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Prognostic values and immune infiltration of KLF15, AQP7, AGPAT9 in glioma and glioblastoma

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Abstract

Backgrounds The overall survival of patients with lower-grade gliomas and glioblastoma varies greatly. No reliable or existing procedures can accurately forecast survival and prognostic biomarkers for early diagnosis in glioma and glioblastoma. However, investigations are progressing in immunotherapy, tumor purity, and tumor microenvironment which may be therapeutic targets for glioma and glioblastoma.

Results This study indicated the possible prognostic signatures that can be used to identify immune-related prognostic biomarkers in the prediction of the survival of low-grade glioma (LGG) patients which may be a possible therapeutic target. In addition, the Kaplan–Meier plot, ESTIMATE algorithm, and TIMER 2.0 analysis indicated that Krüppel-like factor 15 (KLF15) $p=0.030$, Aquaporin 7 (AQP7) $p=0.001$, and Human 1-acylglycerol-3-phosphate O-acyltransferase 9 (AGPAT9) $p=0.005$ are significantly associated in glioma. Hence, they may be possible prognostic biomarkers in glioma. Meanwhile, in the glioblastoma, only KLF15 has a significant association with glioblastoma ($p=0.025$). Stromal and immune scores of gliomas were determined from transcriptomic profiles of LGG cohort from TCGA (The Cancer Genome Atlas) using the ESTIMATE (Estimation of Stromal and Immune cells in Malignant Tumours using Expression data algorithm). The immune infiltration of the KLF15, AQP7, and AGPAT9 for low-grade glioma and glioblastoma was determined using TIMER immune 2.0 which indicates correlation with tumor purity for KLF15, AQP7, and AGPAT9, but only KLF15 and AGPAT9 are significantly associated in both glioma and glioblastoma, respectively.

Conclusions These results highlight the significance of microenvironment monitoring, analysis of glioma and glioblastoma prognosis, and targeted immunotherapy. To our knowledge, this is the first time to investigate an analysis that revealed that KLF15, AQP7, and AGPAT9 may be important prognostic biomarkers for patients with glioma and KLF15 for patients with glioblastoma. Meanwhile, KLF15 and AGPAT9 are significantly associated in both glioma and glioblastoma, respectively, for tumor purity.

Keywords Biomarker, Glioblastoma, Glioma, Immunotherapy, Microenvironment, Prognosis

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Backgrounds

Glioma is the most prevalent primary malignant brain tumor and can be divided into distinct categories. According to the WHO grading system, it can be categorized into astrocytomas, diffuse low-grade, intermediate-grade, oligodendrogliomas, and mixed oligoastrocytomas [1–3]. The most frequent treatment for glioma is surgical resection in combination with chemoradiotherapy. Due to its highly invasive nature, surgical resection may be difficult to treat, and residual tumor could lead to malignant progressions and even reoccurrence in the long run [4]. Although the classification of low-grade glioma (LGG) is recognized worldwide, it may not adequately predict its survival rate; however, clinicians tend to depend on genetic classifications to guide its treatment [5–7]. The survival outcomes of LGG vary widely among different patients [8]. However, some LGGs stay stable for a long period while some progress into glioblastoma [9–11]. Notwithstanding more investigations are required to elucidate whether gliomas progress to glioblastoma. Gliomas account for approximately 75% of primary cancerous brain tumors [12]. In the USA, about 13,000 people die and 18,000 new cases of CNS tumors and malignant brain tumors arise each year due to glioma prognosis and occurrence [13, 14], hence a need for therapeutics and early diagnosis of the diseases [15].

Glioma is a cancerous tumor of the central nervous system that begins in the glial cells that surround and nourish the brain's neurons [16]. In the treatment of gliomas, great progress has been made in genomic, transcriptomic, and epigenetic profiling [17–21]. Astrocytoma, ependymoma, glioblastoma, and oligodendroglioma are some of the different kinds of glioma [22]. Glioblastoma (GBM), the most common and aggressive primary kind of malignant brain tumor, is assumed to have started in glial cells [23–25]. Scientific evidence, on the other hand, reveals that GBM could have developed from a variety of cells with neural stem cell characteristics [26, 27]. GBM is slightly more common in men than in women, as well as in Caucasians and other white races and ethnicities [28, 29]. GBM is usually found in the supratentorial region of the brain such as hypothalamus, pituitary gland, pineal, and the four lobes: temporal, parietal, frontal, and occipital lobes, with cerebellum being a rare exception [30, 31]. Sixty-one percent of all primary gliomas are found in the brain's four lobes: 20% in the temporal lobe, 25% in the frontal lobe, 3% in the occipital lobe, and 13% in the parietal lobe [32]. Glioblastomas are divided into primary and secondary subtypes that originate along different genetic routes and affect individuals of various ages [33, 34]. Quite recently, glioblastoma with oligodendroglioma component is an uncommon subtype of glioblastoma that features certain parts that resemble anaplastic oligodendroglioma, according to the WHO [35, 36].

In clinical practices, mutated genes such as isocitrate dehydrogenase 1 (IDHI), IDH2, tumor protein 53 (TP53), epidermal growth factor receptor (EGFR), and alpha-thalassemia/mental retardation, X-linked (ATRX) are factors for the prognosis of patients with LGG [37–39]. Some other biomarkers, including 1p/19q codeletion and methylguanine methyltransferase (MGMT) promoter methylation, are also well-recognized and essential prognostic factors for LGGs [40–42]. Sometimes, these genetic factors fail to indicate accurate survival outcomes [43, 44]. Hence, further investigations are required to elucidate the functions and the mechanisms of the prognostic signatures.

