ISSN: 0067-2904

# Evaluation the Age and Gender Association in Iraqi Patients with High Grade Glioma

**Hadeer Hashim Shamsuldeen[1]*, Abed Hassan Barraj[1], Sameer Hameed Hammadi[2]**
[1] *Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq..*
[2]*Ministry of Health and Environment, Al-Rusafa health Department, Neurosurgery teaching hospitals, Baghdad, Iraq.*

Received: 9/6/2024 Accepted: 24/9/2024 Published: 30/10/2025

**Abstract**

The objective of this study is to investigate the potential association between age, gender, and the incidence of glioma. Thirty-four paraffin embedded tissue samples from patients with high grade glioma, (13female and 21 male), and thirty as control (20 female and 10 male) were randomly selected. All samples with age range (13-70 years) with mean age of 44.94 ± 2.99. Patient samples were collected from the archives of the Neurological Hospital in Baghdad. Tissue sections were stained with haematoxylin and eosin for histopathological examinations conducted from December 2022 to July 2023. The results indicated a significant difference $P \leq 0.05$ between Glioma and gender p-value 0.0437) in both sexes, with male patients have a higher incidence according to the percentage (61.76%) with age average (51.62). A highly significant correlation ($P \leq 0.01$) was found between glioma and age group, with the highest infection rate (47.06%) observed at the age group 46-65year, it was also noted that females are infected at a younger age with age average younger than (35).

**Keywords:** Cancer, Brain tumors, Glioma, Age, Gender.

# تقييم أرتباط العمر والجنس لدى المرضى المصابين بالورم الدبقي عالي الدرجة

**هدير هاشم شمس الدين[1]*, عبد حسن براج[1], سمير حميد حمادي[2]**
[1] قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق
[2]مستشفى الجملة العصبية، دائرة صحة الرصافة، وزارة الصحة والبيئة، بغداد، العراق

**الخلاصة**

الهدف من هذه الدراسة هو التحقيق في الارتباط المحتمل بين العمر والجنس ومعدل الإصابة بالورم الدبقي. تم اختيار أربع وثلاثين عينة من الأنسجة المغطاة بالبارافين من مرضى مصابين بالورم الدبقي عالي الدرجة (13 أنثى و 21 ذكرًا) وثلاثين عينة كمجموعة تحكم (20 أنثى و 10 ذكور) بشكل عشوائي. جميع العينات ذات الفئة العمرية (13–70 عامًا) بمتوسط عمر 44.94 ± 2.99. تم جمع عينات المرضى من أرشيف مستشفى الجملة العصبية في بغداد. تم صبغ مقاطع الأنسجة بالهيماتوكسيلين والأيوسين للفحوصات النسيجية التي أجريت من ديسمبر 2022 إلى يوليو 2023. أشارت النتائج إلى وجود دلالة معنوية($P \leq 0.05$) بين

*Email: hadeeralusi@yahoo.com

الورم الدبقي والجنس (قيمة p 0.0437) في كلا الجنسين، حيث كان لدى المرضى الذكور معدل إصابة أعلى وفقًا للنسبة المئوية (61.76٪) مع متوسط العمر (51.62). ووجد دلالة معنوية عالية (P≤0.01) بين الورم الدبقي والفئة العمرية، حيث كان أعلى معدل إصابة (47.06%) في الفئة العمرية 46–65 سنة، كما لوحظ أن الإناث يصبن في سن أصغر بمتوسط عمر أقل من (35).

## 1. Introduction

In Iraq, cancer ranks as the second most common cause of death, following closely behind cardiovascular diseases, highlighting the need for accurate incidence and mortality estimates to inform national health policy and cancer control strategies [1]. The primary reason for cancer-related deaths in patients is the ability of cancer cells to spread from a primary lesion to distant organs. Several cellular mechanisms are involved in the distribution of cells from primary tumors; one of these mechanisms is invasion of or collaboration with the stroma [2]. Tumors also impair immune function [3]. Recent studies on solid tumors like Al-Khateeb and Alkhafaji [4] study, and Dalerba *et al.* [5] study, the population of tumor cells varies in terms of their proliferation and differentiation; therefore, not all tumor cells are equally capable of continuing the tumor's growth.

A brain tumor is defined as a mass of abnormal cells in the brain that either originate in the brain there or, in the case of a metastatic brain tumors, migrate from other parts of the body. Benign tumors consist of cells that develop extremely slowly, often have well-defined boundaries, and do not spread to surrounding tissue. In contrast, malignant brain tumors, commonly referred to as brain cancer, are usually fast growing and have no clear boundaries [6]. Gliomas are a type of tumors that arises from the brain parenchyma and can be categorized by their histological features through their similarity to different types of glial cells [7]. A malignant brain tumor or glioma originates from the supporting tissue of the brain known as glial tissue [8]. In adults, malignant gliomas are the most common primary brain tumors, characterized by an unexplained etiology and are generally fatal despite all modern therapies [9].

The most common primary malignant brain tumor, known as glioma, accounts for over 80% of cases. While gliomas can develop in any part of the central nervous system in adults, they predominantly affect the brain and glial tissue, the annual incidence of central nervous system tumors is between 10 and 17/100,000 people, with intra-spinal tumors, nearly half to three quarters being primary tumors and the rest being metastases [10]. In Iraq, CNS tumors rank as the sixth most common tumors in adults and the second most common in childhood [11].

The most recognized types of glioma in adults include infiltrative astrocytomas of many grades (diffuse astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), glioblastoma (WHO grade IV), with grade III and IV being considered high-grade and aggressive [12]. Recently, information at the molecular level is widely used and listed in the revised 2016 WHO classification of central nervous system tumors [13], these tumors can occur at any age, irrespective of gender or ethnicity. Currently, there is no cure for gliomas, and regardless of aggressive therapy, morbidity is high, the most aggressive type of glioma is WHO grade IV, it is also called glioblastoma multiform (GBM) [14].

