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Significance of Notch1 Gene Expression in Patients with Astrocytic Glioma Tumors

Meera Vora [a], Mittal Mistry [a], Neha Bhalala [a] and Trupti Trivedi [a*]

[a] Molecular Diagnostics & Research Laboratory I, The Gujarat Cancer & Research Institute, Ahmedabad, Gujarat, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Glioma, a prevalent primary brain malignancy, involves multiple signaling pathways crucial for its progression. This study aimed to investigate the clinical significance of Notch1 in patients with glioma, particularly the most common, Astrocytoma tumors.
Methods and Materials: In this study, 48 histopathologically confirmed astrocytoma tumors were comprehensively incorporated for the assessment of Notch1 gene expression through Real-time PCR. Following ΔΔCT computation, Notch1 expression was systematically assessed in correlation with clinicopathological parameters, progression-free survival, and overall survival in glioma patients using SPSS software. Significance was determined at *P* values ≤ 0.05.
Results: The study found abnormal Notch1 expression in 90% of patients, among 70% patients showed up-regulated Notch1. The up-regulated Notch1 demonstrated significant positive correlation

**Corresponding author: E-mail: trupti.trivedi@gcriindia.org;*

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with higher KPS (Karnofsky Performance Status) score (*P* = .006) and trends towards significance with grade of tumors (*P* = .07). Kaplan-Meier univariate survival analysis for 24 months progression-free survival and overall survival demonstrated that a part from high KPS score (progression-free survival: *P* = <.001, overall survival: *P* = <.001) and patients with up-regulated Notch1 had a significantly increase progression-free survival (*P* = .009) and better overall survival (*P* = <.001) compared with patients with down-regulated Notch1, indicating favorable prognosticator. Also, grade 4 IDH wild-type showed inversed correlation with worse overall survival (*P* = .005), however, patients who had tumors in frontal lobes, showed significantly better overall survival than their respective counterparts. In multivariate survival analysis, only low KPS score emerged as significant independent parameter for predicting reduced progression-free survival and poorer overall survival. However, other conventional parameters including Notch1, lost their significance in multivariate survival analysis.

Conclusion: Our study revealed that up-regulated Notch1 in low-grade gliomas, correlating with extended progression-free survival and overall survival. Consequently, we conclude that high Notch1 expression serves as a positive prognostic indicator for patients with astrocytoma tumors, however, further studies are needed for validation in larger sample size.

Keywords: Notch1; glioma; astrocytoma; Kaplan-Meier survival; multivariate analysis.

1. INTRODUCTION

Gliomas, the predominant primary malignant brain tumors, exhibit extensive infiltration, significant morbidity, and a high relapse rate, contributing to an unfavorable prognosis. Several molecular markers such as IDH gene mutation, ATRX mutation, p53 mutation, 1p/19q co-deletion are incorporated in the WHO classification for CNS tumors [1]. The global occurrence of primary malignant brain and CNS tumors is 3.5 per 100,000 individuals, and despite notable advancements in standard treatment, the 5-year survival rate is around 5% [2]. Glioma tumors, being highly heterogeneous and characterized by invasive proliferation, present challenges in therapeutic interventions. This complexity may stem from an incomplete comprehension of gene expression patterns crucial to glioma development [3]. Thus, unravelling molecular pathways and identifying specific markers, alongside histological observations and understanding the tumor microenvironment, is imperative for enhancing diagnostic precision, refining therapeutic strategies, and optimizing patient prognosis. Multiple signaling pathways are dysregulated in various astrocytic tumors [4]. The Notch signalling pathway is essential for cell fate determination, development, and tissue homeostasis, and remains active in adult brains despite being traditionally seen as a developmental pathway [5]. Aberrant activation of Notch signalling is implicated in tumor initiation, progression, angiogenesis, and therapy resistance. Notch1 can behaves as an oncogene or tumor suppressor gene depending on the biological setting. Dysregulation of Notch1 signaling is linked to various cancers, including glioma, breast cancer, and leukemia, among others [6]. Hence, the aim of the current study was to examine the expression of the Notch1 gene in various grades of astrocytic glioma tumors and to establish a connections between its expression, clinicopathological factors, and the outcomes of glioma patients.

