

Revisiting the Relationship Between Ethnicity and Outcome in Glioblastoma Patients

Ashish H. Shah¹, Eric Barbarite², Christopher Scoma², Manish Kuchakulla², Sahil Parikh², Amade Bregy², Ricardo J. Komotar¹

1. Neurological Surgery, University of Miami Miller School of Medicine, Miami, USA 2. Department of Neurological Surgery, University of Miami Miller School of Medicine

✉ **Corresponding author:** Eric Barbarite, e.barbarite@med.miami.edu

Disclosures can be found in Additional Information at the end of the article

Abstract

Background: Relationships between various ethnicities and glioma subtype have recently been established. As a tertiary referral center for Latin America and the Caribbean, our institution treats a diverse glioblastoma (GBM) population. We sought to clarify the role of ethnicity on patient prognosis in GBM and also compared these findings to a group consisting of elderly patients. We included 'elderly' as a group because the subgroups for ethnicities within them were too small. It allowed us to put in scope the effects of ethnicities on the overall survival.

Material and Methods: After Institutional Review Board approval, 235 patients with GBM were retrospectively identified. A total of 140 patients were separated into four groups: White adults (n = 47), Hispanic adults (n = 27), elderly (n = 58), and Black adults (n = 6). Overall survival (OS) was our primary endpoint.

Results: Overall survival in the White adult group was 24.3 months, compared to 13.0 months in the Hispanic adult group, 20.2 months in the Black group, and 13.8 months in the elderly group (p = 0.01). In the Hispanic group, hypertension (37.9%, p = 0.01) and diabetes (24.1%, p = 0.009) were significantly more prevalent compared to the White adult cohort. No difference in insurance status or postoperative complications was found between subgroups.

Conclusion: Based on our analysis, Hispanic adults may have a decreased survival compared to White adults. However, the incidence of hypertension and diabetes was markedly higher in our Hispanic adult cohort; thus, estimating the risk of ethnicity and comorbidities on patient prognosis may be difficult. A prospective study correlating the genome and subgroup prognosis may help elucidate the role of ethnicity in GBM patients.

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Introduction

Over the last decade, therapy for glioblastoma multiforme (GBM) has been centered on maximal safe surgical resection with combination radiotherapy and adjuvant temozolomide chemotherapy [1]. Despite optimal treatment, the overall five-year survival still remains poor with an average survival of 14 months after diagnosis [1-3]. Specific subsets of patients with unfavorable prognoses, including the elderly, the uninsured, and patients with low preoperative

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Karnofsky performance scores, have been identified [4-18]. Previously, it had been proposed that ethnicity did not influence prognosis in patients with GBM [3]. However, with the development of microRNA and mutational analyses, relationships between ethnicity and glioma subtype incidence have been identified so far in African-Americans, Whites, and East Asians [19-21]. Nevertheless, a correlation between ethnicity and prognosis in patients with GBM has yet to be identified [22].

As a tertiary referral center for South Florida, the Caribbean, and Latin America, our institution treats a diverse patient population, including numerous Hispanics. As a result, we sought to clarify the relationship between ethnicity and outcome in GBM patients at our institution.

Materials And Methods

The University of Miami Miller School of Medicine Institutional Review Board (IRB# 20110821) approved this study prior to retrospective review of patient data. From 1995-2006, 235 patients with intracranial glioblastoma were identified from an electronic billing database at a single tertiary care referral center. In all cases, a neuropathologist confirmed the diagnosis of glioblastoma using standard diagnostic classification systems (World Health Organization (WHO) Classification System) [23]. All patients were initially screened by age (> 18 years), location (intracranial), and pathology (WHO Grade IV glioma). Patients with multicentric/multifocal GBM were included in the study. For all patients included, an attempt to safely maximize the extent of resection was made when possible. Patients without adequate follow-up/outcome data, operative reports, or hospitalization information were excluded. If follow-up was inadequate (< 6 weeks), patients were excluded.

Patients who did not identify ethnicity/race on clinical documentation were excluded. No attempt was made to assume ethnic or racial data based on the last name.

