Original Article

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Pathology Section

Evaluation of Glial-Mesenchymal Transition Using SNAIL and IDH as Prognostic Markers in Glioma Patients: A Cohort Study from a Tertiary Care Centre in Tamil Nadu, India

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ABSTRACT

Introduction: The incidence of gliomas is increasing in India. Several poor prognostic indicators of glioma include Snail family transcriptional repressor 1 (SNAIL), Snail Family Transcriptional Repressor 2 (SLUG), and Twist Family bHLH Transcription Factor 1 (TWIST), which belong to the zinc-finger family of transcriptional repressors involved in Epithelial-Mesenchymal Transition (EMT). In gliomas, EMT is referred to as Glial-Mesenchymal Transition (GMT). During GMT, glial cells acquire mesenchymal properties, facilitating invasion into the brain parenchyma. This increases the expression of GMT markers which is associated with high-grade gliomas, higher recurrence and poor survival rates.

Aim: To evaluate the prognostic significance of SNAIL expression and its association with Isocitrate Dehydrogenase (IDH) mutation in glioma patients.

Materials and Methods: The present cohort study was conducted in the Department of Pathology, at Chettinad Hospital and Research Institute over a period of seven years and three months from March 2015 to June 2021, a tertiary healthcare center in Tamil Nadu, India. Paraffin blocks and medical records of 25 histologically confirmed glioma cases were retrieved from the archives of the Department of Pathology. Immunohistochemistry (IHC) was performed using SNAIL and IDH-Mutant (IDH-M) antibodies. The association of SNAIL and IDH expression with clinicopathological parameters and patient outcome was analysed using the chi-square test and Fisher's exact test. Survival analysis was carried out using the Kaplan-Meier method.

Results: Of the 25 glioma cases, 3 were Grade I, 10 Grade II, 2 Grade III, and 7 Grade IV. During a follow-up period of seven years and three months, 14 patients (56%) died and 11 (44%) were alive. Strong SNAIL expression in glioma patients was associated with poor survival, with a mortality rate of 83.3% (10 cases), compared to moderate SNAIL expression (44.4%, 4 cases) and weak expression (0%). The association between SNAIL grading and patient outcome was statistically significant (p=0.002). Only 2 (25%) of IDH-mutant-positive cases resulted in death, compared to 12 (70.58%) deaths among IDH-mutant–negative cases, which was also statistically significant (p=0.039).

Conclusion: GMT plays a crucial role in transforming glial cells into mesenchymal-like cells, thereby enhancing tumour invasiveness. SNAIL, a key marker of GMT, is associated with higher World Health Organisation (WHO) tumour grade, increased recurrence, and poor prognosis in gliomas. Additionally, IDH-M gliomas demonstrate a better prognosis compared to IDH-wild-type tumours. SNAIL may serve as a potential prognostic biomarker and therapeutic target in glioma.

Keywords: Basic helix-loop-helix, Glioma, Isocitrate dehydrogenase mutation, Prognosis, Snail family transcriptional repressor 1

INTRODUCTION

Gliomas are primary tumours arising from the glial cells of the central nervous system and constitute the most common group of primary brain tumours [1]. In India, the Central Nervous System (CNS) tumours account for approximately 2% of all malignancies, with an incidence ranging from 5 to 10 per 100,000 population, showing a significant increasing trend [2]. Among the various types of gliomas, the most common tumour is diffuse astrocytoma (38.7%), among which the majority are high grade gliomas (59.5%) [3]. According to the 2021 WHO Classification of CNS Tumours [4], which incorporate a hybrid classification showing both histology and molecular characteristics of the gliomas, the common adult type diffuse gliomas, are classified into three types, astrocytoma IDH mutant (grades 2-4); Oligodendroglioma (IDH Mutant, 1p/19q co-deleted) (grades 2-3), Glioblastoma (GBM) (IDH Wild type grade 4) [5]. Despite the advances in the present clinical science, the overall survival of the GBM patients is very poor, approximately the life expectancy is about 12-15 months after surgery [6]. Recurrence and treatment resistance are the major challenges in glioma management. Most patients with GBM develop recurrence within two years of the surgery [7]. Even tumours lacking overt high-grade histological features may recur or undergo malignant transformation. Therefore, identifying reliable prognostic markers is essential [8]. The rate of proliferation and the recurrence of the glioma is mainly regulated by EMT process which is induced by zinc finger family transcriptional repressors that includes SNAIL, SLUG and TWIST [8] This EMT process is very well studied in carcinomas like breast [9], pancreas [10], and colon [11]. This EMT process is described as GMT in gliomas [12]. In GMT, due to the expression of the zinc finger family transcriptional repressor genes like SNAIL, SLUG and TWIST, the glial cells acquire the property of a mesenchymal cells and facilitate the invasion of the tumour cells into the brain parenchyma. So, evaluating the expression of the main transcriptional repressor genes, SNAIL becomes essential to assess the prognosis of the patients [12]. There are not many studies to determine the role of SNAIL in the prognosis of the glioma patients. Hence, the present study was undertaken to evaluate the role of SNAIL as a prognostic biomarker and potential therapeutic target in glioma.

