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## Original Article

# Expression of P53 and Ki-67 in Different Grades of Astrocytomas

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## ABSTRACT

**Background:** Astrocytomas are considered the most prevalent central nervous system [CNS] tumors. Diffuse astrocytomas are evaluated by a three-tiered system [II, III, and IV] according to the 2007 WHO classification. The WHO grading scheme is based on the existence or lack of four histological features: mitosis, nuclear atypia, microvascular proliferation, and necrosis. Pilocytic astrocytoma is classified as WHO grade I in histological grading of localized astrocytic tumors. In many cases of human neoplasms, including astrocytoma, p53, and Ki67, the expression increases, especially in aggressive and high-grade tumors.

**The Aim of the work:** We aimed to validate the p53 and Ki 67 immunohistochemical expression in various grades of astrocytic tumors and correlate this expression with clinicopathologic findings and histopathologic grading.

**Patients and methods:** Immunohistochemical analysis [IHC] of p53 and Ki67 were used to evaluate 45 paraffin-embedded samples, which included different grades of astrocytoma [10 participants of pilocytic astrocytoma, 12 participants of diffuse astrocytoma grade II, 9 participants of anaplastic type, and 14 participants of glioblastoma type]. Tumor tissue blocks and clinical information of the cases were gathered from the files of Pathology Department of Al-Azhar University Hospitals [Al-Hussein & Al-Zahraa] and from the archives of some private laboratories from March 2018 to June 2021.

**Results:** Immunohistochemical [IHC] expression of p53 and Ki 67 had a significant positive association with histopathological grading of astrocytoma. High expressions were detected in high-grade astrocytoma [grade III, IV] versus low-grade types [I, II].

**Conclusion:** p53 and Ki 67 immunohistochemical expression is up regulated in high-grade astrocytoma. Their overexpression seems to indicate a more malignant phenotype.

**Keywords:** Astrocytoma; Histopathological grading; Immunohistochemistry

## INTRODUCTION

Glioma neuropathologic grading is based upon St. Anne/Mayo method, which comprises cellular atypia, mitotic count, endothelial proliferation, and/or necrosis [1].

Astrocytic tumors are considered the commonest glial tumors, which represent more than 25% of all CNS tumors and include a diverse group of neoplasms that differs in terms of their location all over the CNS, gender and age distribution, growing biologic behavior, and therapy options [2, 3].

Pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma [WHO grade I, II, III, and IV, respectively] are all examples of astrocytic tumors [4]. Mutations in the p53 gene, which modulates anti-proliferative cellular responses are the most frequent changes in high-grade astrocytic gliomas. Ki-67 labelling index [LI] is widely utilized as a cellular proliferative marker in many tumors, like gliomas [1]. Various studies show that Ki-67 and P53 are essential biomarkers for determining astrocytoma's prognostic and predictive results [1].

## PATIENTS AND METHODS

An overall of 45 formalin-fixed paraffin-embedded blocks of astrocytoma were used in this retrospective study. During the period from March 2018 to June 2021, the blocks were collected from the surgical files of Histo-pathology departments of Al-Azhar University Hospitals [Al-Hussein and Al-Zahraa] as well as the archives of several private laboratories after gaining informed consent and the approval of a local ethics committee. All cases of astrocytic tumors were surgically removed. Clinico-pathological data were obtained from medical charts. They included 30 male and 15 female individuals aged 7 to 75 years.

Three sections of 5-micron thickness were cut from the paraffin blocks; one section was stained with hematoxylin and eosin and the other two sections were mounted upon adhesive slides and immunostained by monoclonal antibodies against Ki 67 and P53 antibodies. The tumors were typed and graded according to WHO classification 2007 into 10 participants of pilocytic astrocytomas [grade I], 12 participants of fibrillary astrocytomas [grade II], 9 participants of anaplastic astrocytomas [grade III], and 14 participants of glioblastoma [grade IV].

### Immunohistochemistry

For immunohistochemical preparation, the preparation of unstained adhesive slides [Biogenix] was performed from each paraffin block for immunostaining with monoclonal antibody versus Ki67 & P53 [Lab vision/Neo marker, Fremont, California, USA]. The staining of sections was conducted utilizing an automatic immunohistochemical staining tool [Benchmark XT; Ventana Medical System, Tucson, Arizona, USA].

