Clinicopathologic Significance of Fascin Expression in Different Grades of Gliomas

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Abstract

Background: Gliomas account for more than two-thirds of all malignant brain tumors. Fascin is a cytoskeleton cell protein that plays a crucial role in invasion and spread of the tumor. However the exact role is not clear.

Objectives: The purpose of this study is to 1) assess Fascin expression in different types and grades of gliomas and 2) find out the relationship between its expression and the clincopathological factors.

Patients and methods: Immunohistochemical (IHC) staining with Fascin was studied on 70 cases of gliomas using a mouse monoclonal antibody against human fascin protein, immunoreactivity score of cytoplasmic and membranous staining was used to assess the immunoexpression of fascin in tumor cells.

Results: There was a noteworthy correlation discovered between Fascin expression and histological type (p=0.032), and tumor grade (p= 0.02). However, there was no correlation between Fascin expression and age, sex, tumor site, and tumor size.

Conclusion: Fascin is a good marker of predicting poorer outcomes in glioma patients, but further work is needed to implement this marker in clinical practice

Keywords: Glioma; Glioblastoma multiform; Fascin

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Introduction

Glioma is a frequently occurring malignant tumor of the central nervous system, it accounts for over two-thirds of all malignant brain tumors **(Ji et al., 2023)**. The Pathological Grading Standard of the World Health Organization (WHO) states (2007 version), gliomas are divided into four levels. Patients in grade I have the best prognosis and a lower incidence of malignancy. However, patients with grade IV cancer have the worst prognosis and the highest degree of malignancy **(Louis et al., 2007).** Despite the fact that the recommended course of treatment including radiation, concurrent and maintenance chemotherapy, and the safest surgical resection possible **(Weller et al., 2015)**, the prognosis for glioma patients remains poor and nearly every patient eventually relapses. Patients with GBM still have a median survival period of about a year, and their 5-year overall survival rate is less than 5% **(Jhanwar-Uniyal et al., 2015)**.

Tumor appearance, development, and metastasis are all directly related to cell migration and invasion. The cytoskeleton expression levels and structural abnormalities are linked to these biological reactions of tumor cells **(Peckham, 2016)**. Fascin protein is a cytoskeleton-organizing protein with a relative molecular mass of 55 kDa **(Ishikawa et al., 2003)**. It can alter the integrity of intercellular connections and cause structural alterations in cell membranes, which can encourage tumor cell invasion and metastasis **(Hashimoto et al., 2009)**. Previous research has demonstrated that fascin is strongly expressed in a variety of cancers, such as lung, ovarian, gastric, and esophageal cancers **(Ling et al., 2015)**.

This study is done to evaluate fascin expression in various gliomas types and grades to find out the relationship between its expression and the clincopathological parameters and its effect on the prognosis, hoping to become a new marker in prognosis and treatment modalities of gliomas

Patients and methods

Tissue Specimens

The Medical Research Ethics Committee of - faculty of medicine granted permission to conduct the study under IRB Registeration number: -23-04-19PD. This study comprised of seventy specimens of different grades and histological types of gliomas. Specimens were acquired from cases admitted to the Neurosurgery department and referred to the Pathology Laboratory between November 2017 to 2022 were retrospectively analyzed.

Following surgery, histopathology results were obtained. A retrospective evaluation of the medical records was conducted. Specimens with complete clinical data were included. None of the included patients received pre-operative chemotherapy or radiotherapy. Clinical data were collected from the hospital medical files. Formalin-fixed paraffin-embedded tissue blocks were made from every specimen. Two tissue slices were extracted from each block; the first was stained with H&E, and the second was IHC-stained with the Fascin antibody.

H&E stained sections were re-examined to confirm the diagnosis and evaluate the histological subtype and tumor grade.

Immunohistochemistry

The avidin/biotin peroxidase complex technique was used to carry out immunohistochemical staining using a mouse monoclonal antibody against human fascin protein (55k-2). Mouse anti-human Fascin monoclonal primary antibody (Catalog number # MAB7745, mouse IgG2A clone # 833223, Biotechne, at dilution 1:100)

was incubated on the tissues for the entire night.

