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Research Article

Social determinants of health and survival on Brazilian patients with glioblastoma: a retrospective analysis of a large populational database

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ABSTRACT

Background: The majority of patients diagnosed with glioblastoma develop recurrent disease resulting in poor prognoses. The current study aimed to determine the survival rates of patients diagnosed with glioblastoma in Brazil accounting for the influence of age, treatment modalities, public and private practices, and educational level using a population-based national database.

Methods: Patients diagnosed with glioblastoma from 1999-2020 were identified from The Fundação Oncocentro de São Paulo database to create a retrospective cohort. Patients were described according to age, education level treatment modalities and medical practice. In a Cox proportional hazards model, controlled for confounding factors for overall survival, the hazard ratio and 95% CI of overall survival in adults was evaluated.

Findings: A total of 4,511 patients were included. The median lengths of survival for patients treated in the public and private settings were 8 and 17 months ($p<0.001$), respectively. Young patients had longer median overall survival (OS: 18 to 40 years, 41 to 60 years, 61 to 65 years, 66 to 70 years and over than 70 years was 22 months, 10 months, 6 months, 5 months, 4 months, respectively ($p<0.001$). In general, combined treatments were associated with higher median survival compared to monotherapy. The higher educational level, the higher median survival was observed (4 months for illiterate versus 14 months for university degree). In the multivariable analyses, the significant independent predictors for overall survival were practice setting, educational level, age and treatment modalities.

Interpretation: Public practice, older patients, less intensive treatment, and lower educational level were associated with worse survival outcomes in Brazilian glioblastoma patients.

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Research in context

Evidence before this study

The majority of patients diagnosed with glioblastoma develop recurrent disease resulting in poor prognoses. There is limited literature concerning treatment patterns and survival outcomes of glioblastoma patients in low- and middle-income countries. The impact of insurance status and educational level on the survival rates in glioblastoma patients has not been investigated in Brazil.

Added value of this study

The current study is the first to report the survival outcomes in a population-based cohort of patients with glioblastoma in Brazil. Our findings indicate that a public practice setting, a lower educational level, an older age and not undergoing multimodal treatment were independent risk factors of poorer overall survival.

Implications of all the available evidence

We addressed social and health aspects of a large sample of patients diagnosed with glioblastoma. The article brings important data from Brazilian environment and which point to factors whose intervention could potentially improve the diagnosis, treatment and prognosis of patients with this severe disease.

1. Introduction

Glioblastoma is a common primary brain tumor in adults, and it is normally diagnosed in patients aged 55 to 60 years. Combined-modality management is the current standard of care for most glioblastoma patients and is comprised of surgery, post-operative radiotherapy and chemotherapy. Despite this multimodal approach, the median survival for patients diagnosed with glioblastoma is around 15 - 16 months and the 5-year survival rate is less than 5%. [1-3] These figures become exacerbated when patients cannot receive standard treatment due to a lack of clinical conditions or medical access. [4,5]

Several factors are associated with glioblastoma patient prognoses. These include treatment modalities, tumor characteristics (e.g, presence or absence O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase (IDH) type 1 or type 2 mutations), location and extent of the tumor, patients' age, patients' performance status, and socioeconomic factors. [6,7] The influence of insurance status and assess to public and privately funded practices may impact the prognosis of patients with glioblastoma. [8]

Studies have previously investigated this effect,[9-11] however, to the best of our knowledge, there is limited literature concerning treatment patterns and survival outcomes of glioblastoma patients in low- and middle-income countries. The impact of insurance status and educational level on the survival rates in glioblastoma patients has not been investigated in Brazil. Therefore, we performed a large retrospective cohort study to assess the impact of age, treatment modalities, public and private practices, and educational level on the overall survival of glioblastoma patients in Brazil.

2. Methods

2.1. Patients and Methods

The cohort was established from the Fundação Oncocentro de São Paulo (FOSP) http://www.fosp.saude.sp.gov.br) database. FOSP maintains a prospective database of all hospital and oncology departments in Sao Paulo State, Brazil. The database captured patient information including age at diagnosis, gender, medical practice (public or private insured), educational level, and treatment modalities (surgery, radiotherapy, and chemotherapy).