In a nutshell, 5-mm-thick slices were collected on poly-L-lysine-coated adhesive slides and dried for 30 minutes at 62$^{o}$C. The specimens were incubated with primary monoclonal antibodies for Ki-67 Antigen, clone M 7240, Monoclonal Mouse Anti-Human p53, Clone DO – 7 after epitope retrieval with conventional heat treatment for half an hour in ethylenediaminetetraacetic acid [pH 8.0] in an autostainer. Peroxidase-labeled streptavidin [LSAB Kit; Lab vision], biotinylated anti-mouse immune-globulins, and 3,30-diamino-benzidine were used to incubate the sections, which were then counterstained with Harris hematoxylin.

For positive control, the section of chronic tonsillitis tissue was utilized as a positive control for Ki67 and another section of colon carcinoma for P53. As negative controls, tumor tissues were processed, but the primary antibodies were omitted, and phosphate buffer solution was utilized instead.

### Assessment of Immunostaining

Regarding Ki 67 immunoexpression, each slide was graded according to the percentage of positive stained nuclei. The following scores were used: **1**: <5%, **2**: from 5% to 10%, **3**: >10% [5]. Samples with Ki-67 nuclear staining equal to or above 10% were considered a high LI [labeling index], whereas nuclear positivity below 10% was considered a low LI [6]. As regard p53, the score was calculated as: **0**: complete negative nuclear staining, **1 [mild]**: <5% positive nuclei, **2 [moderate]**: 5-30% positive nuclei, **3 [high]**: >30% positive nuclei [1].

**Statistical Analysis:** Data were measured utilizing Statistical Program for Social Science [SPSS] version 20.0. The following tests were carried out: Chi-square [$X^2$] and Probability [P-value] which is regarded as significant if the value $\leq$ 0.05, while P-value > 0.05 was being insignificant.

## RESULTS

An overall of 45 cases of astrocytic tumors were included in our study. The cases were graded as follows: 22 low-grade astrocytomas [48.9 %], including 10 participants with pilocytic astrocytomas [WHO grade I] [22.2 %], 12 participants with fibrillary astrocytoma [WHO grade II] [26.7 %]; as well as 23 cases with high-grade astrocytoma [51.1%], including 9 participants with anaplastic astrocytoma [WHO grade III] [20 %] &14 participants with glioblastoma multiforme [WHO grade IV] [31.1 %] [Fig. 1,2]

The age of the patients varies from 7 to 75**.** There are 30 cases of males [67 %], and 15 females [33 %] with ratio of male to female is 2:1. Most cases [15 cases, 33 %] are presented in the frontoparietal area of the cerebral hemisphere **[Table 1].**

**Immunohistochemical Ki 67 expression:** Ki67 expression was confined to the nucleus of tumor cells. A total of 15 out of 45 participants [33.3%] indicate mild expression, 10 participants [22.2%] demonstrate moderate expression, and 20 participants [ 44.4%] reveal great expression [Table 2].

Regarding the age of patients, the expression of Ki-67 is significantly raised in older age of patients [P-value = 0.02]. Concerning the gender of patients, the expression of Ki-67 is not statistically significant with the sex of patients, using the Chi-square test with [P-value = 0.159]. According to tumor grade; The percentage of expression of Ki-67 was increased significantly in high-grade astrocytoma [P-value < 0.001] [Fig. 3-6]. The majority of cases with high expression [90%] are graded III, and IV. The remaining cases with high expression [10%] are graded I. All cases with mild expression [100%] are graded I & II, while grades III & IV did not show any case with a mild expression. [Table 2].

The estimate for mean values of Ki-67 in grade I, II, III, and IV tumors are 3.5, 4.2, 10.5, and 17.6, respectively [Table 3].

**Immunohistochemical expression of P53:** P53 expression was confined to the nucleus of tumor cells in 38 out of 45 cases [84.4%]. Regarding the age of patients, the expression of P53 is statistically insignificant [P-value = 0.061]. Regarding the gender of patients, the expression of P53 is statistically significant with the sex of patients [P-value 0.024] [Table 4].

According to tumor grade; The percentage of expression of P53 is raised significantly in high-grade astrocytoma [P-value 0.03] [Fig. 3-6]. Most studied cases with moderate to severe expression [77.8%] are graded IV. The remaining cases with moderate to high expression [22.2 %] are graded III, while grade I did not show any case with high expression. Most of the cases with no expression [negative] [57%] are grade I, while grade IV did not show any case with no expression [Table 4].

