Impact of age and gender on survival of glioblastoma multiforme patients: A multicentric retrospective study

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Abstract

Background: Glioblastoma multiforme (GBM) poses a significant health challenge as the most common primary malignancy of the adult central nervous system. Gender and age-related differences in GBM influence prognosis and treatment complexities. This multicenter retrospective study explores gender and age disparities in GBM patients, investigating their impact on occurrence and survival outcomes. **Methods:** This STROBE-compliant retrospective study involved GBM patients who received medical care in Guilan Province, Iran. Patients' data, including age, gender, tumor location, and histopathological diagnosis date, was collected from medical records. **Results:** In a cohort of 164 GBM patients, the average age was 54 years, with higher prevalence in men (59.8%) as well as patients [?]60 years (64.6%). The tumor sites exhibited overlapping features in 68% of cases, with the frontal and temporal lobes being the most prevalent specific locations. The mean survival was 12.88 ± 14.14 months, one-year survival of 45%, with women showing higher one-year survival (60% vs. 40%) and longer mean survival (16.14 ± 17.35 vs. 10.75 ± 11.15 months). Patients [?]60 years had higher one-year survival (75% vs. 35%). In subgroup analysis, women had significantly higher survival rates in patients [?]60 years. However, among patients over 60, women exhibited a more significant reduction in survival rates, and no statistically significant difference was observed between males and females in this age group. **Discussion:** While the biological mechanisms behind gender disparities in GBM remain unclear, studies suggest the potential involvement of sex hormones. Age-related differences, in line with the prior research, highlight the complexity of managing older GBM patients. **Conclusion:** This study underscores age and gender disparities in GBM occurrence and prognosis, emphasizing the necessity for further investigations and innovative approaches to address the potential pathogenesis.

Impact of age and gender on survival of glioblastoma multiforme patients: A multicentric retrospective study

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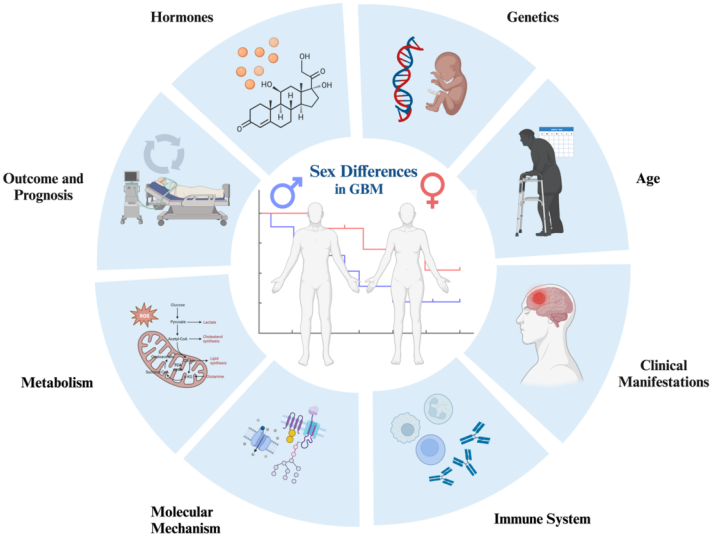
Abstract:

Background: Glioblastoma multiforme (GBM) poses a significant health challenge as the most common primary malignancy of the adult central nervous system. Gender and age-related differences in GBM influence prognosis and treatment complexities. This multicenter retrospective study explores gender and age disparities in GBM patients, investigating their impact on occurrence and survival outcomes.**Methods:** This STROBE-compliant retrospective study involved GBM patients who received medical care in Guilan Province, Iran. Patients' data, including age, gender, tumor location, and histopathological diagnosis date, was collected from medical records. **Results:** In a cohort of 164 GBM patients, the average age was 54 years, with higher prevalence in men (59.8%) as well as patients [?]60 years (64.6%). The tumor sites exhibited overlapping features in 68% of cases, with the frontal and temporal lobes being the most prevalent specific locations. The mean survival was 12.88 ± 14.14 months, one-year survival of 45%, with women showing higher one-year survival (60% vs. 40%) and longer mean survival (16.14 ± 17.35 vs. 10.75 ± 11.15 months). Patients [?]60 years had higher one-year survival (75% vs. 35%). In subgroup analysis, women had significantly higher survival rates in patients [?]60 years. However, among patients over 60, women exhibited a more significant reduction in survival rates, and no statistically significant difference was observed between males and females in this age group. **Discussion:** While the biological mechanisms behind gender disparities in GBM remain unclear, studies suggest the potential involvement of sex hormones. Age-related differences, in line with the prior research, highlight the complexity of managing older GBM patients.**Conclusion:** This study underscores age and gender disparities in GBM occurrence and prognosis, emphasizing the necessity for further investigations and innovative approaches to address the potential pathogenesis.