Several studies have shown that cancer recurrence and progression are caused not only by the tumor's underlying genetic changes but also by tumor microenvironment (TME) [45–47]. The TME is basically composed of numerous cytokines, extracellular matrix molecules, immune cells, chemokines, fluids, and stromal cells [23, 48, 49]. The cells found in the TME reflect the evolutionary nature of cancer and together, promotes the tumor immune escape, tumor growth, and metastasis [50, 51]. Cancer researchers are not vividly aware of the impact of the TME on immune response or tumor progressions although multiple genetic mutations increase the prevalence of cancer [52]. TME can induce metabolic stress on immune cell infiltration thereby causing local immunosuppression and limited reinvigoration of antitumor immunity [53, 54]. However, having an in-depth understanding of the epigenetic, molecular composition, and function of the TME is essential to manage and treat cancer progressions, recurrence, and immune response [55–57]. Integrating multiple gene biomarkers instead of a single model would improve the accuracy of the prediction significantly [58–61].

The survival of glioma patients has received so much research and discovery in the aspect of neurosurgery, radiotherapy, and chemotherapy. However, a lot of challenges of glioma are yet to be solved. Currently, immunotherapy has unveiled possible therapy for cancer [54, 62, 63]. Investigations are currently going on in the area of immunotherapy, but there is still need for efficient molecular biomarkers to differentiate patients with possible sensitivity to immunotherapy [64, 65]. Therefore, it is very crucial to identify immune-related prognostic biomarkers which may be a possible therapeutic target and may be utilized for immunotherapy in patients.

Taken together, differential expressed genes (DEGs) using an immune stromal score in glioma and glioblastoma, transcriptional microarray of glioma cases from multiple TCGA cohorts were investigated to predict the

survival of LGG and GBM patients. The following prognostic signatures, such as KLF15, AQP7, and AGPAT9, were used in this investigation to determine whether they have a significant association with glioma and glioblastoma using TCGA and the immune infiltration was unveiled for precise immunotherapy. To our knowledge, this is the first time to use these signatures for glioma and glioblastoma, hence unveiling prognostic biomarker and immune infiltration.

Methods

In this investigation, utilization of the Kaplan–Meier plots using Xena bower (http://xena.ucsc.edu/), ESTIMATE algorithm (Estimation of Stromal and Immune cells in Malignant Tumours using Expression), Timer 2.0 (http://timer.comp-genomics.org/timer/), and The Cancer Genome Atlas (TCGA) database were used to unveil the prognostic signature and immune infiltration of glioma and glioblastoma analysis.

Bioinformatics approaches were applied to integrate copy number variations and differential expressed genes of low-grade glioma. The immune cell proportion of the prognostic signatures, such as KLF15, AQP7, and AGPAT9, were determined using TIMER immune 2.0. In TIMER, the Gene module was used to identify the relationship between tumor gene expression and immune infiltration in low-grade glioma and glioblastoma. Stromal and immune scores of gliomas were estimated in transcriptomic profiles of LGG cohort from TCGA using the ESTIMATE. One hundred entries of TCGA cohort were entered and used to plot the graph showing the presence of stromal scores in tumor tissues, immune scores for the infiltration of immune cells in tumor tissues, and the ESTIMATE scores that infers tumor purity. Herein, we analyzed the immune infiltration landscape in LGGs, by applying single-sample gene set enrichment analysis (ssGSEA) to evaluate the relative abundance of each immune cell subpopulation using RNA sequencing (RNA-Seq V2) data of 100 LGGs from TCGA. The survival analysis of significant DEGs in glioma using TCGA database was determined. Kaplan–Meier curves were used to produce graphs showing the survival probability of prognostic signature genes of glioma and glioblastoma and their statistical significance. For example, p values of less than 0.05 in all tests were significantly linked to low-grade glioma and glioblastoma. The gene expression profiles of the prognostic signatures (KLF15, AQP7, and AGPAT9) were determined using TIMER immune 2.0.

Results

Kaplan–Meier curve showing the expression of KLF 15, AQP7, and AGPAT9 gene in glioma

Herein, we unveiled the survival analysis for glioma patients using the TCGA database and Kaplan–Meier plots and discovered that the KLF 15 is significantly associated ($p=0.03$) with the overall survival of the patient which indicates that it may be a very possible prognostic biomarker useful for glioma patients Fig. 1a. In our investigations, the Kaplan–Meier plot showed that AQP7 is significantly associated ($p=0.001$) with overall survival of the glioma patients using the TCGA database Fig. 1b. Hence, it showed that it may be a prognostic biomarker which may be useful for the glioma patient. The Kaplan–Meier plot showed that AGPAT9 is significantly associated ($p=0.005$) with overall survival of the glioma patients using the TCGA database (Fig. 1c).

Kaplan–Meier curve showing the expression of KLF 15, AQP7, and AGPAT9 gene in glioblastoma

This is a visual representation of expression level of prognostic signature KLF15, which indicates that the p value is 0.025 that means it has a significant association with glioblastoma and thus can be used as a prognostic signature in the early detection of glioblastoma (Fig. 2a). Meanwhile, the expression level of prognostic signature AQP7 has p value of 0.59 that means it has no significant association with glioblastoma and thus cannot be used as a prognostic signature in the early detection for glioblastoma patients (Fig. 2b). Also, AGPAT9 has a p value of 0.10 that means it has no significant association with glioblastoma and thus cannot be used as a prognostic signature in the early detection of glioblastoma. Thus, AQP7 and AGPAT9 have no significant association and so they are predictive biomarkers and may not be potential prognostic signatures for glioblastoma patients. However, KLF15 showed a significant association with glioblastoma and so can be a prognostic biomarker in glioblastoma patients.