**Correlation of Ki 67 expression with P53 expression:** There is a significant direct association between Ki 67 and the P53 expression of the studied cases [P-value is 0.013]. Ki 67 expression is higher in P53 positive cases. The majority of cases with high P53 expression [12 cases] show either moderate [25%] or strong [66.7%] Ki67 expression. Most cases with negative P53 expression show mild [71.4%] Ki67 expression [Table 5].

**Table [1]:** Distribution of tumor site of the study group

| Tumor site distribution of the study group | | |
|---|---|---|
| **Tumor Location** | **No.** | **%** |
| **Cerebellum** | 11 | 24.4 |
| **Frontal** | 8 | 17.8 |
| **Frontoparietal** | 15 | 33.3 |
| **Parietal** | 7 | 15.6 |
| **Temporal** | 4 | 8.9 |
| **Total** | 45 | 100 |

**Table [2]:** Ki 67 expression among astrocytoma cases [regarding age, sex and tumor grade; N= 45]

| Variables | | Ki 67 expression | | | P-value |
|---|---|---|---|---|---|
| | | Mild | Moderate | High | |
| **Age** | ≤15 | 2 [13.3] | 2 [20] | 1 [5] | **0.0237** |
| | 16-30 | 6 [40] | 0 [0] | 3 [15] | |
| | 31-45 | 5[33.3] | 1 [10] | 4 [20] | |
| | 46-60 | 2 [13.3] | 6 [60] | 6 [30] | |
| | >60 | 0 [0] | 1 [10] | 6 [30] | |
| **Sex** | Female | 7 [46.7] | 1 [10] | 7 [35] | 0.159 |
| | Male | 8 [53.3] | 9 [90] | 13 [65] | |
| **Astrocytoma grades** | WHO- G I | 6 [40] | 2 [20] | 2 [10] | **< 0.001** |
| | WHO- G II | 9 [60] | 3 [30] | 0 [0] | |
| | WHO- G III | 0 [0] | 4 [40] | 5 [25] | |
| | WHO- G IV | 0 [0] | 1 [10] | 13 [65] | |
| **Total** | | 15 | 10 | 20 | |

**Table [3]:** P-value on contrasting between different grades of astrocytomas and Ki 67 expression

| Grades of astrocytoma | *P*-value |
|---|---|
| **Grade I and Grade II** | 0.26 |
| **Grade I and Grade III** | 0.019 |
| **Grade I and Grade IV** | < 0.001 |
| **Grade II and Grade III** | 0.34 |
| **Grade II and Grade IV** | < 0.001 |
| **Grade III and Grade IV** | 0.13 |

**Table [4]:** Correlation between research variables and P 53 expression in primary astrocytic brain tumors [N= 45]

| Variables | | P 53 expression | | | | P-value |
|---|---|---|---|---|---|---|
| | | Negative | Mild | Moderate | High | |
| **Age** | ≤15 | 3 [42.9] | 1 [7.1] | 0 [0] | 1 [8.3] | 0.061 |
| | 16-30 | 2 [28.5] | 4 [28.5] | 0 [0] | 3 [25] | |
| | 31-45 | 0 [0] | 5 [35.7] | 2 [16.6] | 3 [25] | |
| | 46-60 | 2 [28.5] | 2 [14.3] | 7 [58.3] | 3 [25] | |
| | >60 | 0 [0] | 2 [14.3] | 3 [25] | 2 [16.6] | |
| **Sex** | Female | 4 [57.1] | 3 [21.4] | 1 [8.3] | 7 [58.3] | **0.024** |
| | Male | 3 [42.9] | 11 [78.6] | 11 [91.7] | 5 [41.7] | |
| **Astrocytoma grades** | WHO- G I | 4 [57.1] | 5 [35.7] | 1 [8.3] | 0 [0] | **0.03** |
| | WHO- G II | 2 [28.6] | 4 [28.6] | 4 [33.3] | 2 [16.7] | |
| | WHO- G III | 1 [14.3] | 2 [14.3] | 4 [33.3] | 2 [16.7] | |
| | WHO- G IV | 0 [0] | 3 [21.4] | 3 [25] | 8 [66.6] | |
| **Total** | | 7 | 14 | 12 | 12 | |

**Table [5]:** Relation between Ki67 expression and P53 expression

| Ki 67 Expression | P53 Expression | | | | P-value |
|---|---|---|---|---|---|
| | **Negative** | **Mild** | **Moderate** | **High** | |
| **Mild** | 5 [71.4] | 8 [57.1] | 1 [8.3] | 1 [8.3] | **0.013** |
| **Moderate** | 0 [0.00] | 3 [21.4] | 4 [33.3] | 3 [25%] | |
| **High** | 2 [28.6] | 3 [21.4] | 7 [58.3] | 8 [66.7] | |
| **Total** | **7** | **14** | **12** | **12** | |