MATERIALS AND METHODS

The present cohort study was conducted in the Department of Pathology, at Chettinad Hospital and research Institute in Tamil Nadu, India, from March 2015 to June 2021 (7 years and 3 months), after obtaining approval from the Institutional Ethical Committee. (586/IHEC/11/19).

Inclusion and Exclusion criteria: A total of 25 histologically confirmed glioma cases were included. Paraffin blocks and slides were retrieved from the archives. Clinical, radiological, and follow-up data were collected from medical records. A telephone call was made to those patients or their attendants for further follow-up details. The patients' age, gender, clinical features, radiological findings, and histopathological diagnosis and grade of tumour were taken into consideration. Distribution of histopathological diagnosis among the study population [Table/Fig-1]. Distribution of Grade of tumour among the study population [Table/Fig-2].

Histopathological diagnosis	n (%)
Anaplastic astrocytoma	2 (8.00)
Anaplastic oligodendroglioma	2 (8.00)
Astrocytoma	1 (4.00)
Astrocytoma (gemistocytic variant)	1 (4.00)
Diffuse astrocytoma	3 (12.00)
Fibrillary astrocytoma	1 (4.00)
Glioblastoma (GBM)	8 (32.00)
Mixed glioma	2 (8.00)
Oligodendroglioma	1 (4.00)
Pilocytic astrocytoma	3 (12.00)
Recurrent diffuse fibrillary astrocytoma	1 (4.00)
Total	25 (100.00)

[Table/Fig-1]: Distribution of Histopathological diagnosis among the study population.

Grade of tumour	Frequency	Percent
I	3	12.00
II	10	40.00
III	4	16.00
IV	8	32.00
Total	25	100.00

[Table/Fig-2]: Distribution of grade of the tumour in the study population.

Immunohistochemistry:

Immunohistochemical staining was performed using:

- IDH1 R132H (mouse monoclonal antibody)
- SNAIL1 polyclonal antibody (1:100 dilution)
- Secondary antibody: 2 steps plus poly-HRP Antimouse/Rabbit Immunoglobulin G (IgG) Detection system (with 3,3'-Diaminobenzidine (DAB) solution) (Category No:E-IR-R217).

Study Procedure

The paraffin sections were deparaffinised and hydrated. Then, the endogenous peroxidase activity was eliminated by incubating with 3% H_2O_2 for 10 minutes. After a wash with Trisbuffer Solution (TBS); for SNAIL, Phosphate Buffer Solution (PBS) and goat serum were added for 30 minutes. IDH1R132H (primary antibody, ready to use), was added for 1-2 hours, followed by a wash with TBS. Polyperoxidase-AntiMouse/Rabbit IgG was added for 20 minutes. Then, washed with TBS or the DAB working solution; with every 1ml of DAB Substrate, one drop of DAB concentrate was added. This freshly prepared DAB concentrate was added for 10 minutes, a tan/brownish-yellow colour was taken as the positive signal. Then, the section was washed in distilled water to terminate the chromogenic reaction, followed by counterstaining using haematoxylin and a water wash. Then, it was dehydrated with alcohol, followed by mounting the slide with xylene and DPX solution.