Relevant variables were obtained, which included sex, age at diagnosis, tumor size (when available), tumor location, the extent of resection, use of adjuvant therapies including chemotherapy/radiotherapy, and follow-up. The extent of resection was determined by either postoperative imaging or by the surgeon's description in the operative report. Comorbid conditions, including heart disease, diabetes, smoking, hyperlipidemia, and hypertension, were also recorded for each patient when available. Time to recurrence was unable to be assessed in many patients due to lack of imaging data prior to electronic medical records. For patients with adequate follow-up in the clinic, progression-free survival (PFS) was analyzed. Death date was determined primarily by the Social Security database (search.ancestry.com/search/db.aspx?dbid=3693). For select patients, in-hospital death information was obtained directly from electronic medical records. Survival was defined as the time from initial diagnosis to death. Overall survival (OS) was defined as the point in which 50% of patients remained alive after initial diagnosis.

Patients were analyzed separately into three groups: White, Hispanic, and Black (as designated by patient). Once separated, additional subgroups were identified: White adults, Hispanic adults, Black adults, and elderly. We included 'elderly' as a group because the subgroups for ethnicities within them were too small. It allowed us to put in scope the effects of ethnicities on the overall survival. All relevant clinical data for each subgroup were collected and analyzed for trends.

Statistical analysis

Univariate t-tests were used to characterize ethnic subgroups to assess for significant discrepancies in age, incidence of comorbidities, the extent of resection, and use of adjuvant therapy in sizeable sample groups ($n > 10$). In addition, t-test analysis was performed to

analyze the difference in OS and PFS in the various subgroups. P-value < 0.05 was considered statistically significant. SOFA statistics software was used for all statistical analysis (version 1.3.5, AGPL3 license, Paton-Simpson & Associates Ltd, New Zealand).

Results

A total of 140 patients were retrospectively reviewed in our study. Ninety-five patients were excluded due to WHO Grade I-III (n = 79) or inadequate follow-up (n = 16). Included patients were split into four groups (White adults, Hispanic adults, Black adults, and elderly). The identification of patients with GBM and exclusion criteria is described in Figure 1. The White adult category was designated as the control group in our study to compare prognostic variables. In the White adult category (n = 47), the mean age was 50 years. Overall, there was no statistical difference in mean age between the different patient groups (p > 0.05). In the control group, the tumor locations (frontal, parietal, occipital, temporal, etc.) were recorded, which are reported in Table 1, and no statistical difference in tumor location was found between the ethnic groups (p > 0.05). Presenting symptoms within the control group ranged from altered mental status (42.5%), headache (55.3%), motor deficit (23.4%), seizure (29.7%), visual impairment (12.75%), or uncontrolled nausea/vomiting (10.6%). A summary of presenting symptoms between ethnic groups is summarized in Table 1. Tumor size was not recorded in this study.