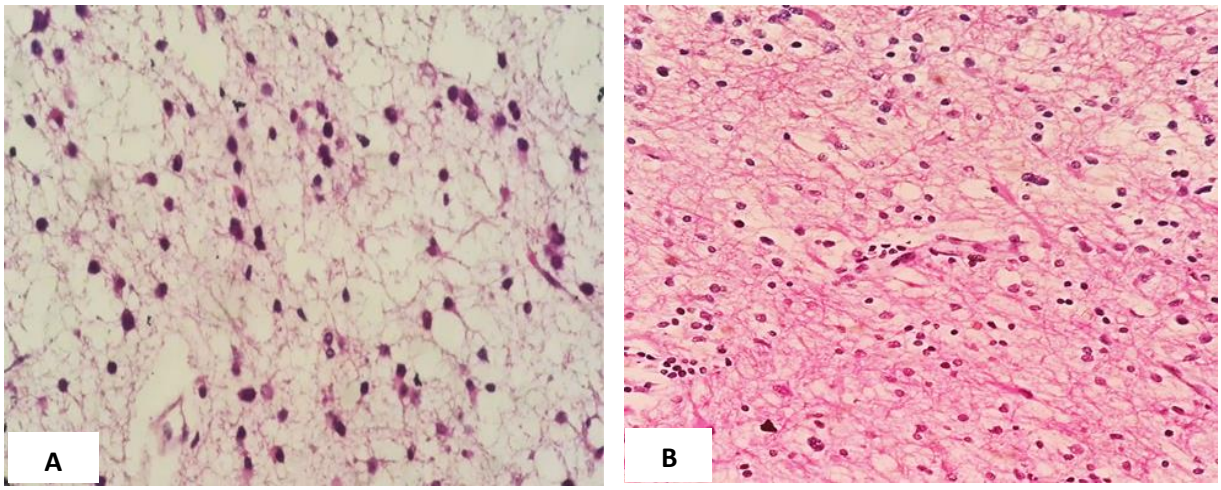


**Figure [1]:** Two cases of low-grade Astrocytoma; [A] Pilocytic Astrocytoma [WHO G I] Pilocytic astrocytoma reveal bipolar astrocytes with elongated hair like processes and areas of loose glial component [original magnification × 200]; [B] Fibrillary Astrocytoma [WHO G II]: Astrocytes show minimal pleomorphism [original magnification × 100].