Interpretation of immunohistochemistry

SNAIL Scoring: Nuclear staining was assessed using a semi-quantitative scoring system (Three-tiered system):

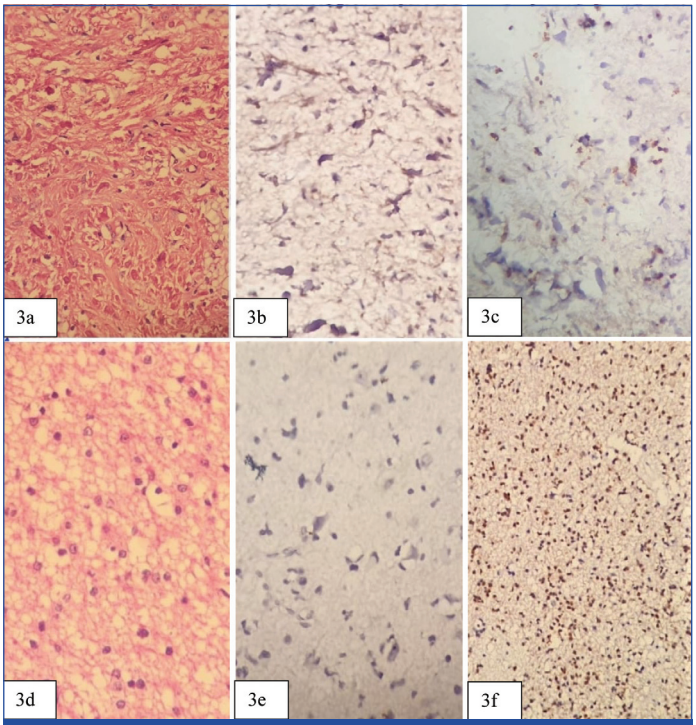
- Intensity: 1 (weak), 2 (moderate), 3 (strong)
- Percentage score: 1 (1-25%), 2 (26-50%), 3 (51-75%), 4 (76-100%)

By counting 1000 positive tumour cells in the representative areas, the percentage of positive tumour cells were determined and recorded as Percentage Score.

Final score=Intensity×Percentage [13]

- 1-4: Weak
- 5-8: Moderate
- 9-12: Strong

The Haematoxylin and Eosin (H&E) stain and IHC-IDH and SNAIL antibody stain in tumour grade I, II, III, recurrent diffuse astrocytoma and grade IV were labelled as following [Table/Fig-3a-f,4a-f;5a-f].



[Table/Fig-3a-f]: **(a)** H&E stained High-Power (HP) view (40×) micro photograph shows a bipolar cell with Rosenthal fibers and microcystic spaces →Pilocytic astrocytoma; **(b)** IHC-IDH stain showing no cytoplasmic positivity - Negative for IDH; **(c)** IHC- SNAIL Ab in HP view show no nuclear positivity - Negative/weak positive for SNAIL; **(d)** The H&E-stained HP view shows a moderately pleomorphic nucleus in the fibrillary background→Grade II Diffuse astrocytoma; **(e)** IHC-IDH Ab-HP showing no cytoplasmic positivity- it is negative for IDH; **(f)** IHC-SNAIL Ab-HP view shows a moderate positivity.

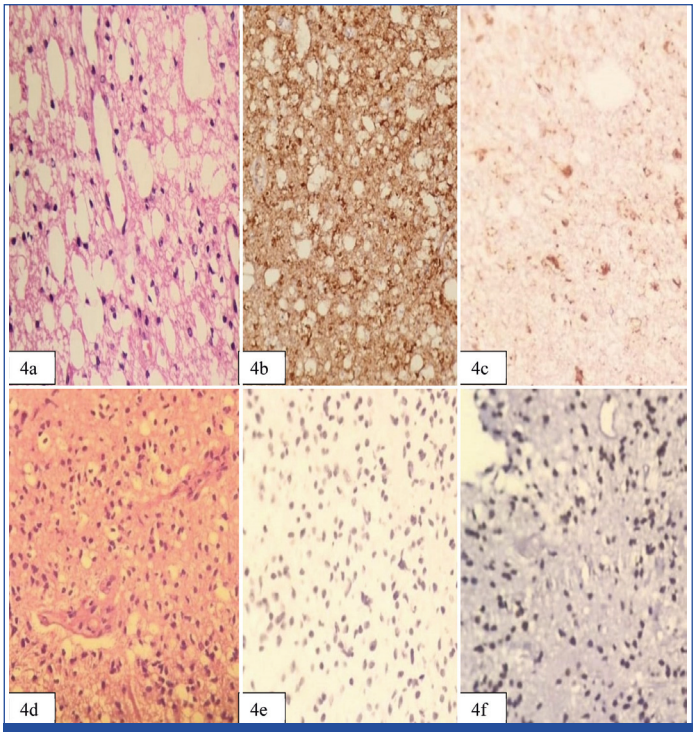
IDH Interpretation: Granular cytoplasmic staining was considered positive [14].