Regrettably, current treatment options and early detection methods have not been shown to significantly impact the prognosis of the disease. Ionizing radiation is an important environmental risk factor for the development of glioma [15]. The causes of glioma, as with

other brain tumors, are unknown, but some risk factors have been described: Ageing, exposure to ionizing radiation, for example (radiotherapy) and family history of glioma [16].
Many studies, such as Yin *et al.* [17] study have shown that gender plays a decisive role in the occurrence and development of cancer, in addition to the metabolism of nutrients and energy, men and women spectacle significant differences in the incidence, prognosis, and treatment response through several types of cancer, it has been observed that male glioma patients have a higher incidence than female patients, but there is currently a limited systematic evaluation of sex differences in gliomas. Likewise Colopi *et al*. [18] study showed that the incidence was highest in men.

Age is closely associated with the incidence and survival rates of all cancer types; therefore, it is also a crucial factor in all aspects of glioma [19]. Gliomas are very common in elderly people, with a peak incidence occurring between the ages of 45 and 65 [20].
Ageing is a well-estimated independent factor that is closely related to incidence and survival in all cancers. Glioma subtypes are more common in childhood and rare in adulthood and vice versa [21]. For individual's ≥65, age is a primary risk factor for all cancers, accounting for 60% of recently diagnosed malignancies and 70% of all cancer-related deaths. Previous studies have shown that the age-adjusted cancer mortality rate in patients ≥65 is about 16 times higher than in patients< 65 [22].

The aging process is complex and multifaceted, influencing cancer development and progression in various ways. One of these is the huge effect of age on everything to do with the immune system, which is known to play an important role in cancer prevention, prognosis and therapy [22].
Sex-specific differences in genetics may explain the differences in glioma incidence between the two sexes [16].
Altered hormone levels may take part in the potential mechanisms and risk of glioma [23]. In the incidence of brain tumor sex differences indicate that the hormonal factor may have a vital role in the etiology of these malignancies. The incidence of gliomas is about 1.5 times more in males than in females, while the incidence of meningiomas is 1.5 times more in females than in males, and there are some reproductive factors that may be a cause of gliomas, such as the use of exogenous hormones [24]. The aim of study is to investigate the potential association between age, gender, and the incidence of glioma.

## 2. Materials and Methods

Thirty-four randomly selected paraffin-embedded tumor tissue samples (wax blocks) with glioma were collected. The samples comprise thirteen females with an average age (34.92) and twenty-one males with average age (51.62), and thirty samples were taken as control groups whose data were collected from the archive of the Histology Laboratory related to the Neurological Hospital in Baghdad during the time from December 2022 to July 2023. The participants included both males and females aged between (13-70 years) with age range of (44.94 ± 2.99) years, they were divided into four age group, the samples that were taken randomly were divided into 21 male and 13 female samples, all glioma samples were classified as high-grade glioma. Clinical data for patients, including age, gender, and grade of disease, were obtained from archived histological reports.
All samples were diagnosed in the histopathology laboratory of the neurological hospital after performing the histological procedure which includes (tissue preparation and staining with haematoxylin and eosin) according to Bancroft and Layton [25] and then examined microscopically by a histopathologist blindly for the purpose of diagnosing the disease and knowing the grade of glioma.

During tissue preparation, samples are fixed in 10% formalin (pH: 7). The fixed tissues were undergoing the standard paraffin wax embedding procedure, which includes dehydration, clearing, infiltration and embedding. Following embedding process, the sectioning step occurs using a microtome is used to section paraffin blocks sagittally with a thickness of 5µm to obtain histological sections that are stained with the haematoxylin and eosin protocol, according to the steps: Dewaxing: It is done using xylene alcohol, which dissolves the paraffin wax. Rehydration: Sections were immersed in a 100%, 95%, 80% and 75% ethanol solution for 3 minutes each, followed by a 5-minute rinse in tap water with distilled water Hematoxylin staining: Sections were stained with hematoxylin for about 5 minutes (30ºC) and then rinsed for 15 minutes before draining. Differentiation: The sections were placed in a liquid solution of 1% hydrochloric acid ethanol differentiation in 5-30 seconds, and then rinse water can be seen blue for around 15 minutes. Eosin stain: washing with tap water for 1 minute, followed by 2 minutes of staining with eosin dye and 1-2 minutes of soaking in a 0.5% eosin alcohol solution. Dehydration: sections were immersed in 95% and 100% ethanol solutions for 5 minutes before dehydration in 95% ethanol for 2 minutes and 100% ethanol for 1 minute. Clearing: The parts were immersed in xylene I and xylene II solutions for 5 minutes each. Sealing adhesive: One or two drops of neutral Canada gum were dripped onto the dry section, which was then quickly removed with tweezers and a clean cover slip. The nucleus was stained blue and the cytoplasm red. After these steps, the slides are ready for microscopic examination by the pathologist, who assigns them a number to describe the grade.

### 2.1 Statistical analysis

To detect the difference effects between the patient and control groups, the data was organized in a datasheet of IBM SPSS version 25.0, which was utilized to do the statistical analysis. For comparing the means significantly LSD- least significant difference & T-test were used while Chi-square test is used for the comparison of percentage. Statistical significance was defined as a probability value ($p \leq 0.05$ and $p \leq 0.01$):

$$\chi^2 = \Sigma \frac{(O-E)^2}{E} \quad (1)$$

Where; $\chi^2$: Chi-square, Σ: Summation, O: Observed No. , E: Expected No

## 3. Result and Discussion

There are notable gender differences in the incidence of most cancers affecting both males and females, indicating that cancer incidence may be influenced by the fundamental biological differences between the sexes [26].

