. 6D). We assessed the effectiveness of our model across three different cohorts. Results indicated that individuals with higher risk scores generally had poorer OS, and our model demonstrated superior predictive accuracy. Our model also performed favorably in two other cohorts, as shown in Fig. 7A–C. Additionally, we noted a correlation between the Risk score and the TIDE score (Fig. 7D). Patients responding to immunotherapy generally had lower risk scores, a trend that was significantly more pronounced in the low-risk group compared to the high-risk group (Fig. 7E and F).

3.7. SLC16A1-AS1 promote the proliferation, invasion and migration ability of gliomas

In our latest exploration of SLC16A1-AS1's impact on glioma cells, we first analyzed RNA levels of SLC16A1-AS1 in various glioma cell lines compared to normal HA cells. This analysis revealed significantly higher expression of SLC16A1-AS1 in glioma cells (Fig. 8A). We then aimed to elucidate its biological role by reducing its expression. Among the strategies tested, sh#3 was the most effective, selected for further studies (Fig. 8B and C). Our experiments, including CCK8 and colony formation assays, demonstrated that decreased SLC16A1-AS1 significantly impairs glioma cell proliferation (Fig. 8D–H). Additionally, Transwell assays indicated that reduced levels of SLC16A1-AS1 significantly inhibit the invasion and migration capabilities of these cells (Fig. 8I–K).

4. Discussion

Gliomas, common brain tumors originating from neural glial cells in the brain or spinal cord, are classified into benign and malignant types [21]. While the exact etiology of these tumors is unclear, genetic and environmental factors are believed to contribute to

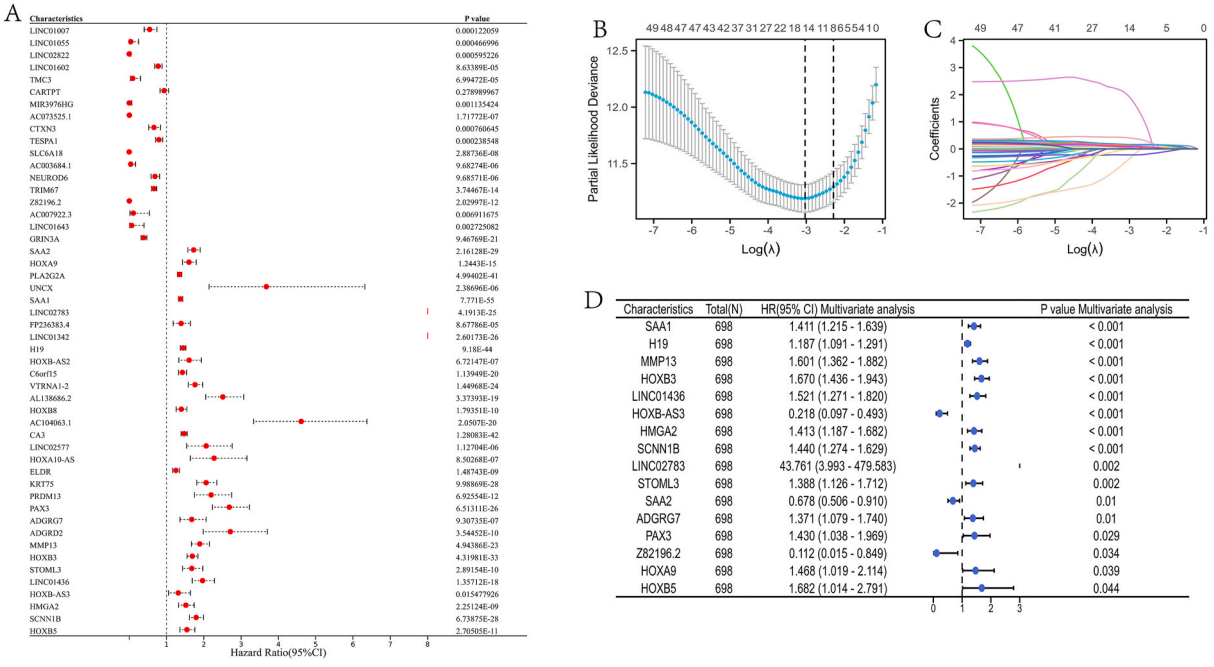

Fig. 6. Construction of prognosis model based on machine learning
(A): The top 50 prognosis-related genes; (B–C): LASSO logistics regression to help find the most suitable variable; (D): Multivariate cox regression analysis.