STATISTICAL ANALYSIS

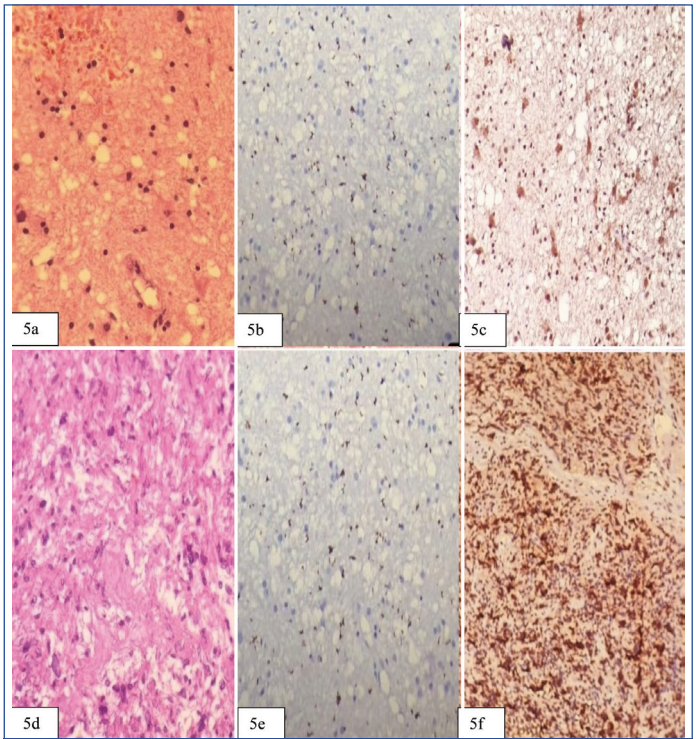
To determine the significance of association between two variables-chi-square test has been used. When more than 20% of cell values have expected cell value <5, then Fisher's exact test has been used. Kaplan-Meier survival curve was used to assess the survival rate of the patients.

RESULTS

Among the 25 glioma patients, 20 (80%) were males and 5 (20%) were females, with a mean age of 40.44±13.13 years. They were followed up for a period of seven years and three months (ranges from 6 months -7 years 3 months). Post-operatively, 11(44%) had



[Table/Fig-4a-f]: **(a):** The H&E-stained HP view shows a tumour cell showing round nucleus with perinuclear halo → Grade II Oligodendroglioma; **(b)**: IDH Ab-HP view showing a strong cytoplasmic positivity- Positive for IDH; **(c)** IHC: SNAIL Ab-HP view shows a weak positivity; **(d)** The H & E stained HP view shows tumour necrosis with pleomorphic tumour cells →Grade III Anaplastic Oligodendroglioma; **(e)** IHC: IDH Ab -HP view shows no cytoplasmic positivity- Negative for IDH; **(f)** IHC: SNAIL Ab- HP view shows moderate positivity.



[Table/Fig-5a-f]: **(a)** The H&E-stained HP view shows→Grade II- recurrent diffuse astrocytoma; **(b)** IHC: IDH Ab-HP view shows weak background positivity-Negative for IDH; **(c)** IHC: SNAIL Ab -HP view shows moderate nuclear positivity; **(d)** The H&E- stained HP view shows tumour necrosis with pleomorphic tumour cells and vascular proliferation→ Grade IV – Glioblastoma (GBM); **(e)** IHC: IDH Ab HP view shows no cytoplasmic positivity -Negative for IDH; **(f)** IHC: SNAIL1 Ab HP view shows strong positivity.

radiotherapy, 5(20%) had chemotherapy and 5(20%) had both chemo and radiotherapy, while 4 (16%) had no postoperative treatment.