Adult patients (aged $\geq$ 18 years) with pathologically confirmed glioblastoma between January 1999 and April 2020 were eligible for inclusion. Patients' age was categorized into 3 groups: young (18 – 40 years); middle age (41 – 60 years); elderly (> 60 years). As the elderly group definition for GBM patients varies in literature [5], we decided to subdivided them into 3 groups: youngest-old (61-65 years), middle-old (66 – 70 years) and oldest-old (> 70 years). The educational level was also classified into 5 groups: illiterate; uncompleted elementary school; completed elementary school; completed high school; university/college degree. Treatment modality was classified as surgery alone; radiotherapy alone; chemotherapy alone; surgery plus radiation therapy; surgery plus chemotherapy; radiotherapy plus chemotherapy; surgery plus radiotherapy plus chemotherapy; other; no treatment.

The primary outcome was overall survival (OS). OS was defined from the date of diagnosis to the death from any cause.

The article was organised based on The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (https://www.equator-network.org/reporting-guidelines/strobe/).

2.2. Statistical analysis

The background demographic and baseline characteristics were described. Categorical variables are described as percentages and frequencies. The categorical parameters were compared by using the two-sided Person Chi-square or Fisher exact test, as appropriate. The association between demographic and treatment factors and overall survival was evaluated using a Cox Proportional Hazard (PH) regression model while accounting for different lengths of participant follow-up. The proportional-hazards assumption of overall survival was examined by a graphical method using log-minus-log plots. If the curves were not parallel, violation of the proportional-hazards assumption would be assumed. Uni- and multivariable Cox proportional-hazards model were used to estimate hazard ratios with corresponding 95% confidence intervals for OS. The Kaplan-Meier (KM) curves were used to visually display survival curves, and the log-rank test was used to compare the estimated KM curves. For all hypothesis tests, 5% the level of significance was considered. SPSS 23.0 (IBM, Armonk, NY) and RStudio (https:// rstudio.com/; R version 3.6.0, https://www.r-project.org/, packages 'survival' version 3.2-7 and 'forest model' version 0.5.0) were used for statistical analyses.

Role of the funding source: There was no funding for this work.

3. Results

3.1. Patient characteristics

A total of 4,511 patients with glioblastoma were included in our cohort. Most of the patients were male (n = 2,645; 58.9%) and were between the ages of 41-60 (n=1,932 (42.8%). The majority of patients were publicly insured (n=2,075, 46%), and did not complete elementary school (n=1,281, 28.4%). 3,089 (68.4%) patients received a surgical procedure with or without post-operative treatment. Surgery, radiotherapy, and chemotherapy were performed in 1,053 (23,3%) patients. (Table 1). The treatment modalities and age according to the public and private setting were presented in Supplementary table 1. The treatment modalities according to the periods 1999 – 2005, 2005 –2014, and 2014 – 2020 were showed in Supplementary table 2.

Table 1
Characteristics of included patients.

Characteristic	Patients (N = 4511)	%
Age (years)		
18 - 40	592	13.1
41 - 60	1,932	42.8
61 - 65	692	15.3
66 - 70	541	12.0
> 70	754	16.7
Gender		
Male	2,645	58.6
Female	1,866	41.4
Medical practice		
Public insured	2,075	46.0
Private insured	313	6.9
Missing	2,123	47.1
Treatment site		
Sao Paulo capital	1,296	28.7
Other cities	3,215	71.3
Education		
Illiterate	177	3.9
Did not complete elementary school	1,281	28.4
Completed elementary school	763	16.9
Completed high school	627	13.9
University degree	380	8.4
Missing	1,283	28.4
Treatment type		
Surgery alone	1,226	27.2
Radiation therapy alone	349	7.7
Chemotherapy alone	46	1.0
Surgery + radiation therapy	689	15.3
Surgery + chemotherapy	121	2.7
Radiation therapy + chemotherapy	282	6.3
Surgery + radiation therapy + chemotherapy	1,053	23.3
Other	314	7.0
No treatment	431	9.6

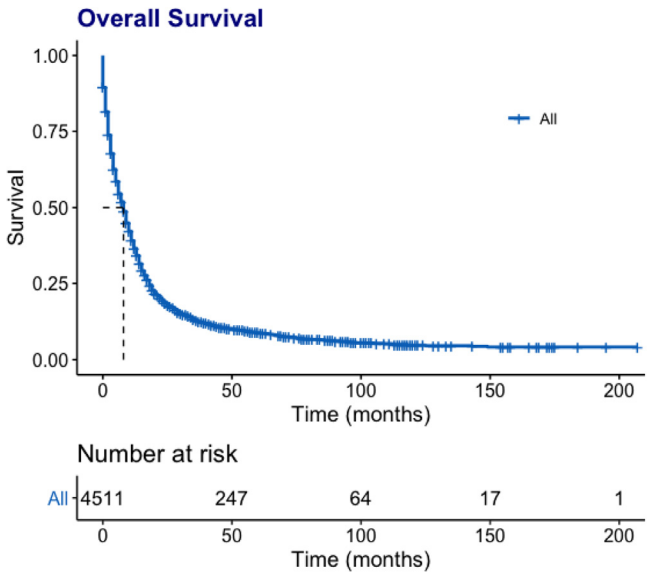

Figure 1. Overall survivalfor allpatients.