For the development of treatment plans for patients with lethal malignancies, further research that identifies the vulnerable sex and age group is very important [27]. Age is identified as a crucial factor related to incidence and survival in all cancers [28]. Aging as a complex process can affect cancer risk through multiple mechanisms, as it has a direct impact on nearly all aspects of the immune system [22].

The result of the present study as shown in Table 1 showed a significant difference ($P \leq 0.05$) between glioma and gender, p-value (0.0437) in males and females, which confirms the existence of a link between the disease and gender.

It was also noted that male patients have a higher incidence of glioma than female patients, the percentage of male patients was (61.76%), which is higher than the percentage of female patients (38.24%), and this is reinforced by Figure 1, this is consistent with the study of Abdulghani *et al*. [7] was primarily higher incident in males 70.9% than in females, supporting the previous findings of Ostrom *et al*. [29].

**Table 1:** Distribution of sample study according to the Gender and Age in control and patient groups.

| Factors | | Control No (%) | Patients No (%) | P-value |
|---|---|---|---|---|
| **Gender** | Male | 12 (40.00%) | 21 (61.76%) | 0.0437 * |
| | Female | 18 (60.00%) | 13 (38.24%) | |
| | Total | 30 | 34 | -- |
| **Age group (year)** | ≤25 | 6 (20.00%) | 6 (17.65%) | 0.0052 ** |
| | 25-45 | 6 (20.00%) | 9 (26.47%) | |
| | 46-65 | 14 (46.67%) | 16 (47.06%) | |
| | >65 | 4 (13.33%) | 3 (8.82%) | |

* (P≤0.05), ** (P≤0.01).

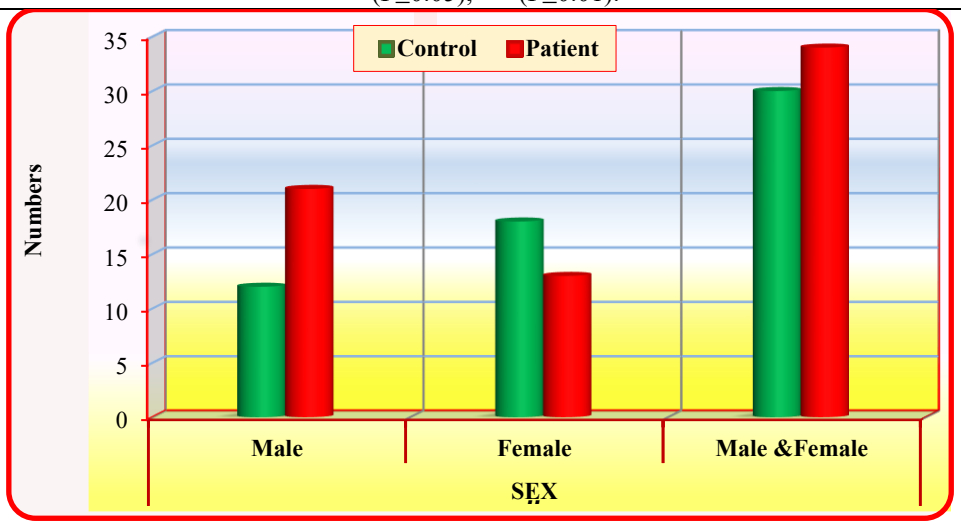


**Figure1:** Distribution of Glioma control and patient according to the gender.

Through our current study, we identified a strong association between glioma and aging by a highly significant (P≤0.01) between glioma and age group of patients, p-value (0.0052), according to the age groups shown in the same table, the highest infection rate was found in the 46-65year age group, which had the highest percentage of 47.06%.

The histopathological examination showed the following changes, as shown in figures 2, 3 and 4, compared to the benign tumor in Figure 5.
Table 2 showed that the average age of males (51.62 years) was higher than that of female (34.92 years). One possible explanation for the greater prevalence of glioma, especially high-grade glioma, in males compared to females can be explained by the association of glioma with older age, giving that most of our patient where old, in addition number of male patients is a greeter of female patient in current study.

These results can be seen in many researches as Bello-Alvarez and Camacho-Arroyo [30] that showed that men are more affected by Glioma than women by ratio of 1.6/1, and this is consistent with the findings of our study.

**Table 2:** Distribution of Glioma control according to the age average

| | Sex | No. | No % | Age average |
|---|---|---|---|---|
| **Patient** | Male | 21 | 61.76% | 51.62 |
| | Female | 13 | 38.24% | 34.92 |
| | Sum | 34 | 100% | |

Same statement can be found in Wang *et al*. [27] study, which showed the incidence of glioma was greater in male patients through all age groups, but in general males have the highest risk of death when compared to female patients, this also agrees with the statistical analysis in our current study.

The outcome of this study matches those of Ostrom *et al*. [21] study, which reveals that there is an increase in the primary malignant glioma incidence going along with growing older and this aspect can be explained through the sequential change of genetic alterations going on the age that make malignant transformation of cells such a chronic process.
Age plays a significant role in the difference in incidence between male and female, by examining the interaction of age and sex influence incidence and survival of glioma patients in the United States [27].

On the other hand, prolonged exposure to benzene, $O_3$, by men may be the cause of injury, and this was demonstrated by a study of Wu *et al*. [31], this may explain why males are more affected.

Yu *et al*. [32] discovered that by blocking TGF-β (transforming growth factor β) receptor signaling, androgen receptor signaling may contribute to the tumor genesis of GBM in adult males [33], this may be one of the reasons that lead to an increase in the incidence of male.
Study Stabellini *et al.* [34] found that like in any other cancer low or high grade males has the highest incidence than females this is consistent with what our study found.
When comparing male to female, there is a heightened susceptibility for malignant transformation in male astrocytes with loss of p53 function which can give a partial explanation [35]. Another research pointed out the role of other genes that may act in conjunction with hormonal factors and environmental effects to illustrate the difference of incidence between the two sexes [36].