Keywords: Glioblastoma, GBM, Overall survival, Brain tumor, Gender, Sex difference



Graphical Abstract

1 | Introduction

Glioblastoma multiforme (GBM) ranks as the most prevalent and highly invasive primary malignancy of the central nervous system(CNS) in adults[1,2], constituting 57.3% of all gliomas and 48.3% of malignant brain tumors [3,4]. As the global population ages, the incidence of GBM increases. Older patients being diagnosed with GBM generally face a less favorable prognosis compared to their younger counterparts [5], experiencing a median overall survival (OS) of 9 months, in contrast to the 15-month OS observed in the general adult population. The management of GBM in older patients can be more complex due to age-related comorbidities and the potential impact of treatment on their quality of life [6]. Moreover, gender influences GBM onset, with a male-to-female ratio of 1.6:1 [7]. Previous studies suggest that females are associated with better outcomes in both adults and children. Although there is some evidence indicating the potential involvement of sex hormones, the exact causes of the observed differences remain unclear[8].

According to the World Health Organization (WHO) classification, glioblastoma multiforme (GBM) is categorized into two subtypes based on genetic characteristics, specifically the presence or absence of isocitrate dehydrogenase (IDH) mutations: IDH-mutant and IDH-wild type.[9,10]. These subtypes are referred to as primary (IDH-wild type) and secondary (IDH-mutant) GBMs. Primary GBMs generally impact older patients, lack precursor lesions, and are associated with a less favorable prognosis. In contrast, secondary GBMs occur in younger individuals, arise from lower-grade gliomas, feature IDH mutations, and show a more extended overall survival (OS)[11,12]. Furthermore, studies have shown that distinct histopathological subtypes exhibit different treatment responses, resulting in varying survival rates. In addition to patient age and sex, predictive factors include clinical parameters, the extent of surgical resection, and tumor imaging characteristics, including tumor size, location, the presence of necrosis, and surrounding edema [13].

The primary treatment involves comprehensive surgical removal while preserving neurological function and minimizing postoperative complications. Preoperative and intraoperative assessments, encompassing laboratory tests, neuronavigation, intraoperative MRI, and fluorescence-guided surgery, are pivotal for safe and maximal tumor resection[14,15]. The treatment protocol extends to postoperative care, including radiotherapy and chemotherapy[14,15]. This often includes using temozolomide (TMZ), an oral chemotherapy agent with methylating properties[16,17]. The unfavorable prognosis associated with the tumor comes from its tendency to persist even after surgical resection and adjuvant therapies. Tumor complete removal is difficult due to the infiltrative tumor growth into the adjacent brain tissue and the brain's vulnerability to surgical interventions, which could lead to functional impairment [18,19]. Despite advancements in medical care, GBM patients have consistently confronted an unfavorable prognosis in recent years, with a survival rate of less than 7% over five years[20], underscoring the persistent challenge of managing this highly aggressive and rapidly progressing malignant tumor. The situation highlights a major challenge in global public health, emphasizing the urgent demand for innovative approaches[21,22].

Within the context of the challenging survival rates of GBM, this study investigates the factors impacting survival, explicitly age and gender. The study's population consists of individuals who sought medical care at educational and medical institutions of Guilan Province, located in northern Iran, from 2014 to 2018. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[23] guidelines.

2 | Materials and methods

2.1. Study Design and Setting:

This retrospective study aimed to investigate registered cases of GBM among individuals who underwent medical treatment at educational and medical facilities in Guilan Province, Iran.

2.2. Participants and Variables

The study incorporated 164 patients diagnosed with GBM registered from 2014 to 2018, utilizing standardized data collection forms derived from hospital medical records. Inclusion criteria encompassed patients with confirmed histopathological and immunohistochemical diagnoses of GBM who received care in

Guilan Province during the specified period. Patient information, including age, gender, tumor location, and histopathological diagnosis date, was collected. Patients with incomplete or insufficient records were excluded from the study. The overall survival status of each patient was verified using their national ID to cross-reference death reports. Survival duration, measured in months from the histopathological diagnosis to the time of death, was calculated for deceased individuals.

2.3. Ethical Consideration

This study adhered to ethical guidelines, obtaining approval from the Institutional Review Board at Guilan University of Medical Sciences, Iran, before data collection and subsequent analysis (Ethics Approval Code: IR.GUMS.REC.1401.461).