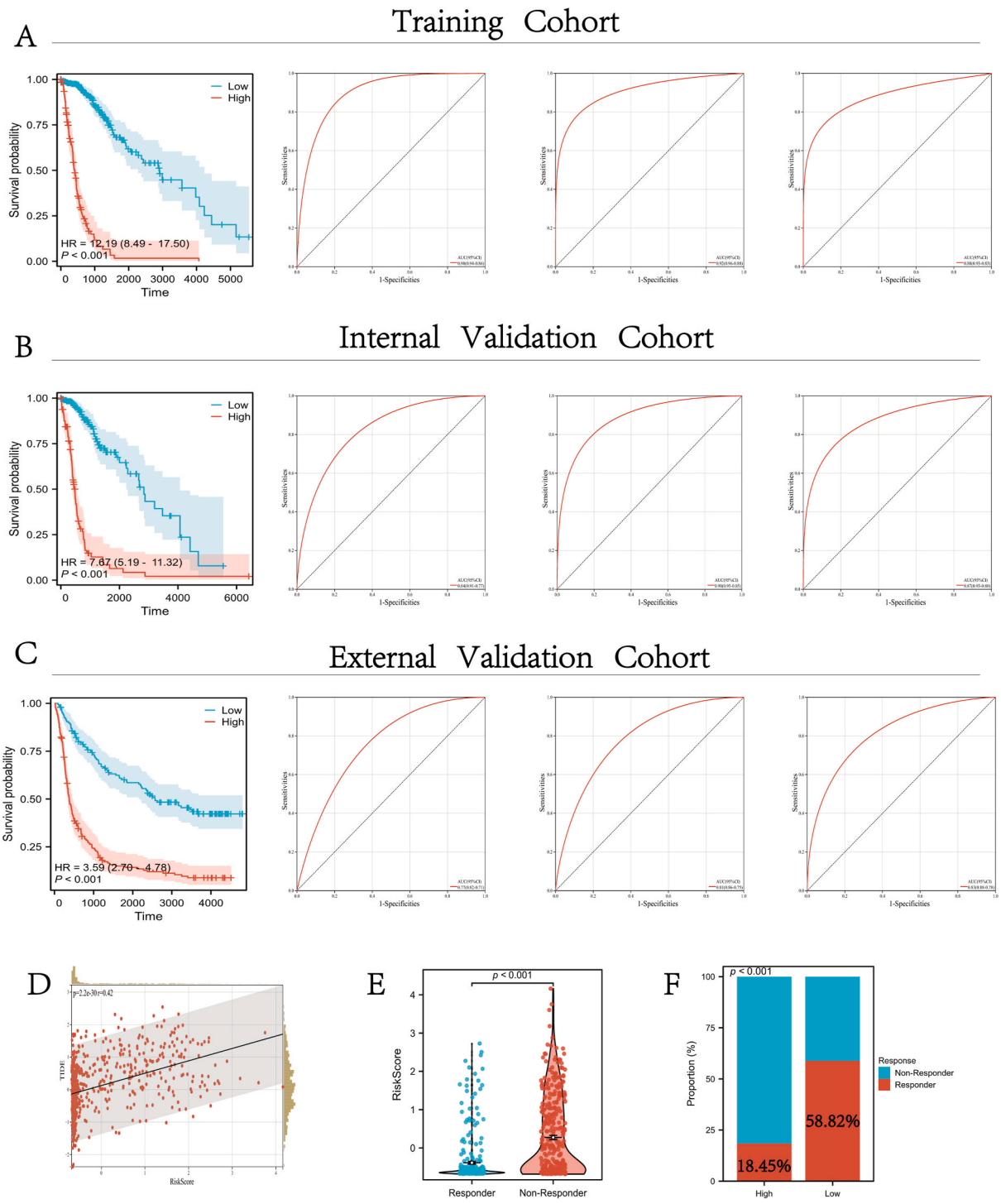

Fig. 7. The clinical predictive value of prognostic model
(A-C): Predictive performance of our prognosis model in three different cohort; (D): Correlation analysis between TIDE and risk-score; (E): The diverse distribution of risks-sore in immunotherapy responders and non-responders; (F): The response rate of immunotherapy in different SLC16A1-AS1 expression groups.

their development [22]. Symptoms of gliomas vary based on location and size, typically including headaches, vomiting, visual disturbances, sensory deficits, and limb weakness [23]. Diagnosis generally involves neuroimaging studies, such as MRI or CT scans, and is confirmed histologically through biopsy [24]. Treatment options include surgical resection, radiation therapy, and chemotherapy,