The results of our study are also consistent with Cowppli-Bony *et al*. [37] which states that the incidence of glioma is twice as a high in men than in women, this trend initial during youth, increasing until 50–54 years old and decreasing after that [26].

The long history of high-grade glioma in males compared to females has long implied a role for sex, and more specifically, gonadal steroid hormones, in the development of high-grade glioma (grade III and IV).
Nowadays, a large number of pieces of evidence about the role of gonadal steroid hormones in Glioblastoma origin and progression have emerged [38].
Several studies, including the research by Qi *et al*. [39], have indicated that exogenous hormone drugs can decrease female Glioma risk; this may be a reason why females are less affected than males. The Eurocare-2 is a project, which focuses on statistical information of European cancer patients, in one million cases that were diagnosed in 1985 to 1989 sex was a significant predictor of survival and females were biologically having a better survival rate than males [40].

For the first time, our study demonstrated that females at an average age 34.92 year or younger are infected with this disease, despite being in the monarch period, it is assumed that the level of incidence is low because the estrogen hormone is considered as protective against the disease, and this was confirmed by study of Omame and Alex-Nmecha [41], but does not agree with Mckinley *et al*. [26] study, though such a protector of estrogen hormone effect is merely speculation, it is also not consistent with what was stated in the results of the study by Ippolito *et al*. [42], which implies that the actions of circulating sex hormones may not be the sole cause of current sex discrepancies, at least when it comes to brain tumors. Likewise, the incidence of Glioma in young women, specifically the high degree, does not agree with the study of Wrensch *et al.* [43], who mentioned in his study that the malignant glioma can occur at any age, the average age of onset for Glioblastoma is 62 years (advanced age).
Moreover, the study by Brennan *et al*. [20], indicated that glioma is more common in older adults, with peak in incidence occurring between the ages of (45 to 65) years old. What we found in our research regarding females becoming infected with Glioma in middle age or younger, it might be because: exposure to smoke and cosmetics as mentioned in Wrensch *et al*. [43] study, or it may be due to the inflammatory response, as demonstrated by many studies like study by Michelson *et al*. [44], that there is a clear relationship between inflammatory response and tumor, one of the main characters of malignant tumor is abnormal inflammation and it can be the trigger point for transformation of low grade to high grade Glioma, in case of inflammation transcription factors will be activated thus promoting the survival and growth of malignant cell. Furthermore, there appears to be a close relationship between incidence of Glioblastoma and patient susceptibility to allergies suggesting an immunological participation in the progress of cancer [45].
Most likely, the tumor of the secondary type, which is common at younger ages, and this is what Yang *et al.* [46], confirmed in his study: primary GBM (high grade Glioma) predominantly affects older patients, whereas secondary is more frequently seen in younger ones, this is consistent with what we have found regarding female infection, as the secondary type is common.

There is a possible reason that may explain the phenomenon of females getting glioma (high grade) at middle age or younger, which is hormonal exposure early in life, and this is what Carrano *et al*. [47] pointed out in their study, which shed light on the highlight the theoretical cooperation of early life hormonal exposure along with possible occurrence of glioma accompanied by the protective effects exerted by exogenous hormonal therapy this may be noticeable in glioplstoma (GBM). On the contrary a Canadian study [48] reveals a slight increase in glioma risk with females of older age at menarche (66%) as compared with the results 64% obtained from females of younger age at menarche giving that there is no correlation between hormonal therapy and increased risk of Glioma, with a late age at menarche, compared with 64% in those with early age at menarche, but the use of hormone therapy had no association with an increased glioma risk.

The explanation for the incidence of high grade glioma infection in females during the youth period may be related to the breastfeeding process, as Andersen *et al.* [49] indicated in his study that was related with an amplified risk of glioma that increased with duration of, Long term use of hormonal contraceptive use. Compared with women who never breast-fed, women who breast-fed >18 months over their lifetime were at increased risk of glioma [24].

The menopausal status and age at menopause were not associated with glioma, but reproductive hormones may impact the incidence of Glioma.

In recent years, there has been a significant increase in the use of narghile (hookah), especially by younger women that can be another cause for glioma. This interpretation is consistent with study, which showed that element found in cigarette smoke, such as N-nitro, which allows chemicals to cross the blood brain barrier. However, it remains unclear whether drinking alcohol plus smoking cigarettes raises the risk of brain cancer [50].

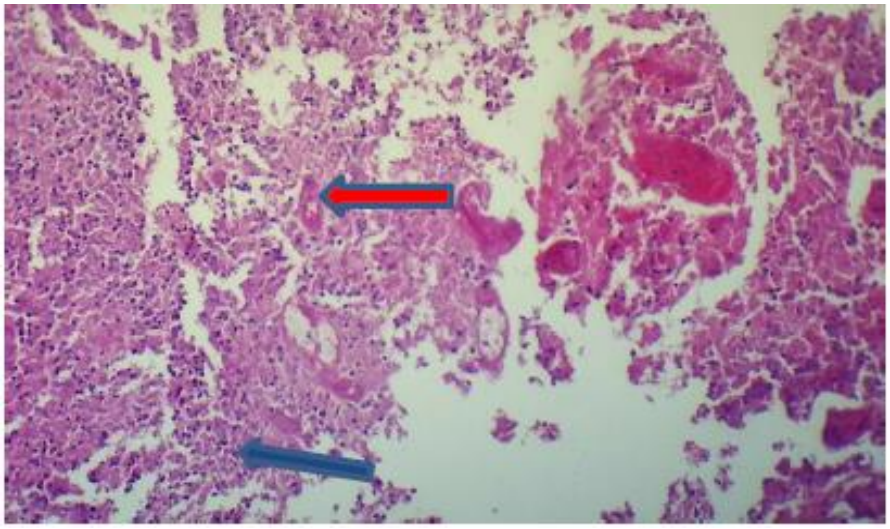

**Figure 2:** Section in brain tumor with high grade Glioma shows Vascular proliferation (red arrows), nuclear atypia of glial cells (blue arrows) (H & E stain 10X)