3.2. Overall Survival

The median survival for the whole cohort was 8 months (95% CI 7.56 – 8.44) - Figure 1. Median survival in different periods 1999 – 2005, 2006 – 2014, and 2015 – 2020 was demonstrated in Supplementary figure 1. When compared to the oldest period with the most recent periods, an increase in survival was observed (1999 – 2005 versus 2006 – 2014: HR 0.85 95%CI 0.78 - 0.92; 1999 – 2005 versus 2015 – 2020: HR 0.825 95% CI 0.75 - 0.90).

The median length of survival for patients treated in the public and private settings were 8 (95%CI 7.3 – 8.7) and 17 (95%CI 15.2 – 18.8) months ($p<0.001$), respectively. Regarding age at diagnosis, the median survival (and its 95% confidence interval) for patients with 18 to 40 years, 41 to 60 years, 61 to 65 years, 66 to 70 years, and more than 70 years was 22 (18.3 – 25.7) months, 10 (9.3 – 10.7) months, 6 (5.2 – 6.8) months, 5 (4.2 – 5.8) months, 4 (3.5 – 4.5) months, respectively (Figure 2). In general, combined treatments were associated with higher median survival compared to monotherapy. In patients that did not receive treatment, the median length of survival was 1 month. A higher educational level was associated with higher median survival (4 [2.6 – 5.2] months for illiterate; 6 [5.2 – 6.8] months for incomplete elementary school; 8 [6.9 – 9.0] months for complete elementary school; 12 [10.5 – 13.5] months for high school; 14 [11.9 – 16.1] months for a university degree), shown in Figure 3.

Considering practice and chemotherapeutic options have changed over the 20 years of the study, we conducted separate Cox models for each of the 3 periods presented in Supplementary table 3 and found no significant differences. In the multivariable analyses, the significant independent predictors for OS were practice setting, educational level, age, and combined treatment modalities (Figure 4).

4. Discussion

The inherent aggressiveness of glioblastoma as well as its resistance to the currently available treatments provides challenges to the management of this primary brain tumor. Despite employing a multimodal approach, most patients with glioblastoma develop recurrent and progressive disease, with a very poor prognosis. [3]

To our knowledge, the current study is the first to report the survival outcomes in a population-based cohort of patients with glioblastoma in Brazil and Latin America. Our findings indicate that a public practice setting, a lower educational level, an older age, and not undergoing multimodal treatment were independent risk factors of poorer OS.

In general, patients with lower socioeconomic status have higher mortality rates compared to those with higher socioeconomic status. Indeed, patients on low incomes may have fewer choices in terms of goods and services, as well as less access to oncology centers or affordability of treatments/drugs. Other factors including unemployment and poverty may also influence the quality of medical assistance of this group of patients. [12-15] Previous authors have reported that insurance status was independently related to presenting cancer stage and death from cancer, but they did not compare insurance status with survival outcomes, or in a population of glioblastoma patients. [12,16,17]

A study from the USA investigated the association between the type of medical care insurance and overall survival in a cohort of 13,665 glioblastoma patients from the Surveillance, Epidemiology, and End Results (SEER) database. They found that uninsured status and Medicaid insurance had shorter overall survival compared with non-Medicaid insurance.[9] Although there are differences between the Brazilian and American health systems, the type of medical insurance might influence survival results in the Brazilian perspective similar to the USA. Currently, the Brazilian health system can be divided into public and private sectors. In the public sector, insurance is provided by the state to all Brazilian citizens (municipal, state, and federal levels). The private sector is comprised of the private health insurance area, with various schemes of health plans or with out-of-pocket expenses. [18] The public sector is organized under the Unified Health System, which aims to offer universal health coverage in Brazil. However, due to ongoing economic and political crises and health system weakness, there are enormous regional differences in access to healthcare facilities and