2. MATERIALS AND METHODS

2.1 Patients

This retrospective study included 48 adult patients with astrocytic glioma tumors treated at the Gujarat Cancer & Research Institute (GCRI) between July 2016 and February 2022. The Institute's Ethics Committee approved, and all participants provided written consent. Demographic data retrieved from the institute's Medical Record Department (Table 1) revealed a median age of 40 years (range: 18-69 years). Notably, 65% of tumors were situated in the frontal lobe. The median KPS score cut-off was 65, with 52% of patients scoring <65 KPS score. Out of 48 patients, 50% (24/50) patients had IDH mutant glioma tumors. Based on 5S WHO (2021) CNS classification [7], 48%, 21%, and 4% patients showed grade 2, 3 and 4 IDH mutant astrocytoma tumors, whereas, 23% patients were diagnosed as glioblastoma (GBM) with histologically grade 4 IDH wild-type tumors. Surgery served as the primary treatment for all patients, followed by adjuvant therapy in the form of radiotherapy and/or chemotherapy. Progression-free survival and overall survival

analysis were performed in 48 patients with available follow-up data across a minimum of 24 months. Over the 24-months observation period, 25% (12/48) patients experienced disease relapse, while 37% (18/48) died of the condition after surgery (Table 1).

FFPE blocks from the same patients were employed for concurrent extraction of DNA and RNA using the QIAamp DNA FFPE Tissue Kit (Qiagen) and High Pure FFPET RNA Isolation Kit (Roche Life Science). The DNA extraction focused on detecting IDH1/2 mutations, while RNA extraction was carried out for RT-PCR analysis of Notch1 gene expression. Subsequently, the Qubit Fluorometer (Invitrogen, USA) was employed to measure DNA and RNA concentrations, and DNA integrity was assessed via electrophoresis on agarose gel.

2.2 ARMS RT-PCR for IDH1/2 Mutation Detection

IDH1/2 gene mutations were detected using ARMS PCR with the Therascreen IDH1/2 RGQ PCR kit as described previously [8].

2.3 Notch1 Gene Expression Using Real-time PCR

For detection of Notch1 gene expression, cDNA synthesis was performed using the High-Capacity cDNA Reverse Transcription Kit with 1 µg RNA [9]. Rotor-Gene Q 5-plex HRM instrument (Qiagen) was utilized for relative quantification. Amplification involved QuantiTect SYBR Green RT-PCR Kit, with 0.4 µl Notch1 forward primers "TGAATGGCGGGAAGTGTGAAG" and reverse primers "GGTTGGGGTCCTGGCATCG", 18s RNA forward primers "GGAGTATGGTTGCAAAGCTGA" and reverse primers "ATCTGTCAATCCTGTCCGTGT", and 10 µl SYBR Green RT-PCR Master Mix in a total 20 µl reaction volume. The protocol included an initial denaturation step at 95°C for 15 min, followed by 45 cycles at 95°C for 15 s, 60°C for 30 s, and 72°C for 30 s. The 18s RNA gene served as a housekeeping gene, and the commercially available normal brain (Takara Bio Inc. US) served as a calibrator. Relative quantification employed the 2-ΔΔCt method, [10] presenting data as a fold change of gene expression. In this study, normal Notch1 gene expression fell within a fold change range of 0.5-2, while a fold change exceeding 2 was deemed indicative of up-regulated Notch1 expression [11].

2.4 Statistical Analysis

Statistical analysis was conducted in SPSS version 20.0 included a two-tailed chi-square ($\chi 2$) test for parameter relationships. Spearman's correlation coefficient (r) assessed correlations with Notch1 gene expression. Kaplan-Meier survival analysis evaluated progression-free survival and overall survival. Multivariate survival analysis utilized the Cox Regression Step-wise Forward LR model, with significance set at $P \leq 0.05$.

Table 1. Patient and tumors characteristics

Characteristic	N = 48	%
Age (Range: 18-69 years; Median 40 years)		
≤ 40 years	24	50
> 40 years	24	50
Gender		
Female	18	38
Male	30	62
Location of tumors		
Frontal	31	65
Parietal	11	23
Temporal	05	10
Occipital	01	02
KPS* Score (Range: 10-95, Median: 65)		
High >65	23	48
Low ≤65	25	52
Grades of tumors		
2	23	48
3	10	21
4 (IDH mutant)	04	08

Characteristic	N = 48	%
4 (GBM)	11	23
Treatment		
Surgery (S) or surgery followed by	23	48
S + Radiotherapy (RT)	04	08
S + Chemotherapy (CT)	04	08
S + RT + CT	17	36
Progression-free survival (n=37)		
GC Well	35	95
Recurrence	02	05
Overall survival (n=37)		
Alive	29	78
Died	08	22
IDH1/2 Mutations		
Absent	24	50
Present	24	50

[*] *KPS (Karnofsky Performance Status)*

3. RESULTS

3.1 Distribution of Notch1 Gene Expression in Patients with Glioma Tumor

Among 48 astrocytoma patients, 10% (05/48) exhibited normal Notch1 expression (fold change 0.5-2), while abnormal expression was seen in 90% (43/48) [Fig. 1].