The overall mortality rate was 56% (14 deaths) and the survival rate was 44% (11 cases). In the study population, the overall mean survival time for all the grades of glioma was 52.6±11.63 months (range: 29.8-75.4 months), and the duration of illness from diagnosis to surgery was 21.04±15.7 months.

Expression of SNAIL Antibody in the Study Population

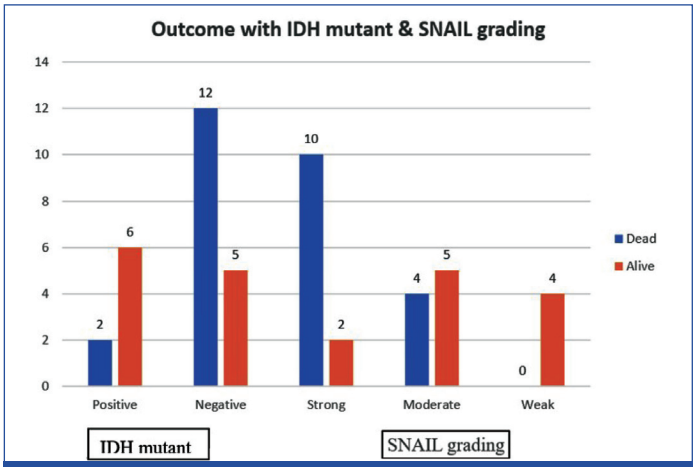
Grade IV tumour had a higher proportion of strong SNAIL grading with seven cases (7/8-87.5%) followed by Grade III tumour with two cases (2/4-50%). Strong SNAIL grading was absent in Grade I tumours (three cases-0/3) and least frequent in Grade II tumours, with three cases (3/10, 30%) showing strong expression. Strong SNAIL expression was significantly associated with higher WHO grade (p=0.001), increased recurrence (p=0.01), and poor survival (p=0.002). The overall mean survival time for glioma among the strong SNAIL grading was 20.08 (±12.2) while, the mean survival time for glioma among the moderate SNAIL grading group was 53.11(±12.1) months. The mean survival time for the weak SNAIL grading group could not be estimated, as there were no deaths among those subjects. The difference in the mean survival time among the three SNAIL grading groups was statistically significant by log rank test (p=0.011).Strong SNAIL grading had a higher proportion of recurrence with 12 cases (100%) (12/12) followed by moderate SNAIL grading with three cases (33.33%) (3/9) and weak SNAIL grading one case (25%) (1/4) recurrence rate. The difference in recurrence rate distribution between different SNAIL grading groups was statistically significant (p-value=0.001).

Expression of IDH Mutation in the Study Population

IDH mutation was more frequent in Grade II tumours but did not show statistically significant association with tumour grade (p=0.1). Among the study population, eight cases were IDH-mutant-positive and 17 cases were IDH-mutant-negative. Total mortality in the study population is 14, among that IDH-M negative patients (12 cases (12/17), 70.58%) but the mortality in the IDH-M positive patient was significantly lower (2 deaths (2/8), 25%) which is statistically significant (p= 0.039). The mean survival time for gliomas among IDH-M positive cases was 69±9.2 months, (ranging from 50.96 to 87.03 months) while the mean survival time for IDH-M negative cases was 36.41 ±12.92 months (ranging from 11.1 to 61.7 months). (p=0.03). An inverse relationship between SNAIL expression and IDH mutation status was observed.

Outcome with IDH mutant and SNAIL grading [Table/ Fig-6a].

Recurrence with SNAIL grading [Table/Fig-6b].