The stromal, immune, and estimate scores of low-grade glioma

To analyze the immune infiltration landscape in LGGs, single-sample gene set enrichment analysis (ssGSEA) was applied to evaluate the relative abundance of each immune cell subpopulation using RNA sequencing (RNA-Seq V2) data of 100 LGGs patients from The Cancer Genome Atlas (TCGA). By performing single-sample gene set enrichment analysis (ssGSEA), we calculated stromal and immune scores to predict the level of infiltrating stromal and immune cells and these form the basis for the ESTIMATE score to infer tumor purity in tumor tissue Fig. 3.

The expression levels of KLF15 in LGG using different immune infiltrate variables

KLF15 has a correlation with low-grade glioma. Correlation value of 0.124 and the genes are highly expressed

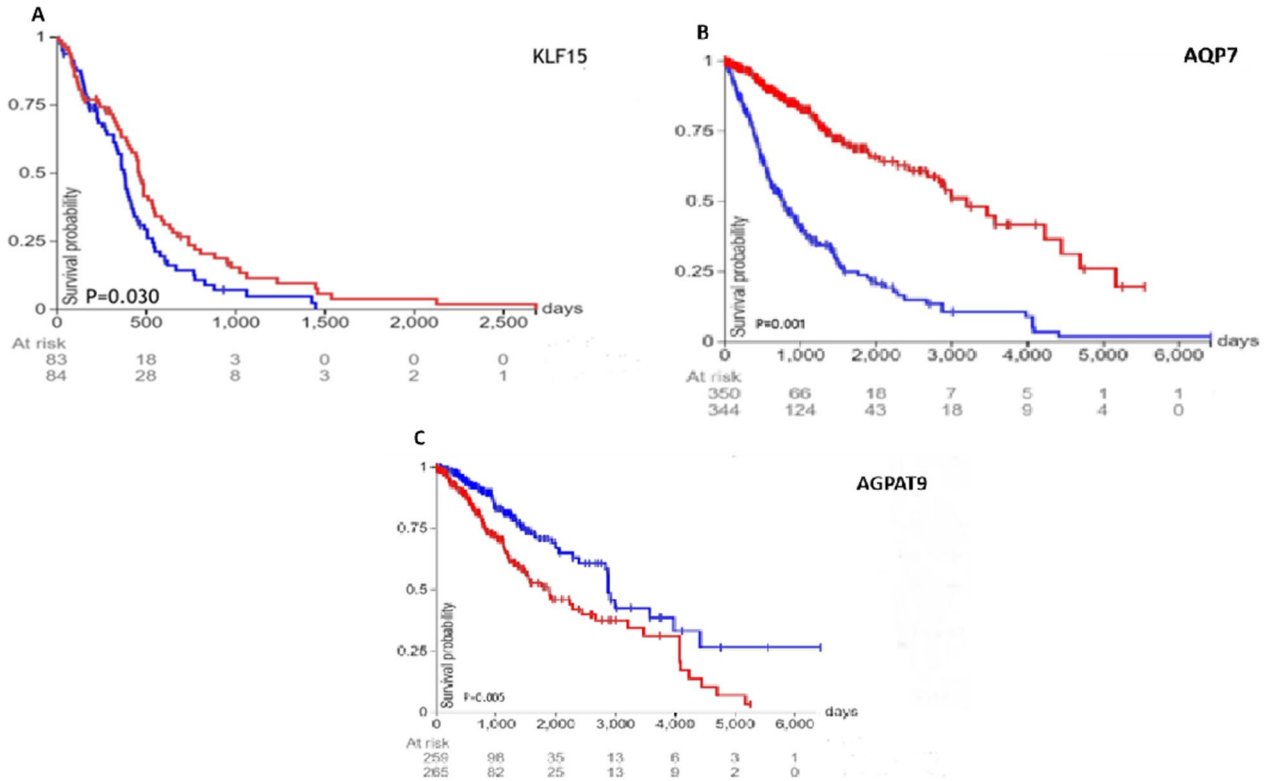

Fig. 1 Kaplan–Meier curve showing the expression of KLF 15, AQP7, and AGPAT9 gene in glioma