Within the latter group, 30% (13/43) displayed down-regulation, and 70% (30/43) exhibited up-regulated Notch1 gene expression [Fig. 2].

3.2 Associating Notch1 Gene Expression with Clinical Features in Glioma Tumors

Notch1 gene expression correlation with clinicopathological parameters is depicted in Table 2, excluding patients with normal Notch1 expression.

A significantly inverse correlation emerged with KPS score. In patients with high KPS scores, Notch1 gene up-regulation was notably higher (90%) compared to those with ≤65 KPS score (52%) ($\chi 2 = 7.25$, r = -0.411, $P = .006$) (Table 2 Fig. 3).

Beyond KPS, a trend toward significance was observed between Notch1 gene expression and glioma tumor grade. Up-regulation incidence significantly decreased with higher tumor grades (Table 2). Up- regulation of Notch1 gene was noted in 80% of grade 2 glioma tumors, followed by 78% and 50% in grade 3 and 4 glioma tumors, respectively ($\chi 2 = 3.86$, r = -0.271, $P = .07$) (Table 2, Fig. 4).

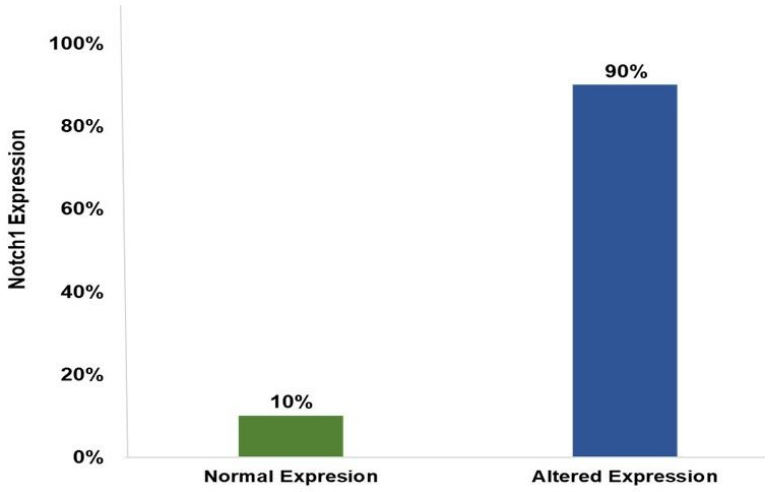

Fig. 1. Notch1 gene expression in glioma patients

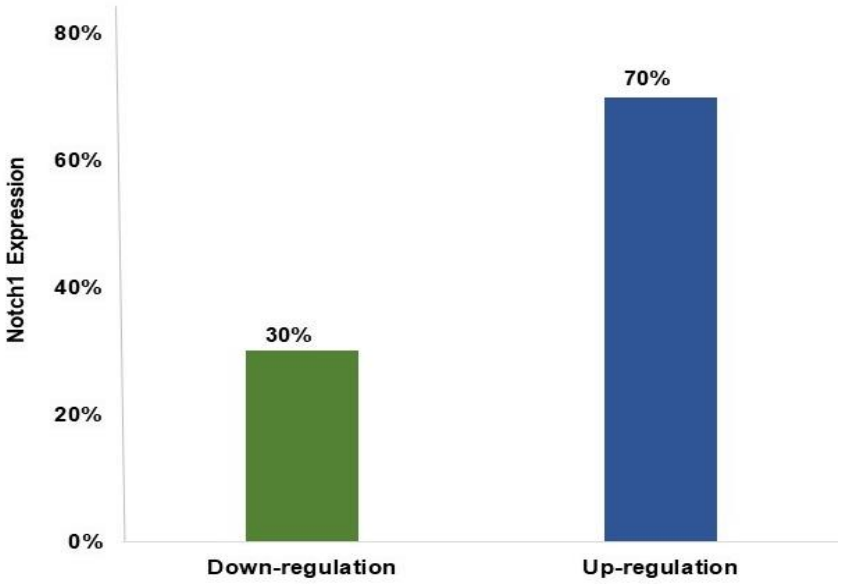

Fig. 2. Altered expression of Notch1 in glioma patients

Table 2. Correlation between clinicopathological parameters and altered Notch1 gene