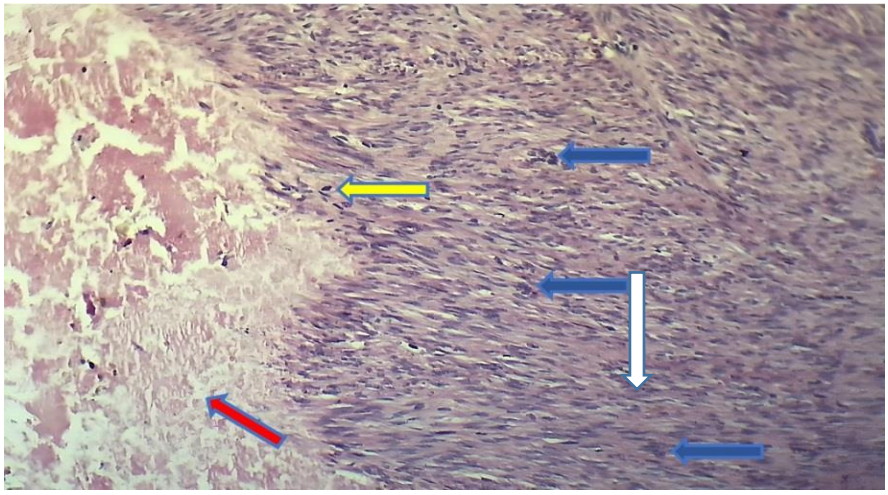

**Figure 3:** Section in brain tumor with high grade Glioma, shows focal hemorrhage and necrosis (blue arrows), vascular proliferation (red arrows), market atypia (yellow arrows),and increase in thickness of vascular wall (white arrows) (H & E stain 10X).

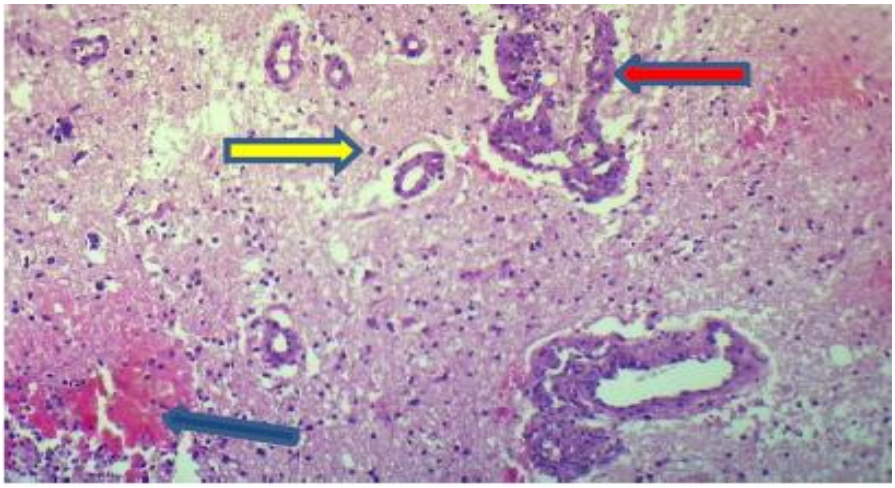

**Figure 4:** Section in brain tumor with high grade Glioma, shows extensive necrosis (red arrows), marked atypia and increased cellularity of glial cells (blue arrows), mitotic figure (yellow arrows) (H & E stain 10X)

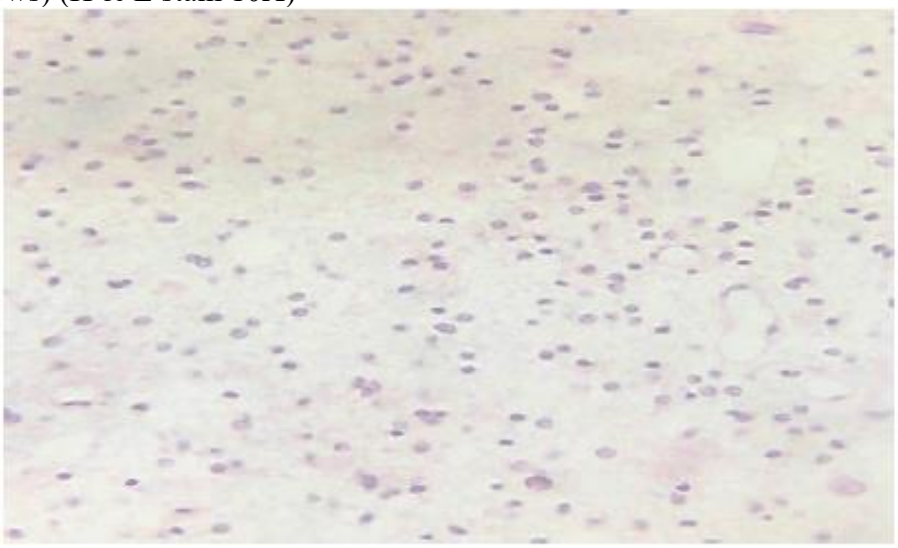

**Figure 5:** Section of benign brain tumor (H & E stain 10X)

## Conclusion

This study reveals that there is a distinguished difference regarding the incidence of Glioma between men and women taking in consideration that all samples were collected randomly from the biggest hospital specialized in CNS tumors in Baghdad. A notable age disparity was observed in this case, consistent with previous studies, which have shown that glioma tends to affect men at an older age and women at a younger age. Nevertheless, more researches are needed to point out any possible differences on which other aspects depend on like the progress of tumor, finding other causes of the diseases and planning suitable treatment for each case or even discovering the underlying causes of glioma.