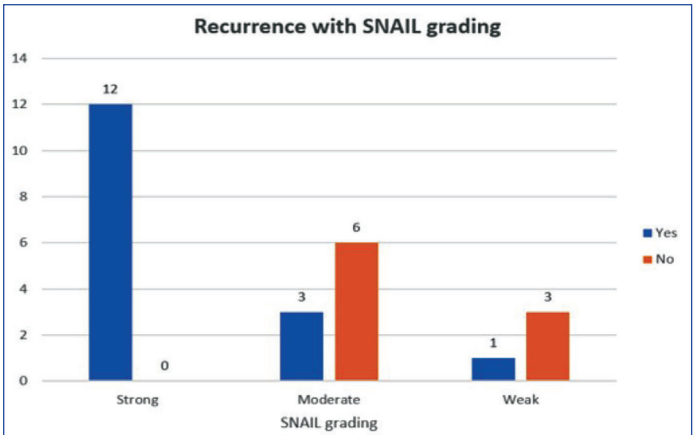
[Table/Fig-6a]: Outcome with IDH mutant and SNAIL grading.

Survival distribution with the SNAIL grading in the study population [Table/Fig-7a].

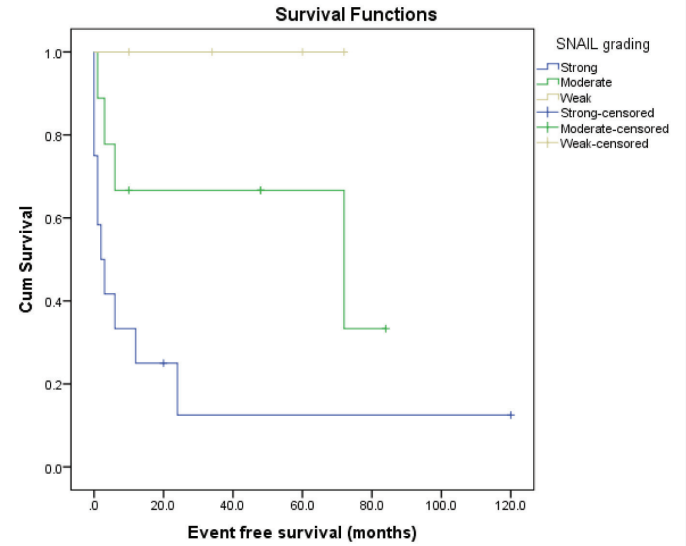
Survival distribution with the IDH mutant in the study population [Table/Fig-7b].

DISCUSSION

Glial-Mesenchymal Transition contributes to tumour invasiveness and therapeutic resistance in gliomas. SNAIL, a zinc-finger transcription factor, represses cell adhesion molecules and promotes a mesenchymal phenotype, thereby enhancing tumour motility [15]. On EMT activation, the transcription factors like Beta catenin



[Table/Fig-6b]: Recurrence with SNAIL grading.



SNAIL grading	Mean	Std. Error	95% Confidence Interval		p-value
			Lower Bound	Upper Bound	
Strong	20.083	12.2	0	43.907	0.011
Moderate	53.111	12.1	29.4	76.779	
Weak	No deaths				
Overall	40.914	11.7	17.9	63.917	

[Table/Fig-7a]: Survival Distribution with the SNAIL grading in the study population. The mean survival time for gliomas among strong SNAIL grading was 20.08 (± 12.2) months ranging from 0 to 43.9 months while the mean survival time for gliomas among moderate SNAIL grading was 53.11 (± 12.1) months ranging from 29.4 to 76.7 months. The mean survival time among weak SNAIL grading could not be estimated since there were no deaths among those subjects.

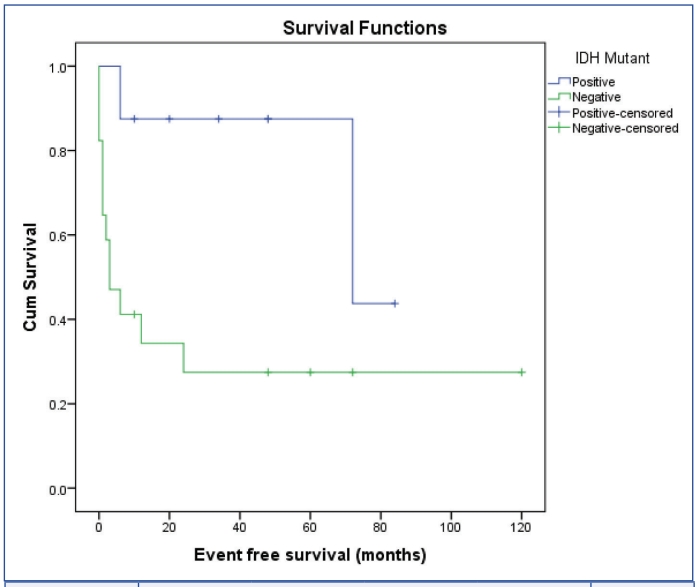
or the epigenetics factors like microRNA-21 (miRNA21) enhance the extra cellular matrix cleavage, suggesting that the major event driving increasing malignancy in glial tumours is this phenomenon of mesenchymal transition [16].