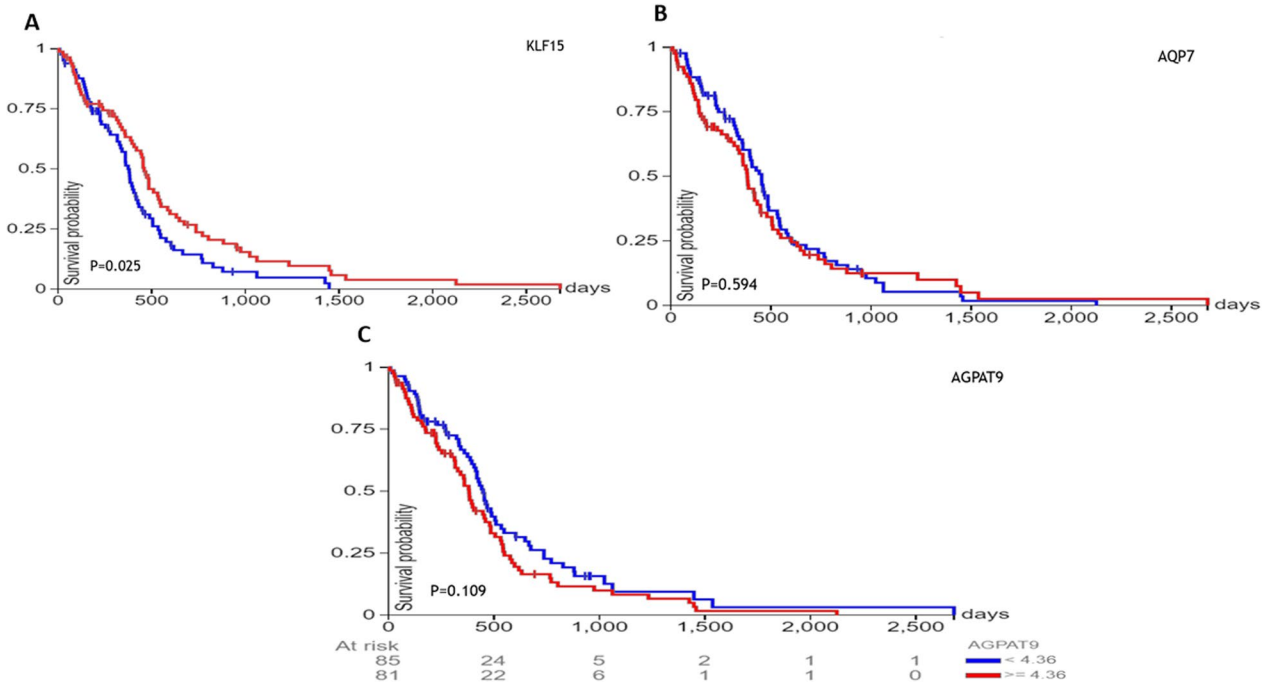

Fig. 2 Kaplan–Meier curve showing the expression of KLF 15, AQP7, and AGPAT9 gene in glioblastoma

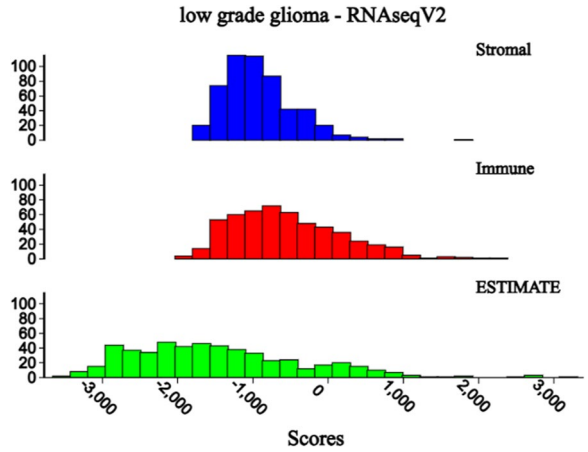

Fig. 3 The stromal, immune, and estimate scores of low-grade glioma

in the tumor cells which show a positive correlation with tumor purity and significantly association ($p = 0.000005$) Fig. 4. B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells are the immune infiltrates which show that the expression level of KLF15 has a partial correlation, and it is significantly associated with immune infiltration in all the cells except that of the macrophages where the P value is 0.07.

The expression levels of AQP7 in LGG using different immune infiltrate variables

Based on investigations, it shows that the tumor purity of AQP7 has a negative correlation with low-grade glioma; correlation value = −0.007 (Fig. 5). Also, purity and B cells do not show a significant association with glioma; p values = 0.8, 0.4, respectively. CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells show that the expression level of AQP7 has a partial correlation with the infiltration level and significantly associated. CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells also show a significant association with glioma with p values of 0.006, 0.05, 0.003, 0.003, and 0.01, respectively.

The expression levels of AGPAT9 IN LGG using different immune infiltrate variables

Based on the investigation, it also shows that tumor purity of AGPAT9 has a negative correlation with low-grade glioma; correlation value = −0.238, and it shows a significant association with the tumor purity with p value ($p = 0.000000014$) (Fig. 6). All the immune cells have positive correlation and show significant association with glioma except macrophages.

The expression levels of KLF15 in GBM using different immune infiltrate variables

The dendritic cells, CD4 T cell, neutrophil, and CD8+ T cell immune infiltrate are significantly associated with glioblastoma. Meanwhile, B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells immune infiltrates indicated that KLF15 expression level is partially correlated with immune infiltration level in GBM, and purity immune infiltrate is correlated. Herein, during the analysis of the KLF15, we realized that the