	N	Notch1 gene expression		χ2	r	*P* -value
	43	Down-regulation N = 13	Up-regulation N = 30			
KPS Score						
High >65	20	02 (10)	18 (90)	7.25	-0.41	0.006
Low ≤65	23	11 (48)	12 (52)			
Grade of Tumors						
2	20	04(20)	16 (80)	3.86	-0.27	0.07
3	09	02(22)	07 (78)			
4	14	07(50)	07 (50)			

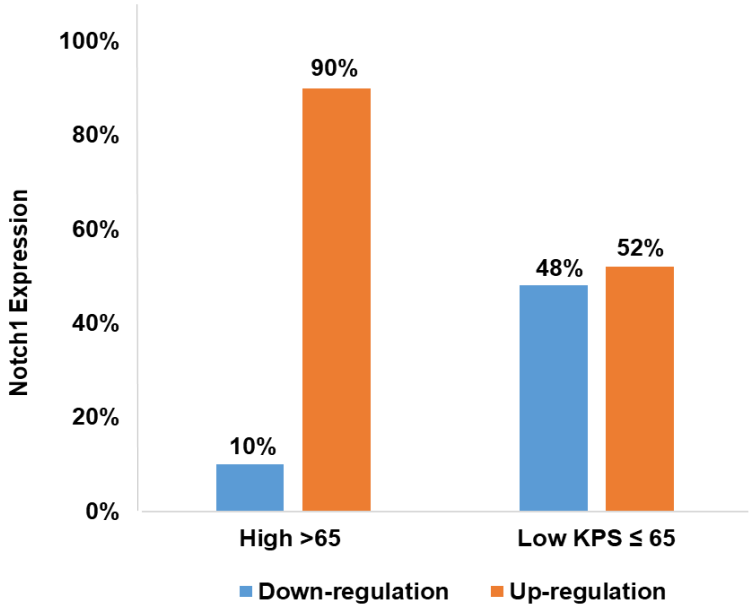

Fig. 3. Correlation between Notch1 gene expression and KPS score

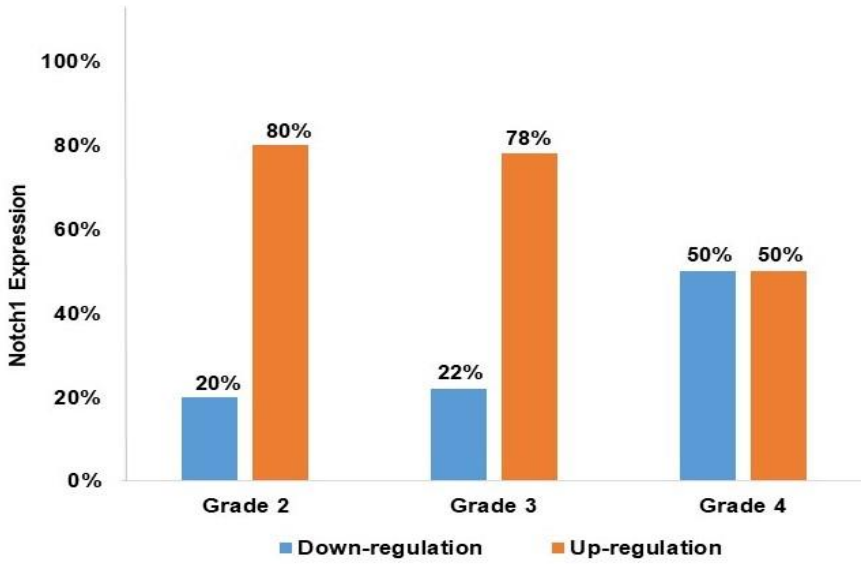

Fig. 4. Notch1 expression association with grade of glioma tumors

3.3 Survival Analysis

To assess the relevance of Notch1 gene expression to disease outcome, univariate and multivariate survival analysis performed using the Kaplan-Meier survival analysis and Cox Proportion Hazard Regression Step-wise Model for 24 months PFS and OS.