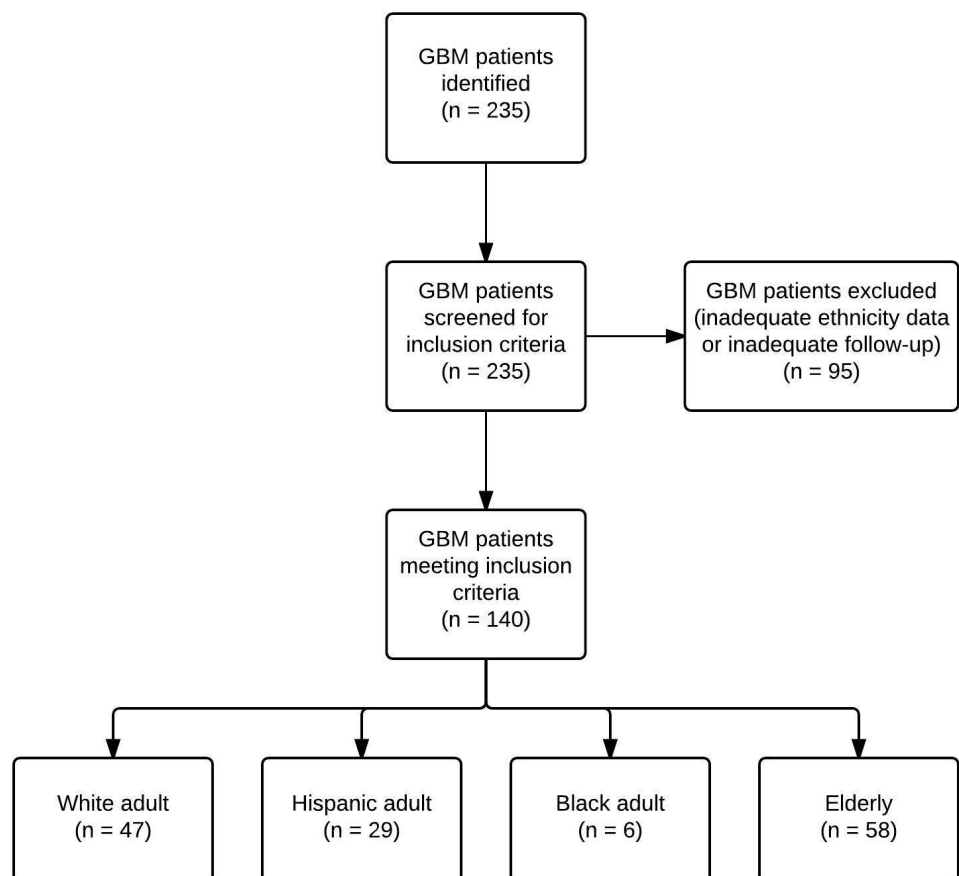


FIGURE 1: Patient Selection Flow Chart

	White Adults (n = 47)	Hispanic Adults (n = 29)	Black Adults (n = 6)	Elderly (n = 58)	P-value*
Average Age, Yrs (n)	50.02	53.586	48.33	74.86	.161
GBM Location					.169
Frontal	22.81%	34.29%	14.29%	35.82%	--
Parietal	17.54%	14.29%	42.86%	19.4%	--
Occipital	8.77%	8.57%	14.29%	10.45%	--
Temporal	35.09%	34.29%	34.29%	29.85%	--
Thalamic	1.75%	2.86%	0%	0%	--
Other	14.04%	5.71%	0%	4.48%	--
Presenting Symptom					
Altered mental status	42.5%	51.7%	50%	55.1%	0.0573
Headache	55.3%	48.2%	66.6%	25.8%	0.573
Hemiparesis	23.4%	41.3%	33.3%	37.9%	0.203
Seizure	29.7%	20.6%	50%	18.9%	0.474
Visual impairment	12.7%	20.6%	0%	13.7%	0.496
Vomiting/Nausea	10.6%	24.1%	50%	3.4%	0.227

TABLE 1: Patient Demographics

P-value performed as a measure of statistical variance between White adults and Hispanic adults only. Chi-squared test was performed to obtain p-values.

Comorbidities

Various common comorbidities were assessed in each ethnic group, including coronary artery disease, hyperlipidemia, smoking history, hypertension, diabetes mellitus (both insulin-dependent and non-insulin dependent), and human immunodeficiency virus (HIV) infection. In the control group, smoking and hypertension were the most common comorbid conditions (21.2% and 12.7%, respectively). In the Hispanic adult cohort, hypertension (37.9%, $p = 0.01$) and diabetes (24.1%, $p = 0.009$) were significantly more prevalent compared to the White adult cohort. A summary of relevant comorbidities for each patient cohort is reported in Table 2. No other statistically significant difference was found for other comorbidities.

	White Adults (n = 47)	Hispanic Adults (n = 29)	Black Adults (n = 6)	Elderly (n = 58)	P-value*
Comorbidities					
Coronary artery disease	2.1%	0%	0%	13.7%	0.429
Hyperlipidemia	4.2%	6.8%	0%	15.5%	0.616
History of Smoking	21.2%	6.8%	16.6%	24.1%	0.771
Hypertension	12.7%	24.1%	16.6%	48.2%	0.011
Diabetes Mellitus	4.2%	24.1%	33.3%	25.8%	0.009
HIV	2.1%	0%	0%	0%	0.429

TABLE 2: Patient Comorbidities

P-value performed as a measure of statistical variance between White Adults and Hispanic Adults only. Chi-squared test was performed to obtain p-values.

Operative complications

All patients in our study were followed-up at least six weeks after surgery until death.

Postoperative morbidity was reported for each ethnic group in Table 3. Common complications included aphasia, altered mental status, motor deficit, infection, stroke, and gastrointestinal symptoms, such as nausea/vomiting. The most common postoperative complication within all patient groups was motor deficits. No statistical significance was found between patient groups.