Scoring of Fascin immunoreactions : With minor adjustments, Foteini et al.'s analysis of the extent, intensity, and cumulative immunoreactivity score of cytoplasmic and membranous staining was used to assess the immunoexpression of fascin in tumor cells **(Foteini et al., 2008)**. Based on the proportion of positive immunostained tumor cells, the degree of immunostaining was divided into four groups. Scores are as follows: 0 for absence, 1 for less than 25%, 2 for 25% to 50%, 3 for 50% to 75%, and 4 for more than 75%. Based on the cytoplasmic and membranous staining of endothelial cells used as internal controls, the intensity of positive immunostaining of tumor cells was divided into four categories: Score 0: Absent, Score 1: Weak (less than endothelial cells), Score 2: Moderate (equal to endothelial cells), and Score 3: Intense (more than endothelial cells). Each case's extent and intensity scores were multiplied to get a combined immunoreactivity score (CIS). Cases were further grouped in to: Absent (0): 0, Mild staining (1): 1-4, Moderate (2): 5-8, and Intense (3): 9-12.

Statistical analysis

Statistical Software Package for Social Science (SPSS software version 20) was used for statistical analysis. Quantitative data were presented as mean ± standard deviation (SD), median and range, while frequencies and percentages were used for qualitative data. T-test was performed for comparing two means. To compare the expression rates across the categories, the chi square (X2) test was used. A p value was deemed highly significant if it was less than 0.001 and statistically significant if it was less than 0.05.

Results

A total of 70 cases of gliomas were included in this study, with a mean age of 56.1 year. 37/70 (52.9%) of them were ≤ 55 years. 55.7% (39/70) of the cases were males. 47/70(67.1%) of the cases were supra-tentorial, 49/70(70%) of the cases were less than 5cm in size. Histologically they were classified into pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, glioblastoma multiform, ependymoma, anaplastic ependymoma, and oligodendroglioma as shown in **(Table.1)**. Regarding the WHO grading, grade II was the most common grade representing 35/70(50%) of cases **(Table.1)**.

Table 1. Clinicopathological data of the 70 studied cases

Clinicopathological Data	Classes	No. of cases (%)
Age	≤55 >60	37 (52.9%) 33(47.1%)
Sex	Female Male	31(44.3%) 39(55.7%)
Site	Supra-tentorial Infra-tentorial	47(67.1%) 23(32.9%)
Tumor size	<5 ≥5	49 (70%) 21(30%)
Histological subtype	Pilocytic astrocytoma Diffuse astrocytoma Anaplastic astrocytoma Glioblastoma multiform Ependymoma	9(12.9%) 23(32.9%) 10(14.3%) 14(20%) 6(8.5%)

	Anaplastic ependymoma Oligodendroglioma	2(2.9%) 6(8.5%)
WHO grade	I II III IV	9(12.8%) 35(50%) 12(17.1%) 14(20%)

Fascin protein expression appeared as brownish cytoplasmic and membranous stain. Its expression was variable among the different grades and types of gliomas.

Fascin expression appeared in 54/70 (77.1%) of studied gliomas, with different degrees of positivity, as it was weak in 18/70 (25.7%), moderate in 21/70 (30%), and strong in 15/70 (21.4%) **(Fig.1)**.