3.3.1 Univariate Survival Analysis Using Kaplan-Meier Survival Analysis

3.3.1.1 Progression-free survival

The Kaplan-Meier Survival curve for progression-free survival indicated that patients with up-regulated Notch1 expression had significantly lower incidence (17%) of relapse within 24 months compared with down-regulated Notch1 expression (54%) (Log rank = 9.389, *P* = .009, Fig. 5a). Similarly, patients with high KPS score (>60) was found to be significantly associated with longer progression-free survival (Log rank = 13.843, *P* = <.001, Fig. 5b). Also, the relapse incidence was significantly higher (50%) in patients with grade 4 IDH mutant tumors compared to grade 3 (30%) and grade 2 tumors (9%) (Log rank = 8.300, *P* = .04, Fig. 5c).

3.3.1.2 Overall survival

In the univariate Kaplan-Meier survival analysis for overall survival, the incidence of death was significantly lower (20%) in patients whose tumors showed up-regulated Notch1 expression compared with patients with down-regulated Notch1 expression (92%) (Fig. 6a), this indicates Notch1 act as a good prognosticator with better 24 overall survival. Similar result we noted for high KPS score (>60 KPS) that showed longer overall survival as compared with lower KPS score (Fig. 5b). Also, patients with grade 4 astrocytoma with IDH wild-type tumors showed high incidence (64%) of death compared with patients with IDH mutant with either grade 3 (50%) or grade 2 (13%) tumors (Fig. 5c). Interestingly, tumor location was found to be significantly associated with disease outcome. Patients whose tumors were located in frontal lobe had significantly better overall survival compared with patients with either in parietal, occipital or temporal lobes (Fig. 5d). With age and gender, no such significant association with progression-free survival was detected.

3.3.2 Multivariate survival analysis using Cox Proportional Hazard Step-wise Regression Model for progression-free survival and overall survival

Multivariate survival analysis for progression-free survival and overall survival demonstrated that only KPS score emerged as significant independent parameter at step 1 (progression-free survival; HR = 17.911, 95% CI = 2.270-141-315, *P* =.006; OS; HR = 8.78, 95% CI = 2.510-30.759, *P* = .001), whereas, Notch1 and grade of tumors failed to predict either progression-free survival or overall survival of glioma patients. Using “enter” method of multivariate survival analysis, significance of Notch1 for progression-free survival and overall survival was evaluated

after adjusting for potential co-factors such as KPS score and grade of tumors. However, Notch1 did not reach at the statistically significant for independently predicting either progression-free survival or overall survival, probably due to less sample size.

4. DISCUSSION

In this study, we assessed Notch1 gene expression in glioma patients and explored its impact on disease outcomes. Our findings suggest that up-regulated Notch1 may serves as a positive prognostic indicator for astrocytic glioma patients. Notch1 fold change expression was correlated with clinicopathological parameters and 24 months progression-free survival and overall survival.

In the overall assessment, 90% of glioma patients exhibited altered Notch1 gene expression, comprising 70% up-regulation and 30% down-regulation. A similar trend in Notch1 gene alteration was reported by Narayanappa et al. [11] in GBM tumors; however, they did not observe down-regulation of this gene. It is important to note that, in addition to Notch1 gene, they found down-regulation of Notch 2, 3, and 4. This discrepancy may be attributed to their specific focus on GBM patients, emphasizing exclusive Notch1 up-regulation.