2.4. Statistical Analysis:

The data were compiled and summarized in a Microsoft Excel (2019) spreadsheet, and subsequent statistical analysis was conducted using SPSS software version 22. Quantitative variables were summarized by mean and standard deviation, while categorical variables were represented through frequency and percentage. The normality of numerical data distribution was assessed through the Kolmogorov–Smirnov test, and variance homogeneity was evaluated using the Levene test. We employed Kaplan–Meier survival curves to determine overall survival rates, and differences between survival curves were compared via the log-rank test. Additionally, we utilized a Cox regression analysis to investigate the impact of independent variables on overall survival. Statistical significance was established at a threshold of 0.05, with results considered significant if the p-value was less than 0.05. All reported findings include a 95% confidence interval to ensure accuracy and reliability.

3 | Result

3.1. Characteristics of the Study Population

The records of 164 patients diagnosed with GBM in Guilan Province from 2014 to 2018 were retrospectively analyzed. The study cohort had a mean age of 54.34 ± 14.16 years, ranging from 3 to 82 years. Among these, 106 patients (64.6%) were 60 years or younger, and 98 (59.8%) were male. The higher prevalence in men and patients aged 60 years or younger was statistically significant ($p < 0.001$) ***(Table 1)***. Moreover, the tumor site displayed overlapping characteristics in 112 patients, constituting 68% of the cases. The most prevalent specific locations were the frontal lobe in 17 cases (10%), the temporal lobe in 11 cases (7%), and the parietal lobe in 10 cases (6%) Figure 1 .

___Table 1___

___Figure 2___

3.2. Overall survival

The mean survival for the entire cohort was 12.88 ± 14.14 months, spanning from 0 days to 85.37 months. Furthermore, the estimated one-year survival rate for all patients was 45% ***(Figure 2)***. A notable disparity was observed upon gender-based analysis, with women demonstrating a more favorable one-year survival rate of 60% compared to men at 40%. Additionally, women exhibited significantly longer mean survival time, with an average of 16.14 ± 17.35 months, while men had a mean survival time of 10.75 ± 11.15 months ($p = 0.023$). Individuals over 60 experienced shorter mean survival times than their younger counterparts, with averages of 7.48 ± 7.06 months vs 15.9 ± 16.21 months, respectively. The age-dependent survival difference was highly statistically significant ($p < 0.001$). Moreover, patients aged 60 or younger demonstrated a significantly higher one-year survival rate compared to their older counterparts (75% vs. 35%)

(Figure 3)

___Figure 2___

___Figure 3___

Subgroup analysis based on gender revealed striking differences in survival outcomes. Specifically, women over 60 exhibited markedly reduced survival durations compared to their younger counterparts (6.18 ± 5.41 months vs. 19.68 ± 18.76 months, $p < 0.001$). A similar trend was observed in men over 60 compared to younger males (7.41 ± 8.19 months vs. 13.27 ± 12.43 months, $p = 0.009$) (Figure 4). In the age subgroup analysis, men exhibited significantly lower survival rates than women in patients aged 60 or younger (13.27 ± 5.41 months vs. 19.68 ± 18.76 months, $P < 0.045$). However, no statistically significant difference was observed between males and females aged over 60 ($p = 0.56$). (Figure 5). The Summary of the results is shown in Table 2 and Table 3 .

___Figure 4___

___Figure 5___

___Table 2___

___Table 3___

4 | Discussion

This study aimed to assess the influence of gender and age on the occurrence and survival outcomes of glioblastoma multiforme (GBM). Analyzing a cohort of 164 GBM patients, the average age was 54, with higher prevalence in men (59.8%) and those aged 60 or younger (64.6%). The cohort's mean survival was 12.88 ± 14.14 months, ranging from 0 days to 85 months, with a 45% estimated one-year survival rate. Women exhibited higher one-year survival (60% vs. 40%) and prolonged average survival (16.14 ± 17.35 vs. 10.75 ± 11.15 months). Patients aged 60 or younger had significantly higher one-year survival (75% vs. 35%). Moreover, Subgroup analysis revealed markedly higher survival rates for women aged 60 or younger ($p < 0.045$). Nonetheless, in individuals over 60, women experienced a more pronounced decline in survival rates, and no statistically significant difference was observed between males and females in this age category. ($p = 0.56$). The accelerated decline in survival among older women could be attributed to the potential protective role of gonadal steroid hormones in younger females, particularly estradiol, which significantly decreases during menopause[24].