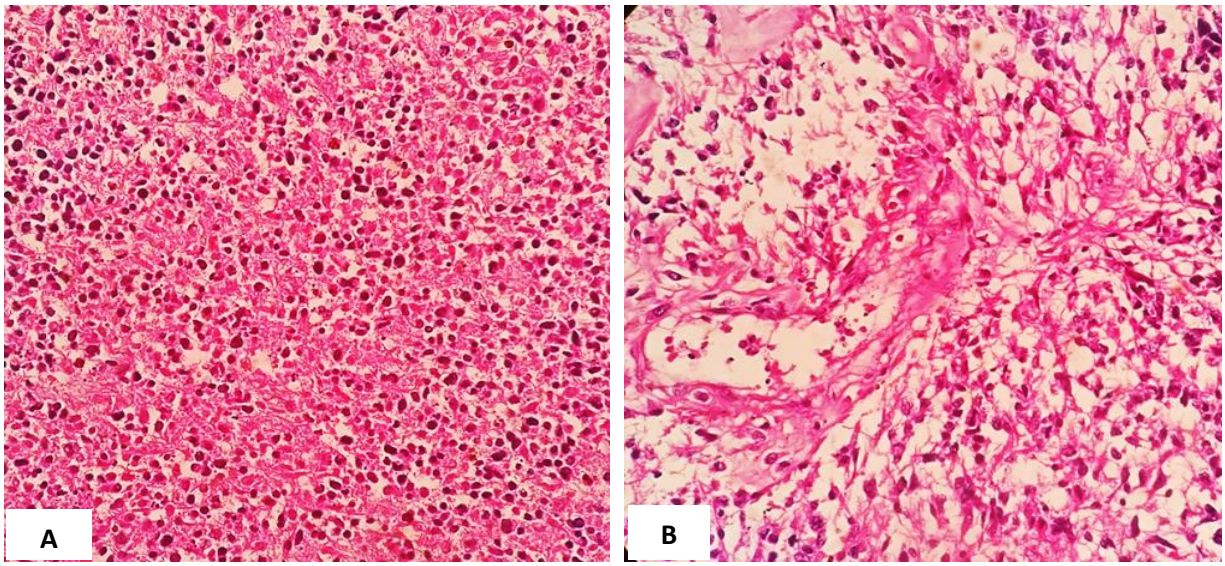


**Figure [2]:** Two cases of High-grade Astrocytoma. A] Anaplastic astrocytoma WHO III: Astrocytes showing marked nuclear pleomorphism [original magnification × 100]; [B] GBM WHO IV: Astrocytes showing marked nuclear pleomorphism and vascular endothelial proliferation [original magnification × 200].

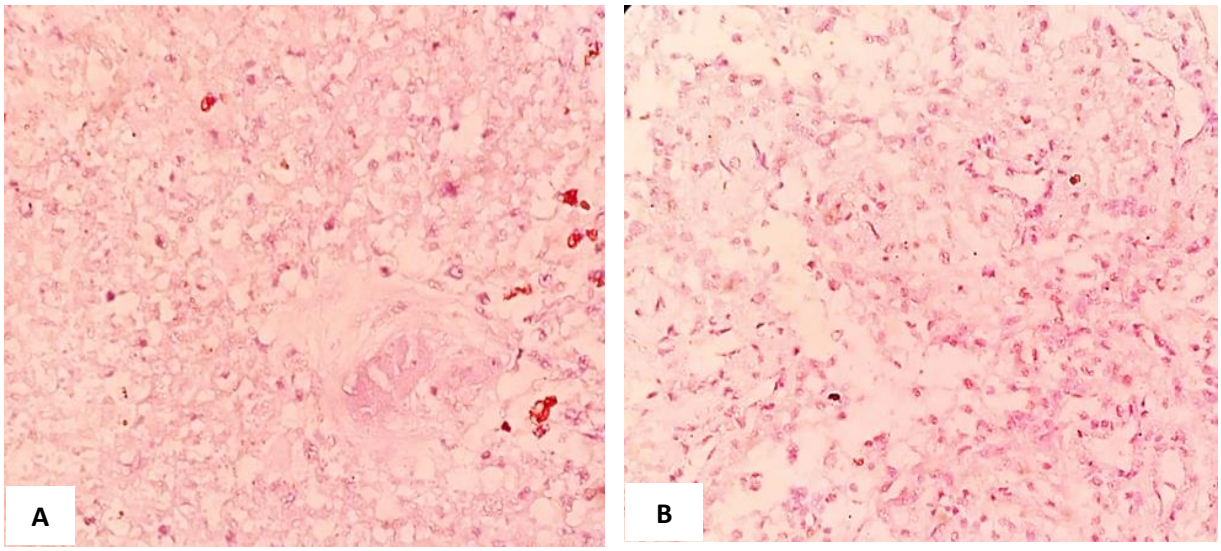


**Figure [3]:** A case of Pilocytic Astrocytoma [Grade I]. A. reveals very low KI67 expression < 5%; B. reveals negative P53 expression. [A&B counterstained with Hx., Original magnification × 100].