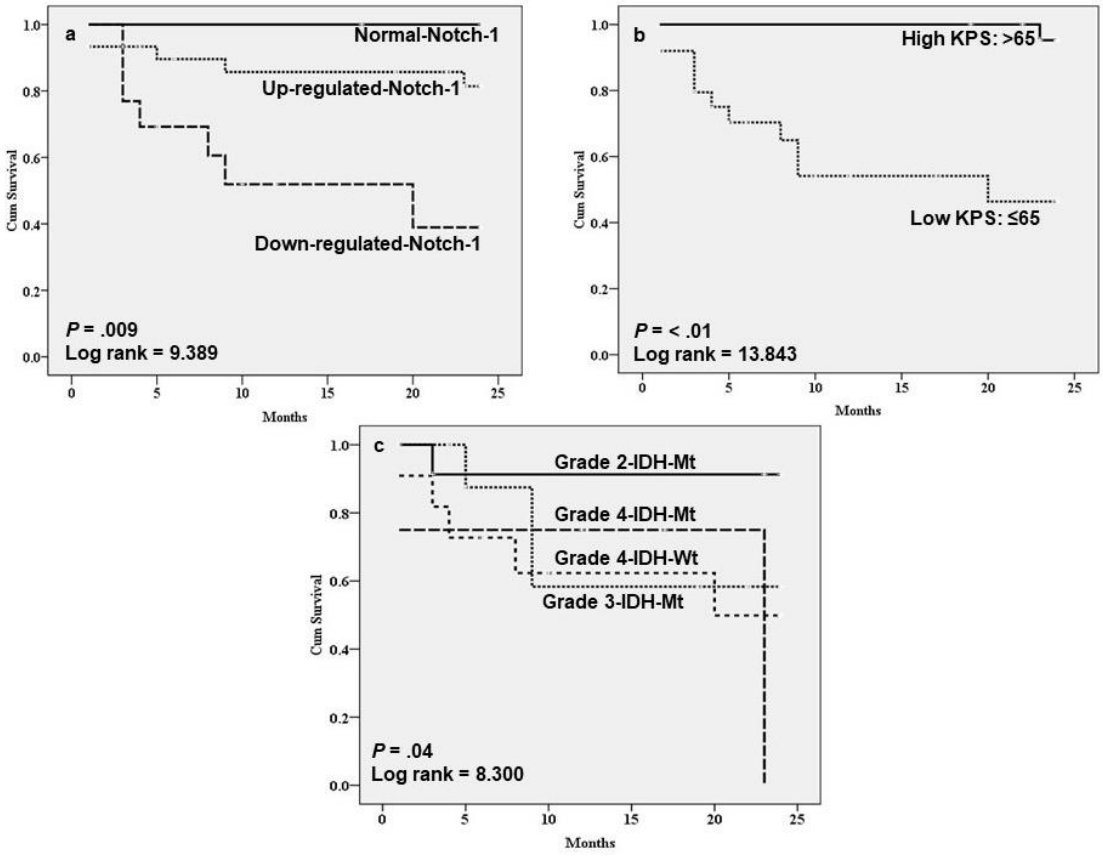

Fig. 5. Kaplan-Meier Survival curves for progression-free survival. a. Patients with different Notch1 gene expression b. Patients with KPS score c. Patients with different grade of tumors

Table 3. Multivariate survival analysis for progression-free survival and overall survival using Cox Proportion Hazard Step-wise Forward LR Method

	Step	HR*	95% CI@		*P* -value
Progression-free survival			**Low**	**High**	
KPS Score	1	17.91	2.270	141.31	0.006
Overall survival KPS Score	1	8.78	2.510	30.759	0.001