Postop Complication	White Adults (n = 47)	Hispanic Adults (n = 29)	Black Adults (n = 6)	Elderly (n = 58)
Aphasia	0%	3.4%	0%	1.7%
Confusion	2.1%	3.4%	0%	5.2%
Motor deficit	6.3%	6.8%	0%	1.7%
Infection	0%	3.4%	0%	0%
Stroke	2.1%	0%	0%	0%
Gastrointestinal	2.1%	0%	0%	3.5%

TABLE 3: Postoperative Complications

Outcomes

Overall survival for each ethnic group was reported in Table 4. For the White adult group, overall survival after diagnosis was 24.3 months. Overall survival within our Hispanic adult cohort was significantly decreased compared to the White adult group (OS = 13.0, $p = 0.01$). The elderly patient cohort had a similar overall survival of 13.8 months. Kaplan-Meier curves for OS and progression-free survival (PFS) are reported in Figures 2-3, respectively. The Hispanic adult group had an overall lower OS and PFS compared to the White adult group. Given the exclusion criteria for follow-up in our retrospective analysis (less than six weeks), only six patients were ultimately included in the Black patient cohort. While the demographic, comorbidity, and postoperative complication data of the Black patient cohort are represented in Tables 1-3, only a fraction of these patients had sufficient data to determine overall survival. As a result, the power of our statistical analysis based on such a small number was low, and overall survival of the Black patient cohort was ultimately not calculated.

	White Adults (n = 47)	Hispanic Adults (n = 29)	Black Adults (n = 6)	Elderly (n = 58)	P-value
Overall Survival	24.3	13.0	20.2	13.8	0.01

TABLE 4: Patient Overall Survival

Overall survival is expressed here in months. P-value performed as a measure of statistical variance between White Adults and Hispanic Adults only. Independent t-test was performed for patient groups against OS.