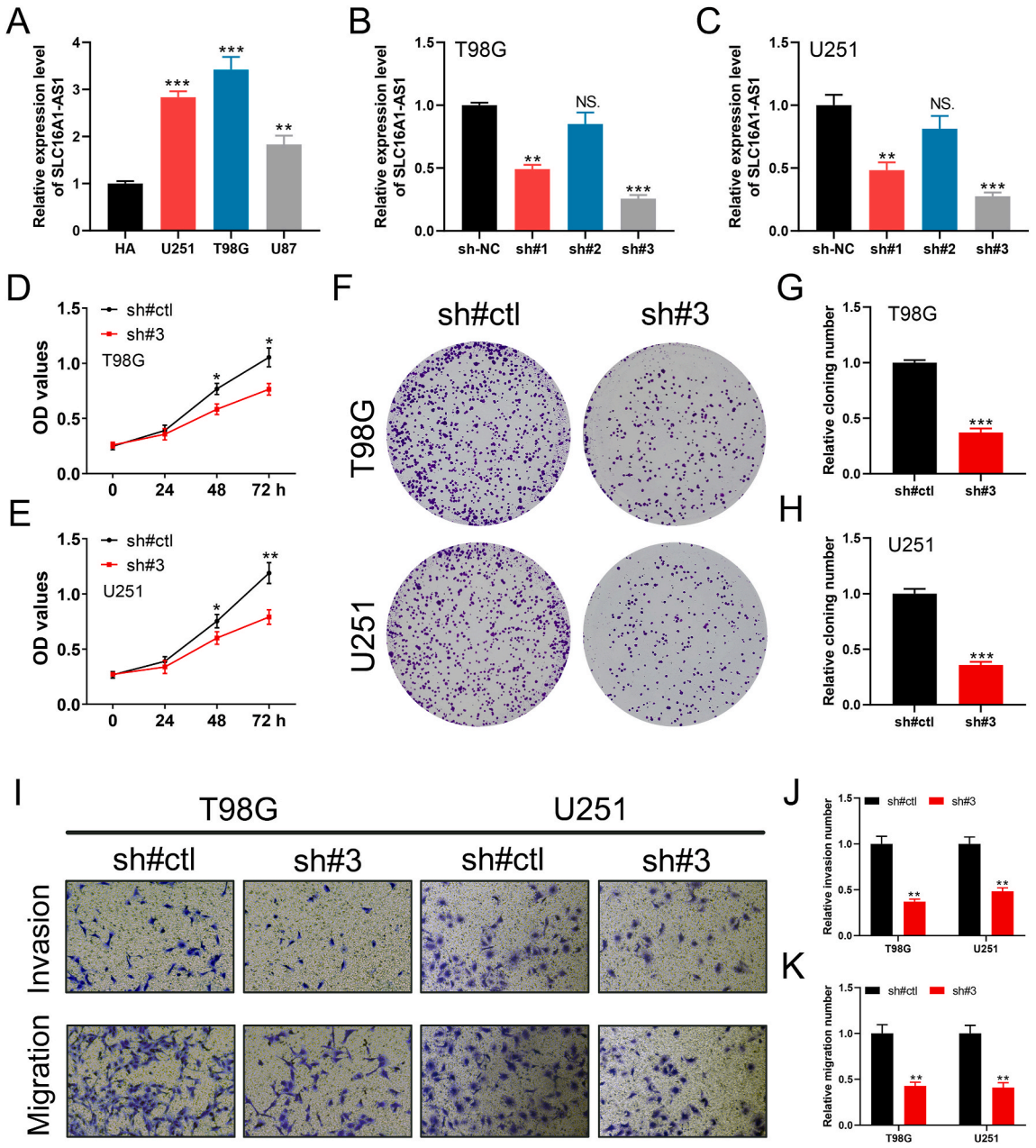

Fig. 8. SLC16A1-AS1 promote proliferation, invasion and migration ability of glioma cells
(A) The expression level of SLC16A1-AS1 in normal and glioma cells; (B–C): The knockdown efficiency of SLC16A1-AS1 in glioma cells; (D–E): CCK8 assay was performed in control and SLC16A1-AS1 knockdown glioma cell; (F–H): Colony formation assay was performed in control and SLC16A1-AS1 knockdown glioma cell; (I–K): Transwell assay was performed in control and SLC16A1-AS1 knockdown glioma cell.

tailored according to tumor type and the patient's overall health [25]. Gliomas pose a serious health challenge, necessitating multi-disciplinary collaboration to enhance patient survival and quality of life [26]. A comprehensive understanding of gliomas is crucial for informed decision-making and effective treatment planning for patients and their families.