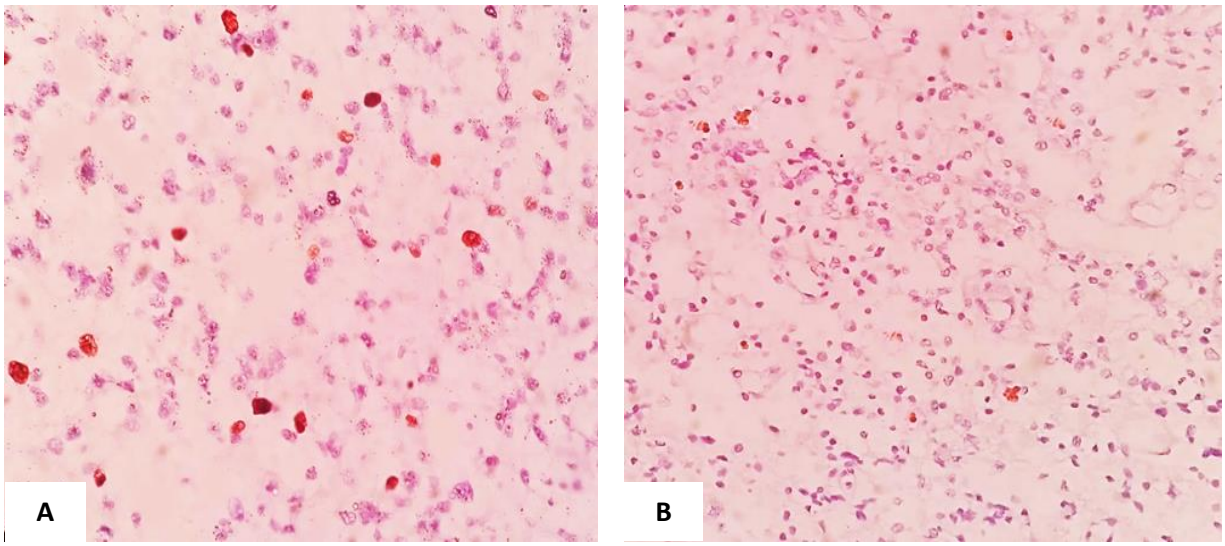


**Figure [4]:** A case of Diffuse Astrocytoma [Grade II]. A. reveals low KI 67 expression [< 7 %]. B. reveals low P53 expression [< 5%]. [A&B counterstained with Hx., Original magnification × 200 & 100 respectively].

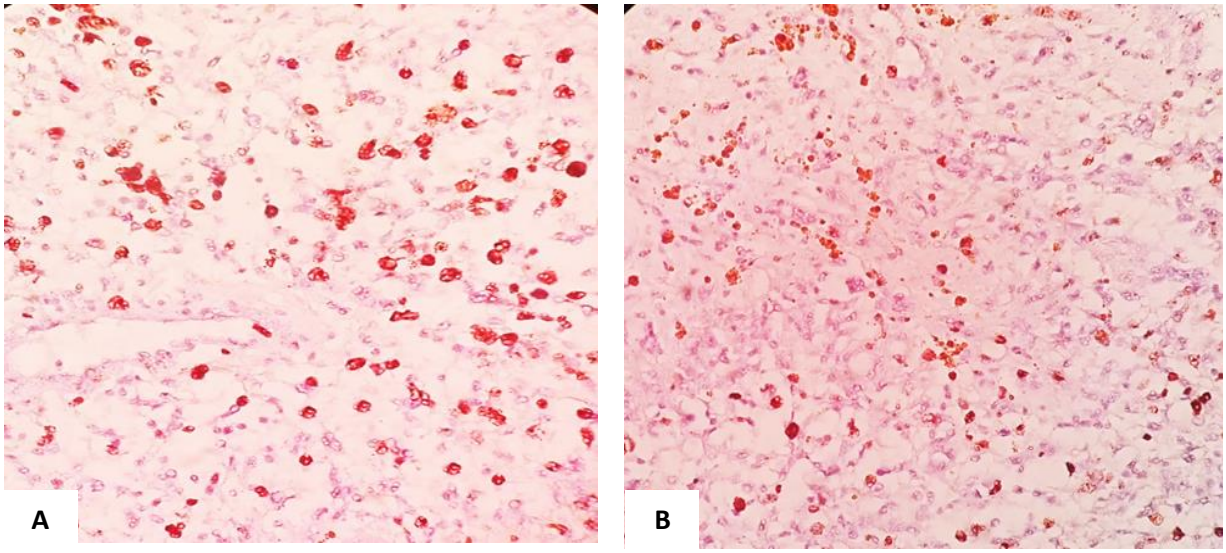


**Figure [5]:** A case of Anaplastic Astrocytoma [Grade III]. A. reveals high KI67 expression [> 10%]. B. reveals moderate P53 expression [<30%]. [A&B counterstained with Hx., Original magnification × 200 & 100 respectively].