## Acknowledgement

We are grateful for the medical staff of the Histology Laboratory related to the Neurological Hospital in Baghdad for their cooperation during the collection of histological samples from patients.

## Conflict of interest

The authors declare that they have no conflicts of interest.

**References**


**[1]** N. A. Alwan, F. Lami, M. Al Nsoor, and D. Kerr, "Trends in the Incidence and Mortality of the Most Common Cancers in Iraq (Iraqi Cancer Registry 1999-2019)," *The Gulf Journal of Oncology,* vol. 1, no. 40, pp. 47-57, 2022.

**[2]** R. N. Mohsin and B. J. Mohamad, "Investigation of CD73 expression in Iraqi patient women with breast tumors," *Journal of Population Therapeutics and Clinical Pharmacology,* vol. 30, no. 3, pp. 240-257, 2023.

**[3]** R. Abd-El-Raouf, S. A. Ouf, M. G. Haggag, K. F. El-Yasergy, and M. M. Zakaria, "Mesenchymal and stemness transdifferentiation via in-vitro infection of T24 cell line with Klebsiella pneumoniae," *Baghdad Science Journal,* vol. 20, no. 3, pp. 0797-0797, 2023.

**[4]** H. M. Al-Khateeb and K. R. Alkhafaji, "Virulence estimation by calculation of relative expression of NESTIN in different grades of astrocytoma from different age groups of Iraqi patients, extracted from brain tumor stem cells," *Journal of the Faculty of Medicine Baghdad,* vol. 61, no. 3, 4, 2019.

**[5]** P. Dalerba, M. Diehn, I. L. Weissman, and M. F. Clarke, "Stem cells, cell differentiation, and cancer," in *Abeloff's Clinical Oncology*: Elsevier, 2020, pp. 97-107. e5.

**[6]** S. G. Turki, A. N. Jassim, and A. H. Ad'hia, "Studying HLA class I polymorphism in brain tumour patients," *Baghdad Science Journal,* vol. 9, no. 3, pp. 481-490, 2012.

**[7]** M. M. Abdulghani, M. N. Abbas, and W. R. Mohammed, "Immunohistochemical expression of epidermal growth factor receptor in astrocytic tumors in iraqi patients," *Open Access Macedonian Journal of Medical Sciences,* vol. 7, no. 21, p. 3514, 2019.

**[8]** A. K. AL-Shalchy, "Low grade Gliomas Multi Modality Approach," *Journal of the Faculty of Medicine Baghdad,* vol. 51, no. 3, pp. 251-253, 2009.

**[9]** S. F. Abdullah and F. A. Mukhlis, "Detection of human cytomegalovirus genome in malignant gliomas by in situ hybridization technique," *Journal of the Faculty of Medicine Baghdad,* vol. 51, no. 2, pp. 178-183, 2009.

**[10]** H. M. Alabassi, "Assessment of ZYXIN and E-cadherin tumour marker in Iraqi patients with glioma lesion of the brain," *Biochemical and Cellular Archives,* vol. 19, no. 2, pp. 4379-4383, 2019.

**[11]** I. C. Registry, "Results of the Iraqi Cancer Registry 2012," Iraqi Cancer Registry Center, Ministry of Health.,, Baghdad, Iraq, 2012.

**[12]** M. Weller, W. Wick, K. Aldape, M. Brada, M. Berger, S. M. Pfister, R. Nishikawa, M. Rosenthal, P. Y. Wen, R. Stupp and G. Reifenberger, "Glioma," *Nature reviews Disease primers,* vol. 1, no. 1, pp. 1-18, 2015.

**[13]** D. N. Louis, A. Perry, G. Reifenberger, A. von Deimling, D. Figarella-Branger, W. K. Cavenee, H. Ohgaki, O. D. Wiestler, P. Kleihues and D. W. Ellison, "The 2016 World Health Organization classification of tumors of the central nervous system: a summary," *Acta neuropathologica,* vol. 131, pp. 803-820, 2016.

**[14]** S. P. Niclou, F. Fack, and U. Rajcevic, "Glioma proteomics: status and perspectives," *Journal of proteomics,* vol. 73, no. 10, pp. 1823-1838, 2010.

**[15]** M. L. Bondy, M. E. Scheurer, B. Malmer, J. S. Barnholtz-Sloan, F. G. Davis, D. Il'yasova, C. Kruchko, B. J. McCarthy, P. Rajaraman, J. A. Schwartzbaum, S. Sadetzki, B. Schlehofer, T. Tihan, J. L. Wiemels, M. Wrensch, P. A. Buffler, and Brain Tumor Epidemiology Consortium, "Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium," *Cancer,* vol. 113, no. S7, pp. 1953-1968, 2008.

**[16]** Q. T. Ostrom, B. Kinnersley, M. R. Wrensch, J. E. Eckel-Passow, G. Armstrong, T. Rice, Y. Chen, J. K. Wiencke, L. S. McCoy, H. M. Hansen, C. I. Amos, J. L. Bernstein, E. B. Claus, D. Il'yasova, C. Johansen, D. H. Lachance, R. K. Lai, R. T. Merrell, S. H. Olson, S. Sadetzki, J. M. Schildkraut, S. Shete, J. B. Rubin, J. D. Lathia, M. E. Berens, U. Andersson, P. Rajaraman, S. J. Chanock, M. S. Linet, Z. Wang, M. Yeager, GliomaScan consortium, R. S. Houlston, R. B. Jenkins, B. Melin, M. L. Bondy and J. S. Barnholtz-Sloan, "Sex-specific glioma genome-wide association study identifies new risk locus at 3p21. 31 in females, and finds sex-differences in risk at 8q24. 21," *Scientific reports,* vol. 8, no. 1, p. 7352, 2018.