In epithelial tumours, this process of EMT showed the metastatic potential of the tumour, whereas in glioma, this GMT process is associated with the invasiveness and the recurrence of the tumour [17].

SNAIL-Family

SNAIL was first found in *Drosophila melanogaster* which participates in mesoderm formation. In vertebrates, three SNAIL family proteins -SNAI1 (also termed SNAIL1), SNAI2 (SLUG), and SNAI3 (SMUC) have been identified. SNAIL, SLUG, and Snail-related gene in Murine Skeletal Muscle Cells (SMUC) were identified [18].

SNAIL and SLUG are the two master transcriptional activators which repress the E-cadherin phenotype in the cancer stem cells. SNAI1 and SNAI2 are associated with increased expression and invasion in malignant gliomas [19]. Recent studies also showed that SNAI3 Antisense RNA 1 (AS1) act as a tumour suppressor gene



IDH mutant	Mean survival time (months)				Log rank p-value
	Mean	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Positive	69	9.2	50.96	87.034	0.03
Negative	36.41	12.92	11.080	61.743	
Overall	52.6	11.63	29.802	75.414	

[Table/Fig-7b]: Survival Distribution with the IDH mutant in the study population. The mean survival time for gliomas among positive IDH mutant was 69 (± 9.2) months ranging from 50.96 to 87.03 months while the mean survival time for gliomas among negative IDH mutant was 36.41 (± 12.92) months ranging from 11.1 to 61.7 months. Kaplan-Meier survival analysis demonstrated significantly longer survival among IDH-mutant positive glioma patients compared to IDH-mutant negative patients (log-rank p=0.03).

in glioma. In a study with mice, it was postulated that the levels of SNAI3 AS1 is reduced in glioma and it is inversely proportional to WHO grades of the tumours [20]. Based on in-vitro studies, it was suggested that increased WNT/beta signaling pathway activity in turn triggers the Zinc finger E-box binding homeobox 2 (ZEB2), TWIST, SNAI1, and SNAI2 which directly or indirectly through the NOTCH signaling pathway activate the EMT-like phenotype in GBM. They suppress the E-cadherin and reduce its function, which results in decreased cell-cell contact, thus increasing motility and upregulating the expression of the mesenchymal phenotypein GBM. Consequently, high expression of SNAIL is associated with a worse prognosis [21]. One of the potential inducers of EMT was the hypoxic microenvironment [22].

Association between IDH mutant and SNAIL1 in the Study Population:

In the present study population,

- Grade I tumours were negative for both IDH-M and SNAIL1.
- Grade II tumours showed IDH-M positivity, and weak to moderate SNAIL1 expression, which is associated with good prognosis.
- Grade III tumours were negative for IDH-M, but showed moderate to strong positivity for SNAIL1, they are associated with relatively poor prognosis.
- Grade IV tumours were negative for IDH-M and strongly positive for SNAIL1 which is associated with poor prognosis.