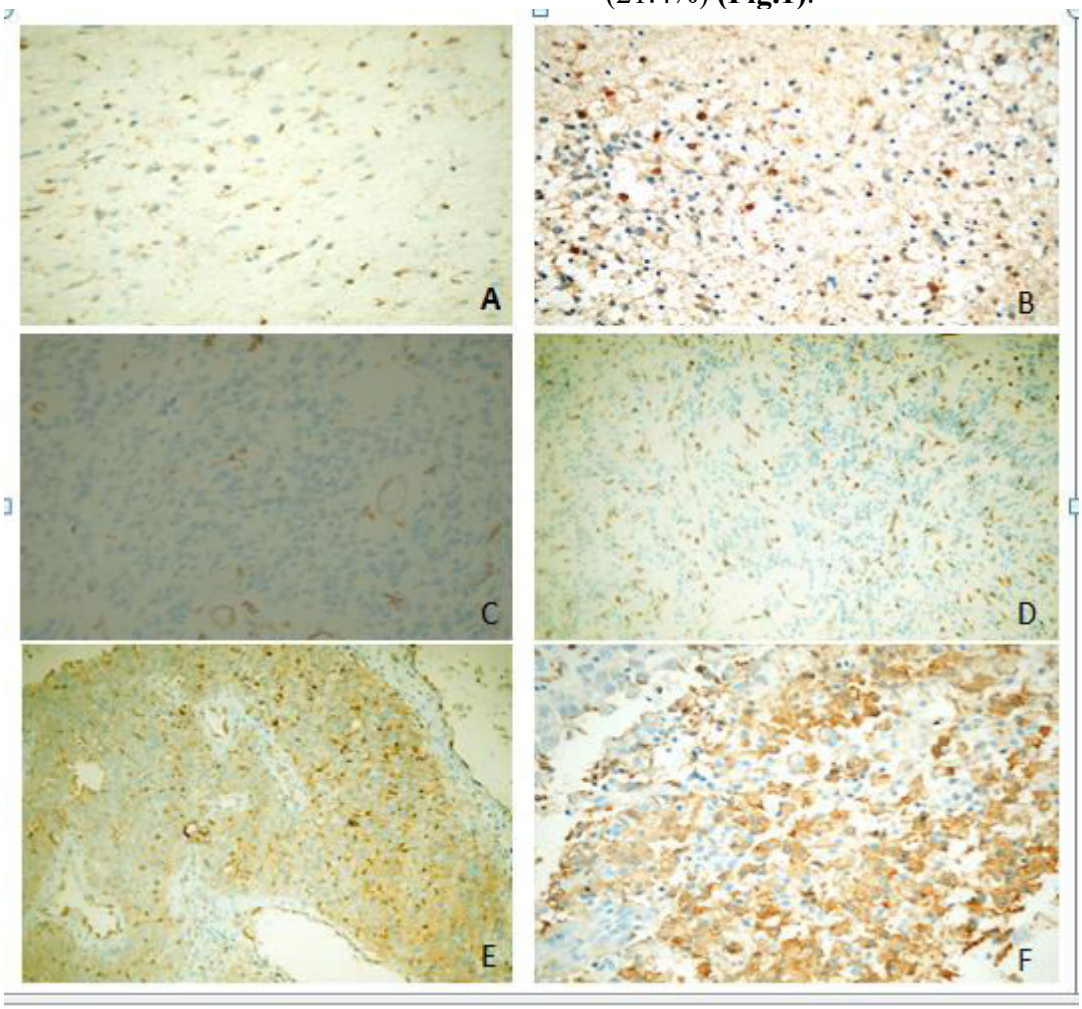

Fig.1. Immunohistochemical expression of Fascin in different histological types and grades of gliomas. (A) Mild expression of Fascin in pilocytic astrocytoma grade 1, **(B)** Moderate expression of Fascin in diffuse astrocytoma grade II, **(C)** Mild expression of Fascin in epedymoma grade II. **(D)** Moderate expression of Fascin in anaplastic ependymoma grade III. **(E)** Intense expression of Fascin in anaplastic astrocytoma grade III. **(F)** Intense expression of Fascin in glioblastoma multiform grade IV. X200 .

Fascin expression in glioma illustrate significant correlation with the histological type and tumor grade (P=0.032, 0.02 respectively). There

was no significant correlation between Fascin expression and other studied parameters including age, sex, site, and tumor size **(Table.2)**.

Table 2. Association between Fascin Expression and Clinico-pathological variables of the studied cases

Variables	Fascin expression				P value
	Absent 16 (22.9%)	Mild 18 (25.7%)	Moderate 21 (30%)	Intense 15 (21.4%)	
Age					
<55(37)	9(24.3%)	10(27.1%)	11(29.7%)	7(18.9%)	0.79
≥55(33)	7(21.2%)	8(24.2%)	10(30.3%)	8(24.2%)	
Sex					
Female (=31)	8(25.8%)	7(22.6%)	10(32.3%)	6(19.4%)	0.46
Male (n=39)	8(20.5%)	11(28.2%)	11(28.2%)	9(23.1%)	
Site					
Supratentorial (47)	11(23.4%)	13(27.7%)	13(27.7%)	10(21.3%)	0.26
Infratentorial (23)	5(21.7%)	5(21.7%)	8(34.8%)	5(21.75%)	
Tumor size					
<5 (n=49)	11(22.4%)	13(26.5%)	14(28.6%)	21(42.9%)	
≥5 (n=21)	5(23.8%)	5(23.8%)	7(33.3%)	11(52.4%)	0.502
Histology					
Pilocytic astrocytoma (9)	3(33.3%)	5(55.6%)	1(11.1%)	0	
Diffuse astrocytoma (23)	6(26.1%)	6(26.1%)	10(43.5%)	1(4.3%)	
Anaplastic astrocytoma (10)	1(10%)	0	5(50%)	4(40%)	0.032*
Glioblastoma multiform (14)	0	2(14.3%)	3(21.4%)	9(64.3%)	
Ependymoma (6)	2(33.3%)	3(50%)	1(16.7%)	0	
Anaplastic ependymoma (2)	0	0	1(50%)	1(50%)	
Oligodendroglioma (6)	4(66.7%)	2(33.3%)	0	0	
WHO grade					
I (9)	4(44.4%)	3(33.3%)	1(11.1%)	1(11.1%)	
II (35)	10(28.6%)	10(28.6%)	11(31.4%)	4(11.4%)	0.02*
III (12)	2(16.7%)	2(16.7%)	5(41.7%)	3(25%)	
IV (14)	0	3(21.4%)	4(28.6%)	7(50%)	