**Hazard ratio, @ Confidential Interval*

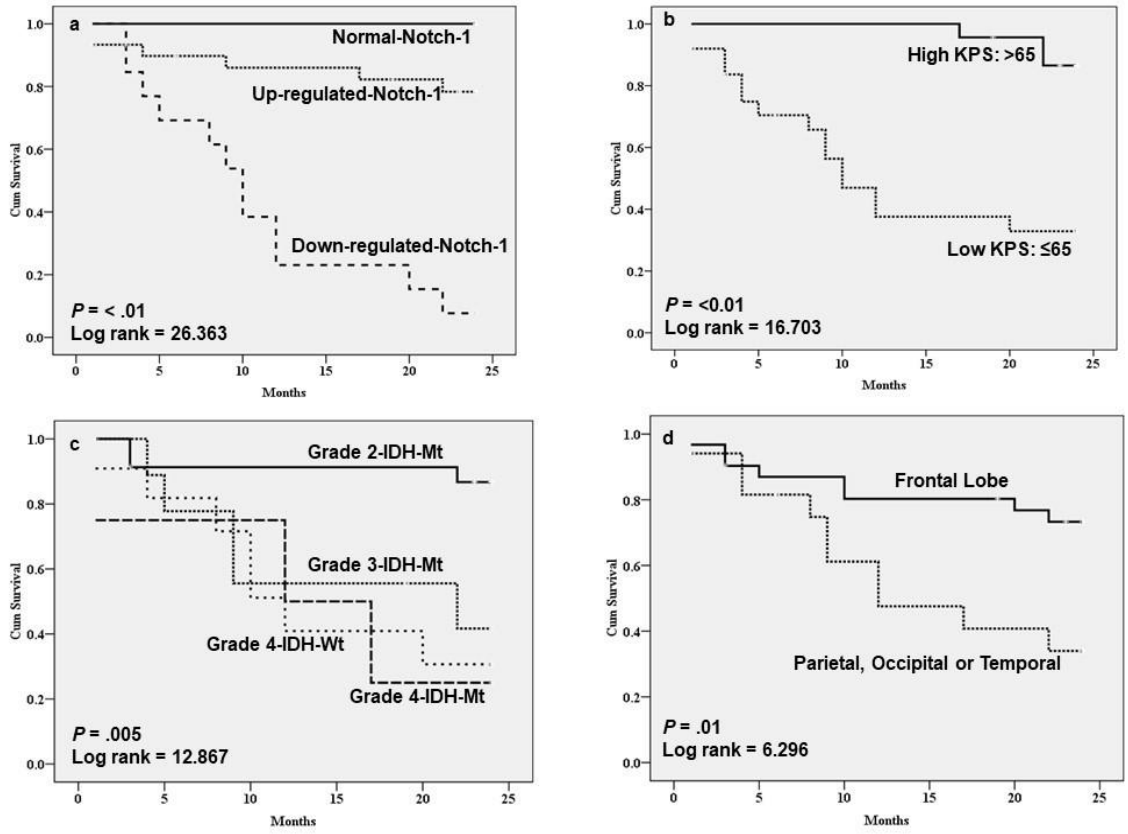

Fig. 6. Kaplan-Meier Survival curves for overall survival. a. Patients with different Notch1 gene expression, b. Patients with KPS score, c. Patients with different grade of tumor d. Location of tumors

KPS score proves to be a significant prognostic factor for glioma patients. In our study, a significant inverse association between Notch1 expression and KPS score was observed. Corroborate to our findings, Li et al. [12] have shown an inverse association between Notch1 expression and KPS score in a study of 33 glioma patients. Patients with a high KPS score at diagnosis exhibited significantly increased Notch1 gene expression, indicative of up-regulation. In contrast, Jiang et al. [13] reported a notable rise in Notch1 expression among patients with a low KPS score. Additionally, Li et al. [14] presented conflicting results, associating heightened Notch1 protein expression notably with a KPS score below 80 rather than exceeding 80. Reduced KPS scores often correlate with diminished survival rates in severe illnesses. Our study established a correlation between elevated Notch1 gene expression and higher KPS scores, suggesting heightened Notch1 expression as a potential predictive factor for enhanced overall survival. This signifies its potential as a favorable prognostic indicator for glioma patients.

Our investigation revealed an increased prevalence of up-regulated Notch1 gene expression in low- grade gliomas compared to high-grade tumors. Notably, with the advancement of tumor grade, the incidence of up-regulated Notch1 gene expression decreased. This aligns with Purow et al.'s [15] findings, demonstrating elevated Notch1 mRNA expression in low-grade gliomas compared to GBM. Conversely, Cheung et al. [16] observed abnormal Notch1 expression across all glioma grades, absent in a subset of grade 4 gliomas. While some studies reported Notch1 overexpression in GBMs [17]. Alternative theories suggest that the activation of Notch induces apoptosis in neural progenitor cells via a pathway dependent on p53 [18]. The reason for reduced Notch1 expression in highly malignant GBM tumors compared to other primary human gliomas remains unclear. The findings indicate the involvement of Notch1 in sustaining the undifferentiated state of glioma cells, and its inhibition facilitates the maturation of these cells into a less aggressive phenotype [19].

Our findings underscore the crucial prognostic significance of Notch1 and KPS score in predicting longer progression-free survival and better overall survival for glioma patients. The Kaplan-Meier survival curves for both, progression-free survival and overall survival indicated that patients with higher Notch1 expression and high KPS score had significantly longer progression-free survival and better overall survival than their respective counter parts. Thus, Notch1 and KPS score remained positive prognosticators for glioma patients. Additionally, particularly notable is patients with grade 4 IDH mutant gliomas, they found to be associated with significantly higher incidence of relapse within 24 months. Grade 4 glioma tumors are most aggressive glioma tumors phenotypically and molecularly also, irrespective of IDH status. They are more heterogeneous and molecularly complex. Therefore, patients having grade 4 tumors showed higher incidence of relapse and worse prognosis.