In line with our findings, prior research has consistently emphasized significant gender disparities in both the occurrence and prognosis of glioma, particularly in the context of glioblastoma[25,26]. Despite multiple investigations on this topic, the biological mechanisms responsible for these gender differences in GBM remain incompletely understood [27,28]. For instance, a study conducted by Sun et al. [29] suggested that this gender gap might be partially attributed to a higher vulnerability to malignant transformation in male astrocytes when both the p53 and NF1 genes lose their normal functions in contrast to female astrocytes. Moreover, in a study by Khan et al. [30], researchers utilized data from The Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) to identify molecular markers that could elucidate gender-based differences. They discovered that specific autosomal genes such as NOX, FRG1BP, and AL354714.2, along with X-linked genes such as PUDP, KDM6A, DDX3X, and SYAP1, displayed varying DNA methylation and gene expression profiles in male and female GBM cases. Furthermore, high expression of estrogen-related receptor alpha (ERRα) is considered a detrimental factor associated with malignant progression and overall prognosis in various cancer types[31–33]. In contrast, Hönikl et al.'s study demonstrated that high expression of estrogen receptor alpha (Erα) and aromatase in 60 GBM tissue samples was associated with longer survival times, and treatment with high concentrations of estradiol resulted in reduced tumor cell viability[34]. Despite contradictory findings on estrogen receptor subtypes as prognostic factors, studies suggest a protective role of estradiol(E2), mainly through estrogen receptor beta (Erβ), with varying effects depending on ERβ isoform quantities[28]. While the estrogen-related pathway has been extensively researched in glioma, it has been challenging to translate this knowledge into practical clinical applications within standard treatment protocols [32].

In 2018, Minjie Tian et al.[35] utilized the Surveillance, Epidemiology, and End-Results (SEER) database to study GBM patients undergoing surgery from 2000 to 2008. Of the 6,586 identified GBM patients, 65.5%

were male, closely aligning with our findings. The study concluded that gender significantly predicts GBM risk. In a 2021 study by Osawa et al.[36], they examined 137 GBM patients, with 22.6% being elderly (over 75 years old). Non-elderly patients had a significantly longer average overall survival (15.8 months) than the elderly group (10.8 months). Similarly, non-elderly patients had a significantly longer average progression-free survival (9.1 months) compared to the elderly group (6.6 months). The study suggested that, for patients aged 75 and older with a Karnofsky Performance Status (KPS) below 70, indicating diminished daily functional capacity, considering less aggressive treatment in addition to radical resection could be a viable therapeutic option. In 2015, Brodbelt et al.[37] analyzed GBM patients' data in England from 2007 to 2011, including 10,743 patients, with 6,451 males and 4,292 females. The average overall survival was 6.1 months, and survival rates at one, two, and five years were 28.4%, 11.5%, and 3.4%, respectively. Survival declined significantly with increasing age, from 16.2 months in the 20-44 age group to 3.2 months in those aged 70 and above. Among patients receiving maximum therapy, those under 70 years had an average survival of 14.9 months. While maximum therapy enhanced overall survival across all age groups, individuals aged over 60 were less inclined to receive complete combination therapy[37]. These age-related differences align with our findings, where 35.4% of GBM patients were over 60, experiencing notably shorter mean overall survival and a lower one-year survival rate compared to their younger counterparts. We performed a bibliometric analysis to highlight the current trends in research related to age and gender within the context of GBM. (Figure 6)

___Figure 6___

Our study has several limitations. The database is restricted to GBM patients in Guilan Province, impacting the generalizability of findings. The low tumor incidence led to limited patient data for several hospitals, underscoring the need for a larger sample size per center to address within-hospital variation. Moreover, the study lacks details regarding the specific types of treatment administered, including the particular chemotherapeutic agents used for each patient. It is possible that these treatment details could have an impact on sex differences in outcomes and survival rates. Further studies utilizing different databases are needed to investigate factors unavailable in our research, such as IDH mutation status, to provide a more comprehensive understanding of sex-based differences in survival and outcomes for gliomas.

5 | Conclusion:

Our study, aligned with the existing literature, emphasizes the ongoing exploration of potential underlying mechanisms of age and gender differences in GBM. Notably, the observed differences in survival rates, especially in the context of hormone-related protective effects, highlight the intricate interaction of biological factors in GBM prognosis.

Declarations

Ethics approval and Consent to participate

This study received approval from the Institutional Review Board at Guilan University of Medical Sciences, with the ethics approval code IR.GUMS.REC.1401.461.

Availability of data and materials

The data used or analyzed to support the findings of this study are available from the corresponding author upon request.

Competing interests

There are no competing interests.

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Authors Contributions

Z.R. and E.A. contributed to this work equally. Z.R. and N.Z conceived the idea and contributed to concept development. E.A. and S.K. wrote the manuscript and were responsible for the design and figures. M.M. collected the data. M.M., H.K., and M.F. were involved in data analysis and interpretation. A.S. provided supervision, overseeing the implementation and writing of the manuscript. All authors participated in drafting the manuscript.

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