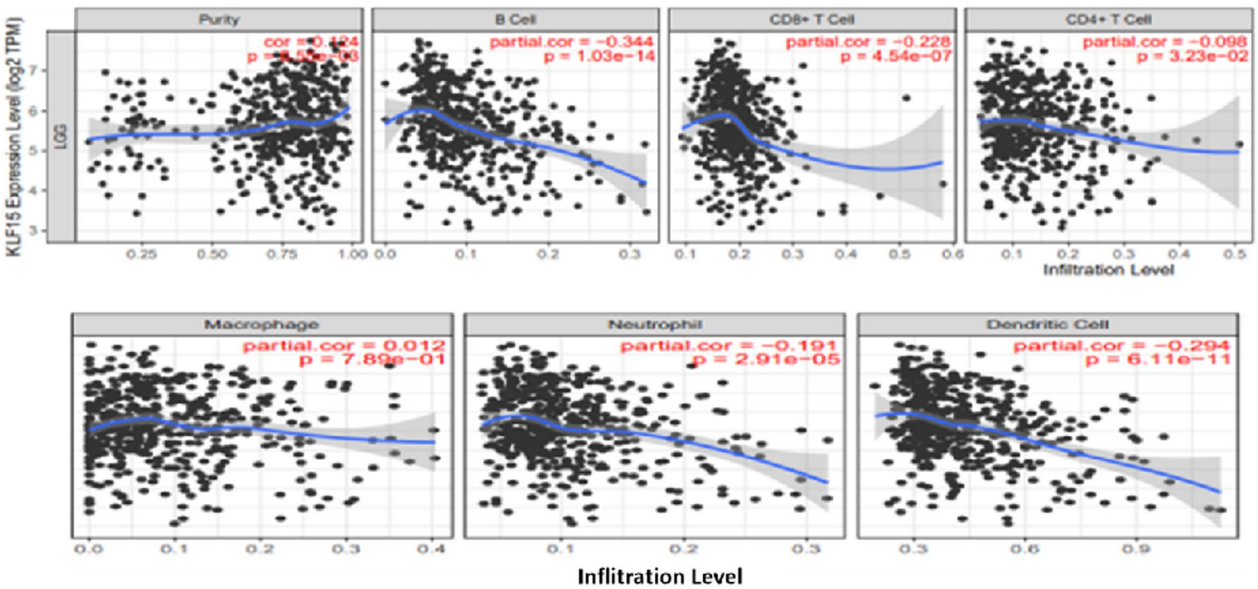

Fig. 4 The expression levels of KLF15 in LGG using different immune infiltrate variables

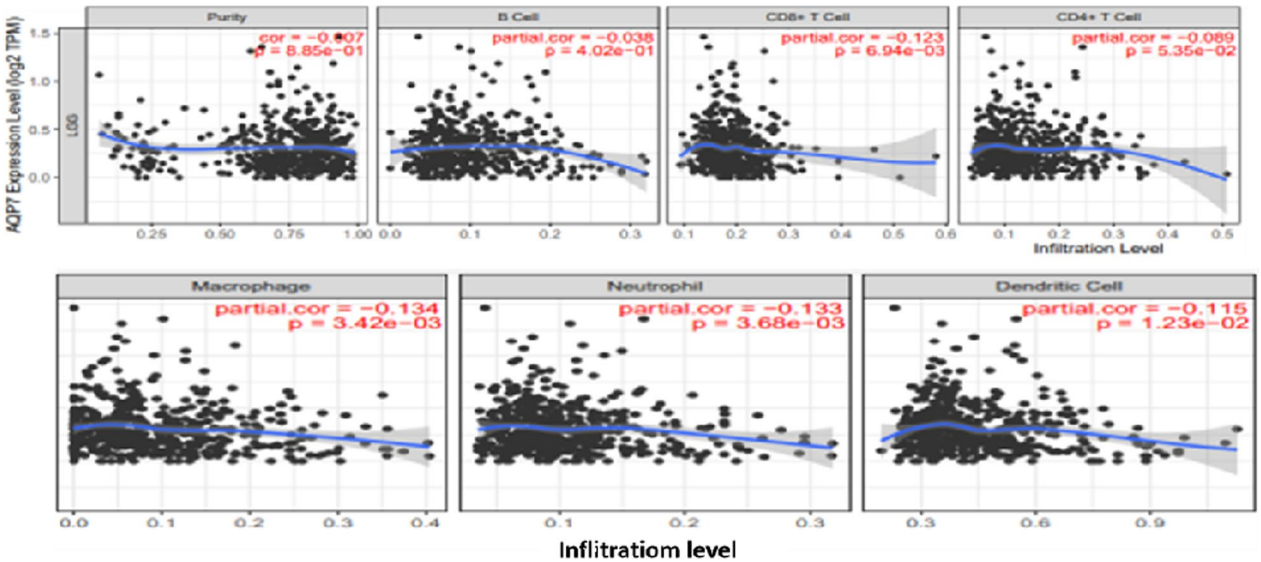

Fig. 5 The expression levels of AQP7 in LGG using different immune infiltrate variables

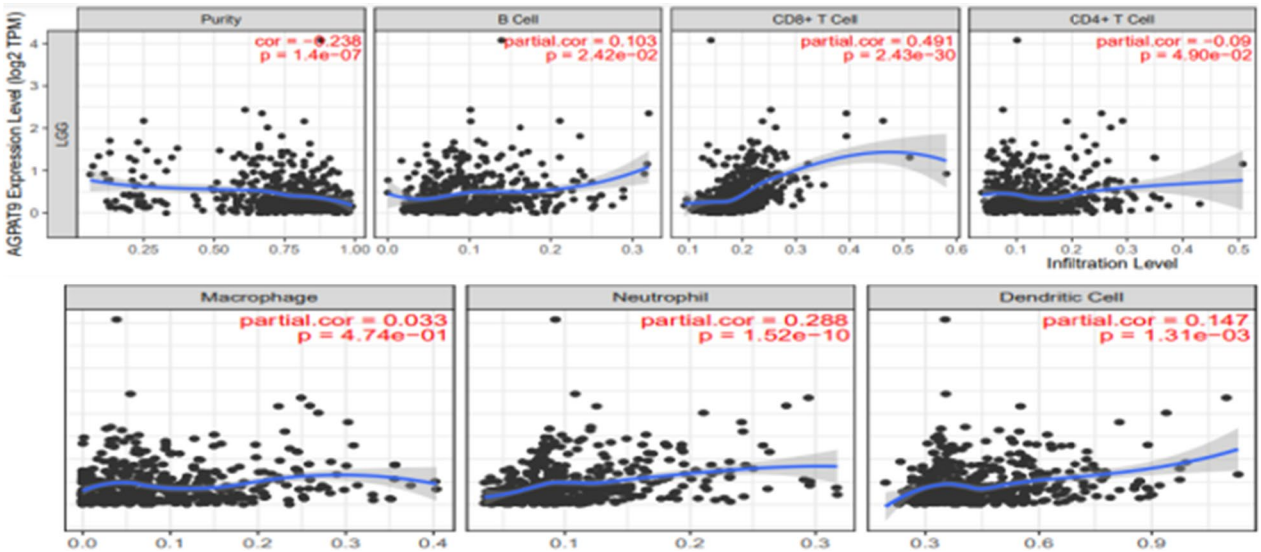

Fig. 6 The expression levels of AGPAT9 IN LGG using different immune infiltrate variables

immune infiltrates are significantly association except that of the B cells ($p=0.1$) and the macrophages ($p=0.3$). The correlation value was 0.254 and the genes are highly expressed in the tumor cells. In the tumor purity, it shows positive correlation and significantly associated ($p=0.00000013$) (Fig. 7) in glioblastoma.