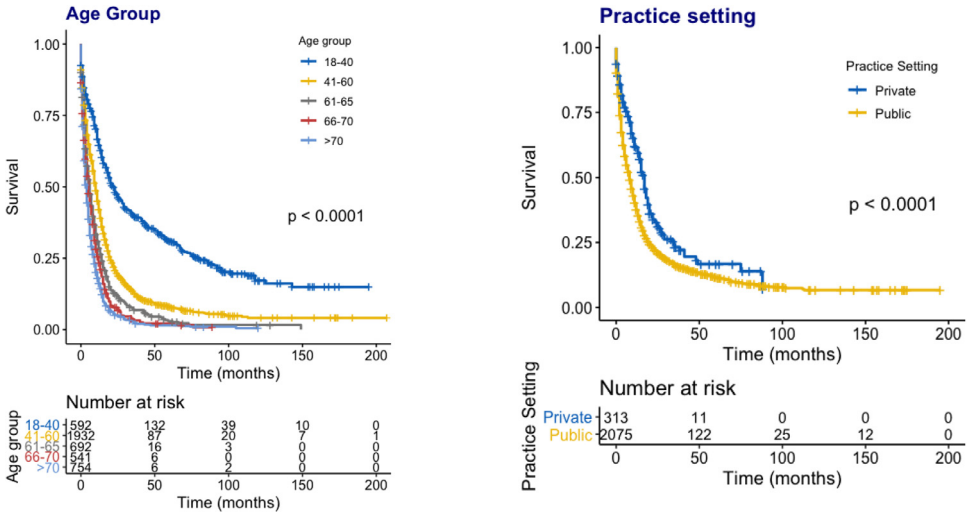

Figure 2. Overall survivalaccordingtoage andpracticesetting.

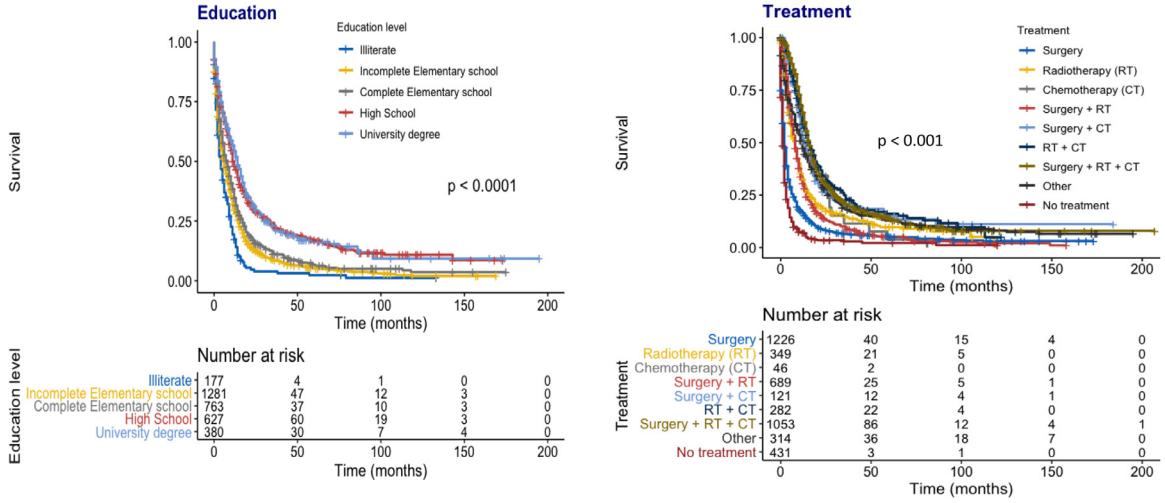

Figure 3. Overall survivalaccordingtoeducationallevelandtreatmentmodality.

Variable		Hazard ratio	p
Practice	Private	Reference	
	Public	1.73 (1.39, 2.16)	<0.001
Education	Low	Reference	
	Medium/High	0.84 (0.75, 0.94)	0.003
Age	18-40	Reference	
	41-60	2.21 (1.82, 2.68)	<0.001
	61-65	3.30 (2.62, 4.15)	<0.001
	66-70	3.79 (2.99, 4.80)	<0.001
	>70	4.19 (3.34, 5.26)	<0.001
Treatment	No treatment	Reference	
	Surgery	0.73 (0.59, 0.90)	0.003
	Radiotherapy (RT)	0.30 (0.23, 0.40)	<0.001
	Chemotherapy (CT)	0.24 (0.14, 0.43)	<0.001
	Surgery + RT	0.30 (0.24, 0.37)	<0.001
	Surgery + CT	0.23 (0.15, 0.36)	<0.001
	RT + CT	0.23 (0.17, 0.31)	<0.001
	Surgery + RT + CT	0.19 (0.15, 0.23)	<0.001
	Other	0.34 (0.26, 0.45)	<0.001

Figure 4. Multivariateanalyzedfor overall survivaladjustedbypracticesetting, educationallevel, age, andtreatmentmodality
Note: Loweducation= includes illiterateandincompleteelementaryschool; medium/high education= includes complete elementaryschoolorhigherdegrees.

health quality. People with lower socioeconomic status and those who come from poorer regions face higher disadvantages and are often provided with inadequate medical care. [19]

Our data demonstrated that despite similar treatment profiles, patients treated in the private sector had a longer length of survival when compared to the public sector. Unexpectedly, there was a higher proportion of younger patients in the public sector. Although younger patients achieved better survival in this cohort, patients treated in the public sector had lower survival.