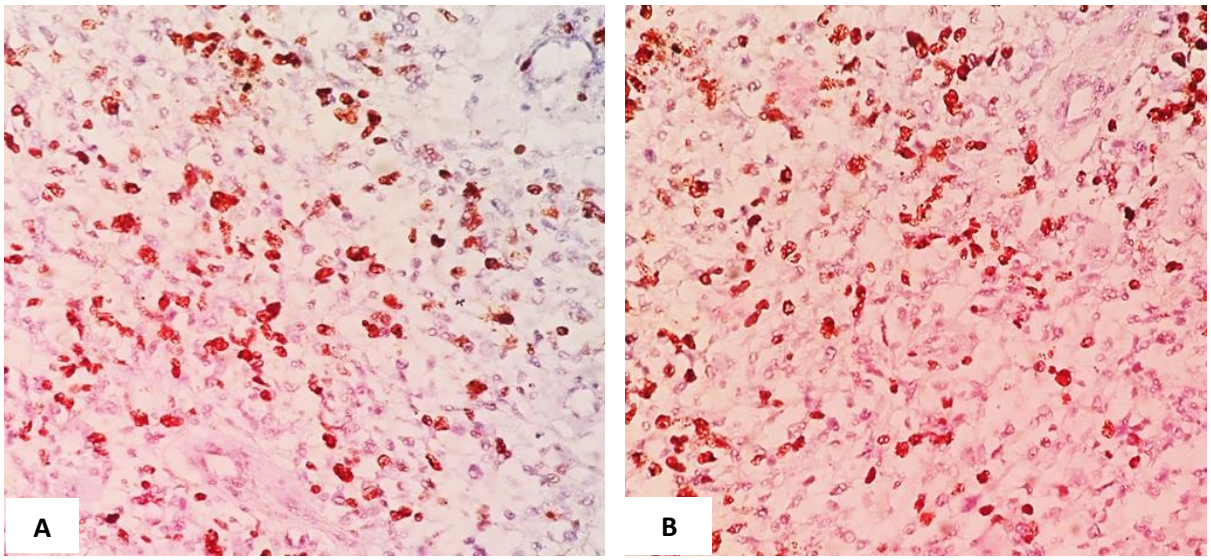


**Figure [6]:** A case of Glioblastoma [Grade IV]; [A] reveals high Ki-67 expression [> 20%] [B] reveals high P53 expression [>30%]. [A&B counterstained with Hx., Original magnification × 200]

## DISCUSSION

proper astrocytoma grading helps neuro-oncologists treat and assess the overall prognosis properly. Glioma treatment is mainly guided by tumor grade, which is evaluated by histologic features, as well as certain markers, which are more accurate for assessing clinical prognosis [7].

According to WHO guidelines 2007, the CNS astrocytic tumors have been divided into four groups as grade I-IV depending on their histopathological characteristics, i.e., cellular atypia, mitosis, microvascular proliferations, +/- necrosis [7]. Regarding grade I astrocytoma, it has the most favorable prognosis while Grade II has less favorable prognosis. Additionally, Grade III astrocytoma has an overall poor patient prognosis and Grade IV astrocytoma [GBM] is characterized by a rapid rate of progression and aggressiveness [3].

In the present work, the majority of the astrocytoma patients were males with an average female to male ratio of 1:2, and these findings agree with those of **Sharma *et al*.; Abu Seadah, and Thotakura *et al*.** [7, 2, 8]. These results are consistent with data from the central nervous system tumors' WHO classification that astrocytoma tumor incidence was higher in males than females [1.8: 1] [3].

Most cases of our study were glioblastoma [31.1%], followed by diffuse fibrillary astrocytoma [26.7 %], pilocytic astrocytoma [22.2 %], and the remaining 20% of cases were anaplastic astrocytoma. These findings are in accordance with the data of **Singh *et al.*** in which glioblastoma multiforme was the most common glial tumor that represented about 30% of cases [1]. Similarly, in research conducted by **Abu Seadah *et al.*,** glioblastoma represented 36% of the cases [2].

Although histopathological assessment is an important tool for astrocytoma diagnosis, the recurrence duration, determination of the grade, and astrocytoma malignancy require assessing proliferative activity. More markers are required for these reasons to improve prognostic and diagnostic accuracy [5].

Ki-67 is a well-known proliferative biomarker and its high expression in tumor cells implies tumor aggressiveness. The p53 gene is a tumor suppressor gene, and its mutation is the commonest genetic alteration linked to human carcinogenesis [9]. A value of Ki-67 higher than 10% is a cut-off point reasonable to reveal an extreme possibility for malignancy and adverse prognosis [11].

In the current work, the p-value for Ki-67 immunostaining of the various grades of astrocytoma was < 0.0005, which was statistically highly significant. This finding matches the studies performed by **Hu *et al.*, Sharma *et al.*, and Singh *et al.*** [10, 7, 1].