The expression levels of AQP7 in GBM using different immune infiltrate variables

Here, no significant association ($p=0.26$). It was also indicated that the tumor purity of AQP7 has a negative correlation with its immune infiltration level; Correlation value = − 0.055 (Fig. 8). However, neutrophil and CD4 T cells have partial correlation and significantly associated in glioblastoma patients with p value of 0.0000195 and 0.0000177, respectively.

The expression levels of AGPAT9 in GBM using different immune infiltrate variables

B cells and macrophages show no significant association with glioblastoma multiforme. The purity, CD8+ T

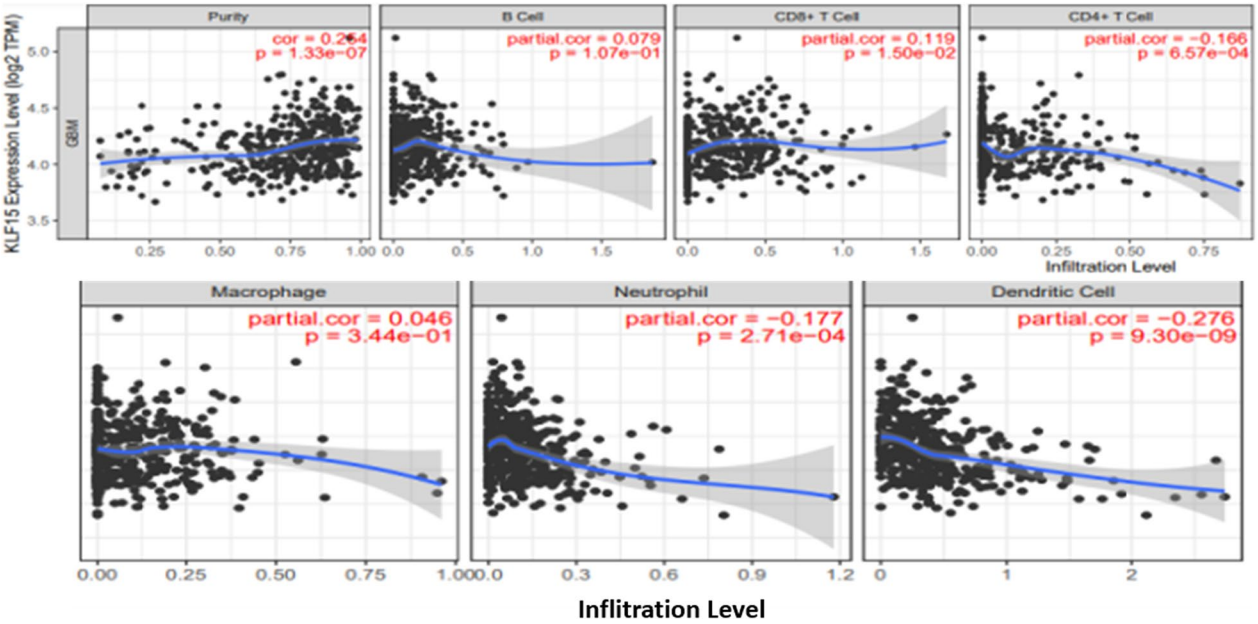

Fig. 7 The expression levels of KLF15 in GBM using different immune infiltrate variables

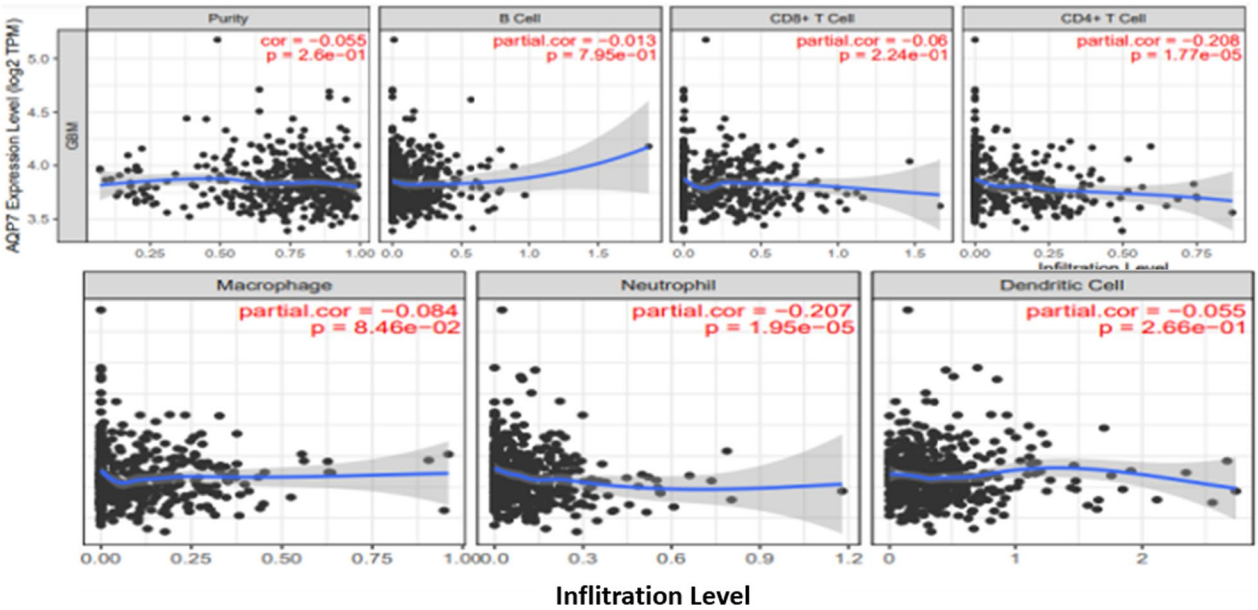

Fig. 8 The expression levels of AQP7 in GBM using different immune infiltrate variables