Lower education level was also associated with inferior survival outcomes. These findings highlighted the real-life influence of lower socioeconomic status on mortality rates in patients with glioblastoma in Brazil. Our results are consistent with a statement by Chandra et al which also suggested that insurance coverage is advantageous for the prognosis of glioblastoma patients. [10] Furthermore, our results are also consistent with previous studies, which found that oncologic patients with higher educational levels tend to have better overall survival. [8,20] It is believed that patients with higher educational levels and likely higher socioeconomic status may have easier and faster access to health care services. This in turn leads to less advanced disease at diagnosis, and subsequently earlier treatment.

It is commonly recognized that age can affect OS in patients with glioblastoma, as was observed in our study.[5] Elderly patients with glioblastoma often do not receive the standard treatment. At baseline, older patients have a lower life expectancy, are often poor candidates for surgery because of a lower ECOG performance status due to additional comorbidities. Consequently, a propensity for shortened treatments is observed. This is a stark contrast to younger patients who frequently undergo longer and more aggressive treatment. [4,5] Our study also found that older patients with glioblastoma present worse survival rates in Brazil.

The treatment modality is also another point to be discussed. The Scotland data found that median OS was improved after adopting the Stupp protocol from 10.7 to 15.3 months. The additional survival benefit was observed with the extent of surgical resection, patients' age, and postoperative treatment. [21] Our study confirmed that combined treatments were associated with a higher median survival compared to a less aggressive approach. The exception was observed for patients who received exclusively chemotherapy. These patients have similar survival rates to patients who received trimodal treatment (surgery, radiotherapy, and chemotherapy). However, we believe this should be interpreted cautiously since only a very small number of patients underwent chemotherapy alone in our study. Of note, an increase in survival was also observed after 2005, probably due to treatment guideline changes resulting in the more frequent use of chemotherapy.

The standard management for glioblastoma patients consists of surgery followed by postoperative chemoradiotherapy and subsequent chemotherapy. We theorize that people with less access to medical care may have a lower probability of receiving full trimodally treatment leading to poorer outcomes. Hence, we suggest that differences in survival outcomes are likely less related to socioeconomic status, and more likely due to a lack of access to quality health care. [11,22]

One key aspect that is lacking in our article (due to the absence of information in the FOSP database) is that survival is described only as overall survival and not glioblastoma-related mortality and non-glioblastoma-related mortality. This aspect should have been described to understand how the social determinants contribute to glioblastoma-related mortality specifically and not just all-cause mortality. This point is explored in Liu et al that showed socioeconomic factors and racial issues impact glioblastoma-specific and non-glioblastoma-associated mortality based on the National Cancer Institute's SEER database for US patients.[23] It is important to highlight that still nothing has been published in Brazil or any other Latin American country in this context.

Our study has other limitations. As a retrospective population database analysis, several bias can occur. These limitations include limited availability of patient data that could influence prognoses such as type of surgery (gross resection versus partial resection), radiotherapy dose schedule, difficulties to patient reaching multidisciplinary approach, type of systemic therapy, tumor prognostic factors (MGMT, IDH status), performance status score and second line of treatments after tumor recurrence. Moreover, medical practice and educational level information was not available for some patients and were therefore excluded from the multivariable analysis. Finally, the FOSP database considers patients from Sao Paulo State only, limiting the generalizability of our findings to the rest of the country. However, this is likely to be of limited consequence, as Sao Paulo is the most populated state in Brazil with a fairly representative population. Despite the stated limitations, we showed an interesting association among patient age, treatment modalities, receiving care in public and private practices and educational level, and the survival in a large population in Brazil.

In conclusion, receiving care in public practice, older patients, less aggressive treatment, and lower educational level were associated with worse survival outcomes in a cohort of Brazilian glioblastoma patients.

Contributors

All authors above contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Data sharing statement

The patients' data can be assessed: http://www.fosp.saude.sp.gov.br.

Declaration of interests

The authors have declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lana.2021.100066.

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