P value was *= significant (Chi-square test)

Discussion

Gliomas are the most common brain tumors. They are characterized by high rates of morbidity, mortality, and recurrence. Although there is much advance in its management through surgery, chemoradiotherapy, and biotherapy, still poor response and the tumor may recur in a short period of time.

. So it is an important challenge to investigate more markers that help in the prediction of the prognosis of the disease and can be used as a line in the treatment of such tumors **(Zhang et al., 2018)**.

Fascin is a 55 kDa protein that performs an essential function in modifying structures based on actin and controls the rearrangement of cytoskeletal elements. Its expression leads to cytoskeletal microfilament reconfiguration and actin cross-linking resulting in increased motility and enabling tumor cells to overcome the intercellular and cell-to-matrix adhesion increasing its invasiveness **(Duffy et al., 2017)**.

Studies including immunohistochemical analysis have revealed that Fascin expression is linked to clinical progression, tumor invasion, and a reduction in short-term survival **(Zhao et al., 2010)**.

Our study included 70 specimens of gliomas, Fascin was positive in 54/70 (77.1%) of cases, its expression was strong in 15/70 (21.4%); moderate in21/70(30%), mild in 18/70 (25.7%), and it was negative in 16/70(22.9%).

The strongly stained specimens were classified histologically, showing that more than half of the cases were glioblastoma multiform 9/16 (56.3%), 4/16 (25%) were anaplastic astrocytoma, while 1/16 was diffuse astrocytoma, and 1 was anaplastic ependymoma.

Numerous studies have demonstrated that the most statistically important prognostic factor for glial neoplasms is its histologic grade, and there is a strong link between increased tumor grade and adverse prognosis **(Arshad et al., 2010)**.

In our study, there was a significant positive correlation between Fascin protein expression and the histologic type of the tumor ($P<0.032$) and the WHO grade of the tumor ($P<0.02$).

In agreement with our results, Peraud et al., 2003 found that there is a significant positive correlation between Fascin expression in gliomas and the grade of the tumors **(Peraud et al., 2003)**. Also, Roma and Prayson 2005, performed immunohistochemical analysis in gliomas, and they found that higher grades tumors express a greater degree of Fascin staining than lower grades tumors **(Roma and prayson, 2005)**. These results are also proved by Zhang et al., 2018, who found the same correlation between Fascin expression and glioma grade **(Zhang et al., 2018)**.

There was no significant correlation between Fascin expression and other studied parameters including age, sex, site, and tumor size. These results were also proved by Zhang et al., 2018, who found no significant correlation between Fascin expression on one side, and age, sex, and size of the tumor on the other side **(Zhang et al., 2018)**.

Few studies regarding Fascin in gliomas were conducted, so more and larger studies on large scale with further evaluation of patients are warranted.

Conclusion

From these findings which indicate the strong correlation between Fascin expression and tumor grade, we conclude that Fascin is a strong adverse prognostic marker for glioma indicating tumor progression and may lead to resistance to therapy.

Abbreviations

GBM: Glioblastoma multiform
H&E: Hematoxylin & eosin
DAB: diaminobenzidine.
IHC: immunohistochemistry
IRS: The immunoreactive score
PBS: phosphate buffer saline.

Ethics approval and consent to participate: This study adhered to the ethical principles outlined in the Declaration of Helsinki. Approval to perform this study was obtained from the Medical Research Ethics Committee faculty of medicine under IRB Registeration number: Med-23-04-19PD.

Consent for publication: Informed consent for publication was obtained from all authors.

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