**[17]** J. Yin, G. Liu, Y. Zhang, Y. Zhou, Y. Pan, Q. Zhang, R. Yu and S. Gao, "Gender differences in gliomas: from epidemiological trends to changes at the hormonal and molecular levels," *Cancer Letters,* p. 217114, 2024.

**[18]** A. Colopi, S. Fuda, S. Santi, A. Onorato, V. Cesarini, M. Salvati, C. R. Balistreri, S. Dolci and E. Guida, "Impact of age and gender on glioblastoma onset, progression, and management," *Mechanisms of ageing and development,* vol. 211, p. 111801, 2023.

**[19]** Z. Lin, R. Yang, K. Li, G. Yi, Z. Li, J. Guo, Z. Zhang, P. Junxiang, Y. Liu, S. Qi and G. Huang, "Establishment of age group classification for risk stratification in glioma patients," *BMC neurology,* vol. 20, pp. 1-11, 2020.

**[20]** C. W. Brennan, R. G. Verhaak, A. McKenna, B. Campos, H. Noushmehr, S. R. Salama, S. Zheng, D. Chakravarty, J. Z. Sanborn, S.H. Berman, R. Beroukhim, B. Bernard, C. J. Wu, G. Genovese, I. Shmulevich, J. Barnholtz-Sloan, L. Zou, R. Vegesna, S. A. Shukla, G. Ciriello, W. K. Yung, W. Zhang, C. Sougnez, T. Mikkelsen, K. Aldape, D. D. Bigner, E. G. Van Meir, M. Prados, A. Sloan, K. L. Black, J. Eschbacher, G. Finocchiaro, W. Friedman, D.W. Andrews, A. Guha, M. Iacocca, B. P. O'Neill, G. Foltz, J. Myers, D. J. Weisenberger, R. Penny, R. Kucherlapati, C. M. Perou, D. N. Hayes, R. Gibbs, M. Marra, G. B. Mills, E. Lander, P. Spellman, R. Wilson, C. Sander, J. Weinstein, M. Meyerson, S. Gabriel, P.W. Laird, D. Haussler, G. Getz, L. Chin and TCGA Research Network, "The somatic genomic landscape of glioblastoma," *cell,* vol. 155, no. 2, pp. 462-477, 2013.

**[21]** Q. T. Ostrom, N. Patil, G. Cioffi, K. Waite, C. Kruchko, and J. S. Barnholtz-Sloan, "CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017," *Neuro-oncology,* vol. 22, no. Supplement_1, pp. iv1-iv96, 2020.

**[22]** E. Ladomersky, D. M. Scholtens, M. Kocherginsky, E. A. Hibler, E.T. Bartom, S. Otto-Meyer, L. Zhai, K. L. Lauing, J. Cho, J. A. Sosman, J. D. Wu, B. Zhang, R. V. Lukas and D. A. Wainwright, "The coincidence between increasing age, immunosuppression, and the incidence of patients with glioblastoma," *Frontiers in pharmacology,* vol. 10, p. 200, 2019.

**[23]** S. Ahn, K. Han, J.-E. Lee, S.-S. Jeun, Y.-M. Park, and S. H. Yang, "Associations of general and abdominal obesity with the risk of glioma development," *Cancers,* vol. 13, no. 12, p. 2859, 2021.

**[24]** K. Huang, E. A. Whelan, A. M. Ruder, E. M. Ward, J. A. Deddens, K. E. Davis-King, T. Carreón, M. A. Waters, M. A. Butler, G. M. Calvert, P. A. Schulte, Z. Zivkovich, E. F. Heineman, J. S. Mandel, R. F. Morton, D. J. Reding, K. D. Rosenman and Brain Cancer Collaborative Study Group, "Reproductive factors and risk of glioma in women," *Cancer Epidemiology Biomarkers & Prevention,* vol. 13, no. 10, pp. 1583-1588, 2004.

**[25]** J. D. Bancroft and C. Layton, "The hematoxylins and eosin," *Bancroft's theory and practice of histological techniques,* vol. 7, pp. 173-186, 2012.

**[26]** B. P. McKinley, A. M. Michalek, R. A. Fenstermaker, and R. J. Plunkett, "The impact of age and gender on the incidence of glial tumors in New York state from 1976–1995," *Journal of neurosurgery,* vol. 93, no. 6, pp. 932-939, 2000.

**[27]** G.-M. Wang, G. Cioffi, N. Patil, K. A. Waite, R. Lanese, Q. T. Ostrom, C. Kruchko, M. E. Berens, J. R. Connor, J. D. Lathia, J. B. Rubin and J. S. Barnholtz-Sloan, "Importance of the intersection of age and sex to understand variation in incidence and survival for primary malignant gliomas," *Neuro-oncology,* vol. 24, no. 2, pp. 302-310, 2022.

**[28]** R. L. Siegel, K. D. Miller, H. E. Fuchs, and A. Jemal, "Cancer statistics, 2022," *CA: a cancer journal for clinicians,* vol. 72, no. 1, 2022.

**[29]** Q. T. Ostrom, H. Gittleman, J. Fulop, M. Liu, R. Blanda, C. Kromer, Y. Wolinsky, C. Kruchko and J. S. Barnholtz-Sloan, "CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012," *Neuro-oncology,* vol. 17, no. suppl_4, pp. iv1-iv62, 2015.

**[30]** C. Bello-Alvarez and I. Camacho-Arroyo, "Impact of sex in the prevalence and progression of glioblastomas: the role of gonadal steroid hormones," *Biology of sex Differences,* vol. 12, pp. 1-13, 2021.