This study identifies key prognostic indicators influencing overall survival, including KPS score, grade of tumors tumor locations and Notch1 expression. A significantly elevated incidence of death was associated with a high KPS score (P = <.001). Consistent with multiple studies, lower KPS scores have been consistently linked to poorer outcomes in glioma patients. Schröder et al. [20], reported a significantly shorter median overall survival in GBM patients with KPS scores of 70 or less compared to those with scores above 70. Further, tumor location proves to be a critical determinant in astrocytic glioma patients. Our investigation reveals that patients with tumors in the frontal lobe exhibit a significantly lower incidence of death within 24 months compared to those with tumors in the parietal and occipital lobes (P = .012). This underscores the tumor heterogeneity across different brain regions. Previous studies, such as the one study by Roux et al. [21] have also reported increased survival with periventricular involvement and suggested a potential survival distinction between left- and right-sided tumors. While gliomas in the parietal lobe is generally linked to a poorer prognosis, individual outcomes can vary due to unique patient factors. Even small gliomas in crucial brain regions pose challenges in treatment, potentially resulting in significant neurological deficits that impact both the patient's quality of life and survival.

Apart from conventional prognostic parameters, in the present study, we found a significant association between Notch1 gene up-regulated status with improved progression-free survival and overall survival of glioma patients (Fig. 5a and Fig. 6a), suggesting that Notch1 up-regulation could serve as a valuable positive prognostic indicator. Patients with Notch1 down-regulation exhibited poorer overall survival compared to those with up-regulation of the Notch1 gene, in which 44% of patients in our study demonstrated Notch1 up-regulation, correlating with superior 24-month overall survival compared to patients with down-regulated Notch1. The results of the present study indorsed a tumor suppressive role of Notch1 in glioma tumors. This result was essentially in agreement with Giachino et al. [22]. They patients found that in glioma, the high expression of specific NOTCH target genes positively correlates with a better prognosis in human glioma tumors. In line of this, in head and neck squamous cell carcinoma, Wirth et al. [23] have reported that high expression of Notch1 was associated with better overall survival and disease-free survival. This association attributed to the role of Notch1 signaling in regulating the proliferation, survival, and migration of astrocytoma cells. Studies by Luistro et al. [24], and Purow et al. [15], have highlighted the involvement of Notch1 signaling in angiogenesis, a critical process for tumor growth and progression. Additionally, Wang J et al. [25], underscored that Notch1 down-regulation is associated with increased resistance to chemotherapy and radiation therapy in astrocytoma, implicating Notch1 signaling in the regulation of genes involved in DNA damage repair and apoptosis. However, in multivariate survival analysis, Notch1 failed to predict progression-free survival and overall survival due to potential conventional prognosticator, KPS score. Also, the small sample size could be the possible reason for not reaching Notch1 as independent prognostic marker in multivariate analysis.

Further, differences in the outcome of Notch modulation likely relate to the stage of disease progression, crosstalk with other signaling pathways, and intra-tumoral cell heterogeneity, and this inter-tumoral heterogeneity could be one critical factor underlying the observed discrepancies in Notch function [26]. Overall, the effects of the Notch signaling heavily rely on the cellular environment and involve intricate crosstalk with other signaling pathways. Therefore, targeting the Notch pathway may intervene in these processes

and potentially bring better therapeutic effects for patients with glioma.

However, there are several limitations of the current study including small sample size, single center study which could be a result bias or a possible reason for not to reach Notch1 at statically significant using multivariate survival analysis. Also, due to significance of potential conventional prognostic factors such as grade of tumors and KPS score hinder Notch1 to reach at statistically significant level. Overall future studies including more number of glioma patients are warranted.

5. CONCLUSION

In conclusion, the study's findings highlight the potential prognostic significance of Notch1 gene in glioma, particularly, its correlation with patient survival and grade of tumors. These results contribute to the understanding of the molecular mechanisms underlying Notch signaling pathway associated with glioma pathogenesis that may have implications for the development of prognostic markers and potential therapeutic strategies. However, further studies are needed to elucidate the precise molecular mechanisms of the Notch signaling pathway in glioma tumors that will be beneficial for developing novel therapeutic strategies. Also, validation of Notch1 in larger patients' cohort is necessary for targeting Notch1 molecule as targeted therapy for glioma patients.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

Written consent were taken from all patients included in this study.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board and Institutional Ethics Review Committee) (IRC Approval No.: IRC/ 2024/P-20).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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