Concerning comparing Ki-67 expression in the studied astrocytoma cases, we found a statistically significant correlation between astrocytoma grade I & grade III [P. value = 0.019]. Our work also showed a high statistically significant correlation between grade II & grade IV [P. value < 0.001]. While there are insignificant differences when comparing between grade I & grade II [P. value = 0.26] or between grade III & grade IV [P. value = 0.1]. Our findings are nearly equivalent to **Singh *et al.*** who noted that the Ki-67 LI between low-grade & high-grade astrocytoma is statistically significant [p= 0.001]. Thus, Ki-67 is essential for differentiating between low-grade & high-grade astrocytoma, but the differentiation between grade I & grade II, or between grade III & grade IV, is more doubtful due to the overlap of values between various tumor grades [1]. Also, **Shivaprasad *et al.*** found that the Ki-67 LI of low-grade [Grade II] and high-grade [Grade III &IV] astrocytoma differed statistically significantly [4]. Moreover, **Thotakura *et al.*** demonstrated that statistically significant p-values [<0.0001] were acquired when comparing diffuse astrocytoma versus anaplastic astrocytoma and glioblastoma, but not with pilocytic astrocytoma [8].

Although mitotic activity is generally low or absent in pilocytic astrocytoma, Ki 67 expression in two cases of pilocytic astrocytoma was similar to that of Grade IV astrocytoma despite the absence of atypical histologic features in the biopsy. This finding agrees with **Thotakura *et al.*** who indicated that proliferation ratios of astrocytoma reflect tumor cell growth and microglial cell proliferation, particularly in pilocytic astrocytoma. As a result, using this marker to distinguish pilocytic astrocytoma from gliosis should be conducted with caution, as it is unreliable for final diagnosis [8]. These observations point to a limited role for Ki 67 in pilocytic astrocytes. As

a result, Ki 67 LI should be used in conjunction with histopathological parameters.

In our work, the mean values for Ki-67 in grade I, II, III, and IV tumors were 3.5, 4.2, 10.5, and 17.6, respectively. While **shivaprasad *et al.*** found that the mean Ki-67 labeling index [LI] in grades I, II, III, and IV was 0.02, 0.81, 9.14, and 17.81, consecutively [4], and **Thotakura *et al.*** found them as 3.36, 7.05, 28.24, 38.7 for grade I, II, III and IV, respectively [8]. While **Singh *et al.*** found that the mean values were 3, 8.5, and 7.95 for GII, GIII, and G IV, respectively [1].

When contrasting the Ki 67 LI values reported by various researchers, it becomes clear that there are significant discrepancies in the Ki 67 LI values of different research. Variations in Ki-67 LI in different reports can be explained by presence of various parameters, including the fixative immunohistochemical protocols such as peroxidase, anti-peroxidase, streptavidin, avidin, different antibody dilutions and incubation times, various fixation methods, and most importantly, and antigen retrieval methods.

According to the age of patients, Ki-67expression of was significantly increased in older age of patients [P-*value* <0.001]. This supports the findings of **Chaloob *et al.***, who noted that the older age of patients was higher expression of Ki 67 [11]. In research done by **Sun *et al.*,** the Ki-67 LI is not related to the patient's age [6]. Also, **Shivaprasad *et al.*,** found that Ki-67 did not differ significantly concerning the age and gender of the individuals [4].

In the present work, there is a statistically significant association between astrocytoma grade and p53 expression [P = 0.03]. Studies performed by **Sharma *et al.*, Belghali *et al.*, and Hu *et al.*,** also recommend similar findings [P-value < 0.05] [7, 12, 10]. While **Singh *et al.*,** found no statistically significant correlation between P53 and astrocytoma grades [P-value 0.07] [1].

Our work also reported a direct correlation between Ki67 & P53, and this result is equivalent to **Sharma *et al.*, and Sengupta *et al.*,** [7, 13]. As a result, the combination of Ki-67 and P53 could be utilized as astrocytoma prognostic and predictive markers for astrocytoma aggressiveness. Both were increased with raising grades of astrocytomas and may benefit in differentiating low grades from high-grade tumors.

**Conclusion**

We may conclude from this research that the p53 expression and ki-67 LI in astrocytoma is related to tumor grade. We recommend analyzing Ki-67 and p53 in all astrocytic brain tumors for a better prognostic stratification. Furthermore, Ki-67 LI was shown to overlap across grades, suggesting that Ki-67 LI cannot be utilized as a diagnostic test alone. Ki-67 LI could be utilized with caution and in conjunction with other clinical and pathologic parameters.

**Conflict of interest and financial disclosure:** None

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