In the present study, one case of astrocytoma showed a grade II morphology but was negative for IDH-M and showed a moderate to strong positivity for SNAIL1. This case presented with multiple recurrences in the long run. Another case of GBM, though showing a morphology of GBM with positivity for IDH-M and strong positivity for SNAIL1, on follow-up showed a comparatively better prognosis but later presented with recurrence. This supports the new WHO

S. No	Study (Author, Year)	Study focus	Key findings	Prognostic significance
1	Myung J et al., 2010 (Neuropathology) [25]	Snail and COX-2 expression in gliomas	Snail and COX-2 expression significantly correlated with higher WHO tumour grade. Increased expression seen in high-grade gliomas (III & IV).	High Snail expression associated with poor overall survival; identified as an independent adverse prognostic factor.
2	Mahabir R et al., 2014 (Neuro-Oncology) [26]	Effect of irradiation on snail and GMT	Radiation induced sustained elevation of Snail expression in malignant glioma cells, promoting GMT and enhancing invasiveness.	Snail-mediated GMT contributed to radio resistance and tumour aggressiveness.
3	Han SP et al., 2011 (Cell Mol Neurobiol) [27]	Role of SNAIL1 in Glioblastoma (GBM) cell biology	SNAI1 promoted proliferation and migration of GBM cells in vitro. Knockdown reduced tumour cell growth and migration.	Suggests SNAI1 acts as an oncogene and a potential therapeutic target.
4	Du L et al., 2017 (Chinese Neurosurgical Journal) [28]	EMT progression in gliomas	Progressive increase in mesenchymal markers with increasing tumour grade. Demonstrated EMT-like changes in glioma progression.	EMT markers correlated with tumour aggressiveness and poor prognosis.
5.	Present study, 2026	Role of SNAIL in glioma	SNAIL expression is significantly associated with higher tumour grade, recurrence, and poor survival in glioma patients. IDH mutation confers a survival advantage.	SNAIL may serve as a potential prognostic biomarker and therapeutic target for the future management of glioma.

[Table/Fig-8]: The comparison of the present study with the previous studies [25-28].

2021 classification protocol, which states that IDH-mutant diffuse astrocytic tumours are classified as astrocytoma, IDH-mutant, CNS WHO grade 2-4. Thus, an IDH-mutant tumour with glioblastoma-like morphology may still be classified as astrocytoma, IDH-mutant, CNS WHO grade 4, rather than glioblastoma. The term "Gioblastoma" is restricted to IDH-wildtype adult-type diffuse astrocytoma fulfilling the required histological or molecular criteria [23]. The essential criteria for grade IV gliomas in the present WHO 2021 classification include Telomerase Reverse Transcriptase (TERT) promoter mutation, +7/-10 chromosome copy number changes, and Epidermal Growth Factor Receptor (EGFR) gene amplification [24]. All these criteria require many molecular studies, but by mere grading of SNAIL1 antibody in these tumours with the simple IHC techniques, the tumour grade was identified as well as its prognosis and the chance of recurrence. It was found that the SNAIL expression is inversely proportional to the expression of the IDH-M, where IDH-M is a proven marker of good prognosis. Thus, it was concluded that SNAIL1 is a marker for poor prognosis and recurrence in glioma.This statement from the present study correlates with the following, All the studies mentioned above concluded that the stronger expression of SNAIL results in increased GMT and increased invasiveness of the tumour, which leads to a poor prognosis. Since most of these studies were conducted in-vitro (tissue culture), they have not extensively addressed tumour recurrence, which is a major challenge in high-grade gliomas. The high-risk of recurrence is the obvious outcome of increased GMT and invasiveness in these glial tumours. The comparison of the present study with the previous studies have been demonstrated in [Table/Fig-8] [25-28].

Limitation(s)

The primary limitation of the present study was the small sample size. The molecular mechanism underlying the activation of zinc finger family transcriptional repressors vary across studies and are primarily based on in-vitro models. Therefore, further studies with larger cohorts are required to validate the role of SNAIL as a robust prognostic and therapeutic marker for glioma patients.

CONCLUSION(S)

From the findings of the present study, the authors conclude that SNAIL expression is significantly associated with higher tumour grade, recurrence, and poor survival in glioma patients. IDH mutation confers a survival advantage. SNAIL may serve as a potential prognostic biomarker and therapeutic target in gliomas. To the best of the authors' knowledge, based on an extensive PubMed review, the present study was the first study to delineate the relationship between IDH mutation and SNAIL expression with WHO tumour grade, recurrence, and long-term clinical outcomes in glioma over a 7-year follow-up. SNAIL has been identified as one of the major genetic factors required for the further progression and invasion of gliomas. Therefore, we suggest SNAIL as a promising therapeutic target for the future management of gliomas.

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