cell, CD4+ T cell, neutrophil, and dendritic cells show a significant association with glioblastoma multiforme. Based on the analysis, the tumor purity of AGPAT9 has a negative correlation with low-grade glioma; correlation value = − 0.363. It also shows a significant association $p = 0.000012$ (Fig. 9).

Discussions

Krüppel-like factor 15 (KLF15) is a signature that is yet to be fully elucidated in the glioma patient, but previous investigations have been done in the area of clear cell renal cell carcinoma [66] adenocarcinoma lung cancer [67]. Krüppel-like factor 15 (KLF15) is useful in a lot of biological processes which include cell proliferation,

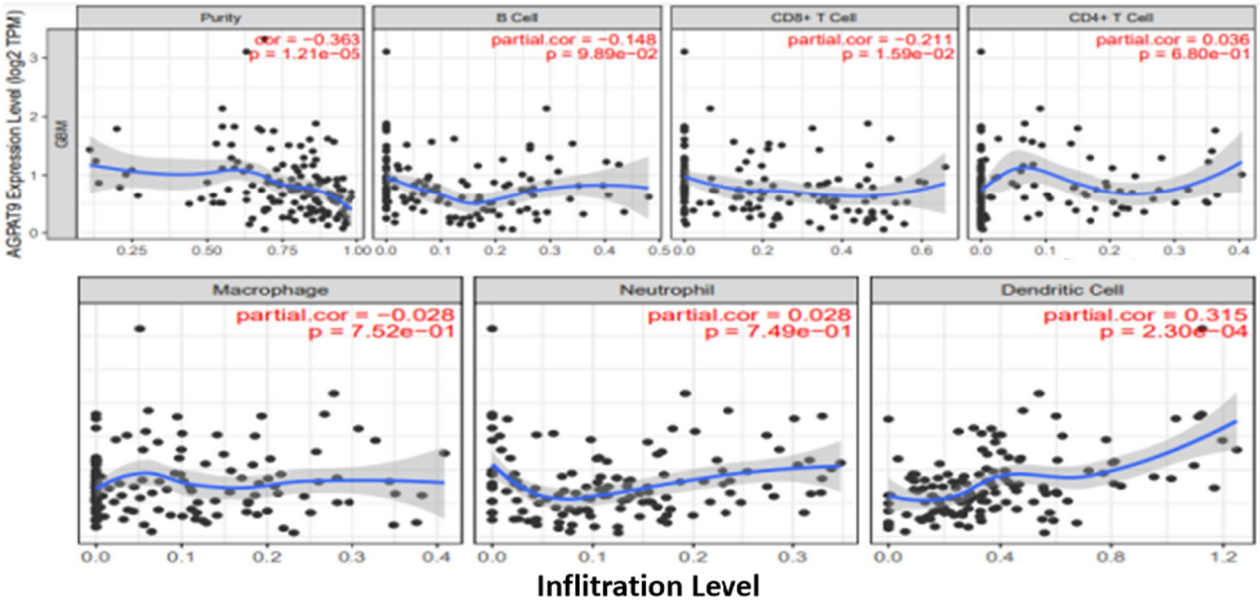

Fig. 9 The expression levels of AGPAT9 in GBM using different immune infiltrate variables

cell cycle, adipogenesis, etc. [68–70]. KLF15 has an important role in RNA polymerase II-specific DNA-binding transcription factor activity [71, 72]. Hence, it is known to have significant functions in different types of cancer. KLF15 is responsible for the suppression and activation of genes in carcinogenesis. Previous investigation has shown that KLF15 is a positive regulator of carcinogenesis [73–76]. Therefore, KLF15 may be useful immune-related prognostic signature in glioma and glioblastoma patients.

Investigations have been conducted on the Aquaporin 7 (AQP7) association with lymphatic metastasis, breast cancer, liver cancer, and clear renal cancer [77–81]. It is otherwise known as water channels which have been known to be related to the invasion, proliferation, and migration of human breast tumors [77, 82–84]. However, investigations are yet to discover the potential roles of AQP7 in glioma and glioblastoma patients as a possible therapeutic target and prognostic biomarker. Aquaporin (AQP) family members were first investigated in 1992 [85–87]. Various investigations have shown that it can be expressed in epithelial and non-epithelial cells [88]. AQP7 is also important in fatty acid metabolism and enhances the migration of water and glycerol [78]. Human 1-acylglycerol-3-phosphate O-acyltransferase 9 (AGPAT9, also known as GPAT3 or LPCAT1) is correlated with tumor progression and tumor microenvironment [89]. It is related to fatty acid metabolisms and involved in a lot of biological processes. It catalyzes de novo synthesis of triacylglycerol [89]. Hence, AQP7 and AGPAT9 indicate usefulness as prognostic biomarker which may be advantageous for the glioma patient.

Stromal and immune scores were estimated from transcriptomic profiles of LGG cohort from TCGA using the ESTIMATE. One hundred entries of TCGA cohort were entered and used for the investigation. Hence, the presence of stromal scores in tumor tissues, immune scores for the infiltration of immune cells in tumor tissues and the ESTIMATE scores that infers tumor purity is observed [90–92].