Our pan-cancer analysis revealed that SLC16A1-AS1 is abnormally expressed in various tumor tissues, underscoring its significance in tumorigenesis. Specifically, in gliomas, low expression of this gene correlated with certain clinical features and higher WHO grades, suggesting its prognostic potential. Additionally, SLC16A1-AS1 showed variable expression across different histological types and was associated with survival outcomes; notably, higher expression correlated with poorer prognosis. This gene's impact on the genomic characteristics of gliomas was clear, displaying positive correlations with TMB and HRD, and negative correlations with MSI and MATH. It also affected the immune microenvironment by influencing various immune cells and relating to immune checkpoints such

as CD274 and CTLA4. In the context of immunotherapy for gliomas, SLC16A1-AS1's correlation with TIDE and exclusion scores suggests its predictive value for therapy response. Drug sensitivity analysis indicated that high SLC16A1-AS1 expression enhances sensitivity to specific drugs. A clinical model incorporating SLC16A1-AS1 expression effectively predicted prognosis. Finally, machine learning techniques identified SLC16A1-AS1-derived molecules significant for prognosis, with the developed model demonstrating substantial predictive accuracy for overall survival, highlighting its potential utility in clinical assessments and treatment planning.

Numerous researchers have explored the impact of SLC16A1-AS1 on cancer cells [27–30]. For instance, Logotheti et al. identified a novel gene regulatory mechanism where E2F1-induced SLC16A1-AS1 interacts with its transcription factor to facilitate metabolic reprogramming in cancer cells. This reprogramming promotes a phenotype that integrates elements of both oxidative phosphorylation and glycolysis, enhancing breast cancer invasiveness [31]. Jiang et al. found that SLC16A1-AS1 could hinder cell cycle progression and reduce the proliferation of triple-negative breast cancer cells by regulating the miR-182/PDCD4 axis [32]. Similarly, Pei et al. showed that SLC16A1-AS1 acts as a tumor suppressor in hepatocellular carcinoma by influencing the miR-301b-3p/CHD5 pathway [33]. Additionally, Li et al. demonstrated that inhibiting SLC16A1-AS1 activates ferroptosis via the miR-143-3p/SLC7A11 pathway in kidney cancer, offering new insights into the mechanisms and potential treatments for renal cell carcinoma [34]. Our study provides a comprehensive exploration of lncRNA SLC16A1-AS1's role in gliomas, enhancing our understanding of its function across various cancers.

We observed that SLC16A1-AS1 was positively correlated with the TMB score. Additionally, SLC16A1-AS1 exhibited differential expression between immunotherapy responders and non-responders, as determined by TIDE analysis. TMB has emerged as a critical biomarker in cancer research and therapy [35]. Defined as the total number of mutations per coding area of a tumor's genome, TMB indicates the level of genomic instability in cancer cells. Research indicates that tumors with higher TMB are more likely to respond to immunotherapy, particularly when treated with immune checkpoint inhibitors [36].

We screened for genes associated with SLC16A1-AS1 and developed a prognostic model based on these genes, which has proven highly effective in predicting patient outcomes. Crucially, this model also demonstrates a significant correlation with immunotherapy response, facilitating more tailored treatment plans that could enhance therapy effectiveness and improve patient survival rates. Notably, the model's association with immunotherapy response is particularly significant. Given the growing importance of immunotherapies in cancer treatment, our model could serve as an essential tool for identifying patients most likely to benefit from these therapies. This approach could lead to more effective and efficient treatment strategies, optimizing patient outcomes and potentially reducing the burden of unnecessary or ineffective treatments. The clinical implications of our prognostic model, based on SLC16A1-AS1-related genes, are profound, offering new avenues for personalized cancer therapy and a deeper understanding of patient-specific tumor environments.

A major limitation of our study stems from the inherent constraints of bioinformatics. Although bioinformatics offers powerful tools for data analysis and interpretation, its efficacy depends on the quality and completeness of the data. Computational predictions and models, while highly informative, may not capture the full complexity of biological interactions occurring in vivo. Additionally, our reliance on publicly available datasets, which underpinned our analysis, introduces specific challenges. These datasets often exhibit biases related to sample collection methods, processing techniques, and particularly, ethnic and racial diversity. For example, most genomic data available today originates from populations of European descent, potentially misrepresenting the genetic diversity of other ethnic groups. This skew in data representation could compromise the generalizability of our findings and may lead to imprecise predictions for populations not adequately represented in the datasets. Therefore, while our study offers valuable insights, these limitations necessitate cautious interpretation of the results and underscore the need for further research with more diverse and comprehensive datasets to validate and enhance our conclusions.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Based on reasonable requirements, all data can be obtained from the corresponding author.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Sen Zhao: Writing – original draft, Software, Funding acquisition, Data curation, Conceptualization. **Meimei Liu:** Software, Formal analysis, Data curation. **Hua Zhou:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36822.

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