**[31]** A. H. Wu, J. Wu, C. Tseng, J. Yang, S. Shariff-Marco, S. Fruin, T. Larson, V. W. Setiawan, S. Masri, J. Porcel, J. Jai, T. C. Chen, D. O. Stram, L. L. Marchand, B. Ritz and I. Cheng, "Association between outdoor air pollution and risk of malignant and benign brain tumors: the Multiethnic Cohort Study," *JNCI cancer spectrum,* vol. 4, no. 2, p. pkz107, 2020.

**[32]** H. Yu, M. Chin, T. Yuan, H. Bian, L. A. Remer, J. M. Prospero, A. Omar, D. Winker, Y. Yang, Y. Zhang, Z. Zhang and C. Zhao, "The fertilizing role of African dust in the Amazon rainforest: A

first multiyear assessment based on data from Cloud-Aerosol Lidar and Infrared Pathfinder Satellite Observations," *Geophysical Research Letters,* vol. 42, no. 6, pp. 1984-1991, 2015.

**[33]** M. Tian, W. Ma, Y. Chen, Y. Yu, d. Zhu, J. Shi, Y. Zhang, "Impact of gender on the survival of patients with glioblastoma," *Bioscience reports,* vol. 38, no. 6, p. BSR20180752, 2018.

**[34]** N. Stabellini, H. Krebs, N. Patil, K. Waite, and J. S. Barnholtz-Sloan, "Sex differences in time to treat and outcomes for gliomas," *Frontiers in Oncology,* vol. 11, p. 630597, 2021.

**[35]** T. Sun, A. Plutynski, S. Ward, and J. B. Rubin, "An integrative view on sex differences in brain tumors," *Cellular and molecular life sciences,* vol. 72, pp. 3323-3342, 2015.

**[36]** H.-I. Kim, H. Lim, and A. Moon, "Sex differences in cancer: epidemiology, genetics and therapy," *Biomolecules & therapeutics,* vol. 26, no. 4, p. 335, 2018.

**[37]** M. Colonna, O. Boussari, A. Cowppli-Bony, P. Delafosse, G. Romain, P. Grosclaude, V. Jooste and French Network of Cancer Registries (FRANCIM), "Time trends and short term projections of cancer prevalence in France," *Cancer epidemiology,* vol. 56, pp. 97-105, 2018.

**[38]** G. C. Kabat, A. M. Etgen, and T. E. Rohan, "Do steroid hormones play a role in the etiology of glioma?," *Cancer epidemiology, biomarkers & prevention,* vol. 19, no. 10, pp. 2421-2427, 2010.

**[39]** Z.-Y. Qi, C. Shao, X. Zhang, G.-Z. Hui, and Z. Wang, "Exogenous and endogenous hormones in relation to glioma in women: a meta-analysis of 11 case-control studies," *PLoS One,* vol. 8, no. 7, p. e68695, 2013.

**[40]** E. Michelia, D. D'Ambrosiob, M. Franceschina, and M. Savino, "Water soluble cationic perylene derivatives as possible telomerase inhibitors: the search for selective G-quadruplex targeting," *Mini Reviews in Medicinal Chemistry,* vol. 9, no. 14, pp. 1622-1632, 2009.

**[41]** I. M. Omame and J. C. Alex-Nmecha, "Artificial intelligence in libraries," in *Managing and adapting library information services for future users*: IGI Global, 2020, pp. 120-144.

**[42]** J. E. Ippolito, A. K.-Y. Yim, J. Luo, P. Chinnaiyan, and J. B. Rubin, "Sexual dimorphism in glioma glycolysis underlies sex differences in survival," *JCI insight,* vol. 2, no. 15, 2017.

**[43]** M. Wrensch, Y. Minn, T. Chew, M. Bondy, and M. S. Berger, "Epidemiology of primary brain tumors: current concepts and review of the literature," *Neuro-oncology,* vol. 4, no. 4, pp. 278-299, 2002.

**[44]** N. Michelson, J. Rincon-Torroella, A. Quiñones-Hinojosa, and J. P. Greenfield, "Exploring the role of inflammation in the malignant transformation of low-grade gliomas," *Journal of neuroimmunology,* vol. 297, pp. 132-140, 2016.

**[45]** R. Dharmajaya and D. K. Sari, "Role and value of inflammatory markers in brain tumors: A case controlled study," *Annals of Medicine and Surgery,* vol. 63, p. 102107, 2021.

**[46]** K. Yang, S. W. Jung, H. Shin, D. H. Lim, J. I. Lee, D. S. Kong, H. J. Seol, S. T. Kim and D. H. Nam, "Cancer genetic markers according to radiotherapeutic response in patients with primary glioblastoma–radiogenomic approach for precision medicine," *Radiotherapy and Oncology,* vol. 131, pp. 66-74, 2019.

**[47]** A. Carrano, J. J. Juarez, D. Incontri, A. Ibarra, and H. G. Cazares, "Sex-specific differences in glioblastoma," *Cells,* vol. 10, no. 7, p. 1783, 2021.

**[48]** A. Wigertz, S. Lönn, T. Mathiesen, A. Ahlbom, P. Hall, and M. Feychting, "Risk of brain tumors associated with exposure to exogenous female sex hormones," *American journal of epidemiology,* vol. 164, no. 7, pp. 629-636, 2006.

**[49]** L. Andersen, S. Friis, J. Hallas, P. Ravn, B. W. Kristensen, and D. Gaist, "Hormonal contraceptive use and risk of glioma among younger women: a nationwide case–control study," *British journal of clinical pharmacology,* vol. 79, no. 4, pp. 677-684, 2015.

**[50]** M. Braganza, P. Rajaraman, Y. Park, P. D. Inskip, N. D. Freedman, A. R. Hollenbeck, A. Berrington de González and C. M. Kitahara, "Cigarette smoking, alcohol intake, and risk of glioma in the NIH-AARP Diet and Health Study," *British journal of cancer,* vol. 110, no. 1, pp. 242-248, 2014.