Immune infiltration of malignancies correlates strongly with clinical outcomes. In terms of chemotherapy and immunotherapy, the makeup of tumor-infiltrating immune cells (TIICs) can serve as biomarkers for predicting treatment response and survival in distinct patient subgroups [93]. Hence, the immune cell proportion of the three-signature for LGG were determined using Timer immune 2.0. The Gene module allows a user to identify the relationship between tumor gene expression and immune infiltration in a fast, comprehensive, and unbiased way [94]. Therefore, the signatures may be a potential prognostic signature for glioma and useful for screening immunotherapy for glioma patients. Hence, this is in consistent with previous investigations [95, 96]. Therefore, B cell, CD8+ T cell, CD4+ T cell, macrophages, Neutrophil, and dendritic cells immune infiltrates indicated that AQP7 expression level is partially correlated with immune infiltration level in LGG [97], while purity infiltrate is correlated. Hence, it may be a potential prognostic signature for glioma and useful for screening immunotherapy for glioma patients [98].

B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells show that the expression level of AGPAT9 has a partial correlation with the infiltration level. Purity, B cell, CD8+ T cell, CD4+ T cell, neutrophil, and dendritic cells show a significant association with glioma [99], while macrophages do not have any significant association with glioma. Therefore, B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells immune infiltrates indicated that AGPAT9 expression level is partially correlated with immune infiltration level in low-grade glioma, while purity immune infiltrate is correlated [100].

Determination of immune cell proportion of the KLF15, AQP7, and AGPAT9 signatures on the glioblastoma multiforme prognostic using Timer immune 2.0 indicated that the tumor purity of KLF15 has a positive correlation with glioma and glioblastoma [101]. Hence, KLF 15 may be a potential prognostic biomarker and useful for screening immunotherapy for glioma and glioblastoma patients. B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells show that the expression level of KLF15 has a partial correlation with the infiltration level. Therefore, CD8+ T cell, CD4+ T cell, neutrophil, and dendritic cells immune infiltrates indicated that KLF15 expression level is significantly associated with the GBM patients. Thus, KLF15 may be a useful signature for monitoring immunotherapy in GBM [102].

B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells show that the expression level of AGPAT9 has a partial correlation with the infiltration level. CD4+ T cell, macrophages, and neutrophil cells do not show a significant association with glioblastoma multiforme. The tumor purity, dendritic cells, and CD8+ T cell immune infiltrate have a significant association with glioblastoma using the AGPAT9 gene [66]. Therefore, B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophil, and dendritic cells immune infiltrates indicated that AGPAT9 expression level is partially correlated with immune infiltration level in GBM [89], while purity immune infiltrate is correlated. Dendritic cells are known for their ability of promoting tumor immunosuppression [103]. Dendritic cells are divided into two forms, myeloid DC and plasmacytoid DC, which can produce large amount of Interferon gamma [104]. It can also induce T cell immunity or tolerance [105, 106]. Hence, AGPT9 may be useful for monitoring immunotherapy in glioblastoma patients. Concerning the association of CD8 T cells, it shows that CD8+ T lymphocytes are crucial components of the tumor-specific adaptive immunity that attacks tumor cells [107]. Clinical outcomes are highly connected to the immune infiltration of malignancies [108]. The composition of tumor-infiltrating immune cells (TIICs) may serve as biomarkers for predicting treatment response and survival in various patients subgroups in terms of chemotherapy and immunotherapy [109, 110].

Conclusions

The analysis revealed that KLF15, AQP7, and AGPAT9 may be prognostic biomarker genes that may be useful for prognosis of patients with glioma. Utilization of bioinformatics tools such as TIMER, ESTIMATE, Kaplan–Meier plot, TCGA database; the immune proportion, stromal and immune scores, various expression levels of the prognostic signatures, infiltrating levels, and tumor purity of glioma and glioblastoma multiforme were determined. Further investigations will be required using X-tile software, Database for Annotation, Visualization, and Integrated Discovery (DAVID), string, cytoscape, Kyoto Encyclopedia of Genes and Genomes (KEGGs) databases to unveil the molecular mechanisms of glioma and glioblastoma. Use of single cell sequencing will be of great usefulness in the treatment of glioma and glioblastoma. Investigations into hormone-based therapy will be fascinating. It would be enormously fascinating to validate maybe the biomarker predicts both precision immunotherapy and prognosis. The determination of real-time quantitative PCR analysis is also important.

Abbreviations

TCGA	The Cancer Genome Atlas
KLF15	Krüppel-like factor 15
AQP7	Aquaporin 7
AGPAT9	Human 1-acylglycerol-3-phosphate O-acyltransferase 9
LGG	Low-grade glioma
GBM	Glioblastoma
ESTIMATE	Estimation of Stromal and Immune cells in Malignant Tumors using Expression data algorithm
TIICs	Tumor-infiltrating immune cells
ssGSEA	Single-sample gene set enrichment analysis.
DEG	Differentially Expressed Genes
DAVID	Database for Annotation, Visualization, and Integrated Discovery
KEGGs	Encyclopedia of Genes and Genomes
TME	Tumor microenvironment
TIMER	Tumor IMmune Estimation Resource

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Author contributions

AMO wrote the manuscript. AMO and OSW performed the experiments, collected, and analyzed data. AKO, RMH, AJ, AA, AMA, and AIA revised the manuscript. AMO conceived and designed the study and revised the manuscript for improved intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request http://xena.ucsc.edu/, TCGA database.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they do not have competing interests.

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