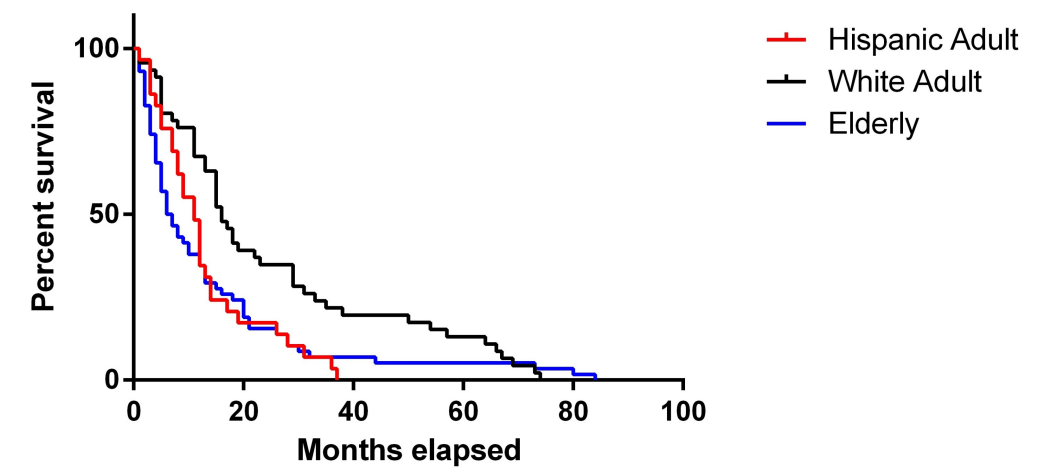


FIGURE 2: Overall Survival Kaplan-Meier Curve

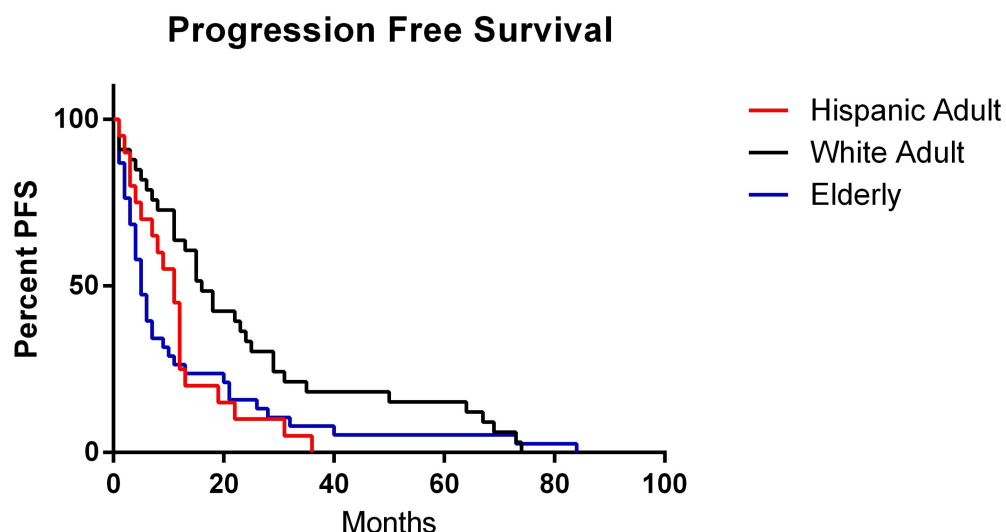


FIGURE 3: Progression-Free Survival Kaplan-Meier Curve

Insurance status

Patients in our study possessed private insurance, Medicaid, Medicare, or received health care using a local public provider. There was no statistical difference in patients who possessed private insurance or public/low-cost insurance providers (Medicaid, local public provider) between all ethnic cohorts in our study.

Discussion

Patients with GBM have a median overall survival of approximately 14 months after surgical resection and concomitant radiochemotherapy [1]. Despite this dismal survival rate, certain prognostic factors have been associated with improved OS in select patient populations. Although many clinical studies compare factors determined postoperatively (extent of resection, chemotherapy, radiotherapy, or MGMT (O-6-methylguanine-DNA methyltransferase) status), few studies have isolated prognosticators in patient demographics, such as ethnicity, gender, and the presence of comorbidities. Published data on preoperative negative prognosticators exists for the elderly GBM patients or patients with large butterfly GBMs [9, 12-13, 24-29]. Nevertheless, data suggesting a relationship between race/ethnicity and prognosis in GBM patients is scarce. For example, select studies in homogeneous single-country ethnic groups (China) have failed to demonstrate significant survival differences from reported literature [3]. Yet, other studies suggest that non-Latino whites are at an increased risk of developing GBM [30]. Although a survival disadvantage has not been linked to specific race/ethnicity as of yet, further research in ethnically diverse centers may reveal the prognostic significance of ethnicity in highly malignant GBM. As a tertiary care center located in one of the most diverse areas in the United States, the University of Miami Miller School of Medicine was poised to adequately assess this.

Survival

In this study of 140 patients with confirmed WHO Grade IV glioblastoma, overall survival was 9.3 months less within our Hispanic adult group (ages: 18 - 65) compared to a cohort of White adults (ages: 18 - 65). The difference in OS between the White adult and Hispanic adult groups was statistically significant ($p = 0.01$). There were no significant differences in postoperative

complications, insurance status, location, or presenting symptoms between the ethnic cohorts. All patients in our study were given similar treatments (surgery + adjuvant radiation + concomitant chemotherapy), and no differences in treatment options were discovered. However, in multivariate analysis, hypertension and diabetes were more prevalent in the Hispanic adult patient group compared to other groups.

Comorbidities

In our diverse patient population, the incidence of diabetes, coronary artery disease risk factors, and hypertension may be elevated in certain minority populations [31-32]. The reasons for such health discrepancies may be multifactorial: socioeconomic status, access to care, dietary differences, cultural resistance to allopathic medicine, and genetic predisposition [33-36]. Previously, it has been shown that the presence of comorbidities in the elderly GBM population may influence the treatment effect and, ultimately, OS [9, 37]. However, a relationship between OS and presence of comorbidities in the general adult GBM population has not been clear. In our study, the presence of more comorbidities in the Hispanic adult group may confound our primary outcomes; nevertheless, such data may give us insight on yet another preoperative risk factor within select patient populations. Due to the nature of our study and the confounding factors, an explanation for a survival disadvantage within Hispanic adults could not be found.

Limiting factors

Our study was performed as a retrospective review of select patients treated at our institution over the last 10 years for whom full data sets were available. Although we were able to isolate data from well over 140 patients with histologically confirmed GBM, several patients were not included in our study due to lack of follow-up, an incomplete search strategy, and an absence of identifiable information. The latter may explain the paucity of Black adults (n = 6) in our study. After accounting for these limitations, our patient population was nevertheless adequate for statistical analysis.

Secondly, because our study was conducted as a retrospective review, the true attributable death risk of Hispanic adults with GBM could not be calculated. Additionally, the presence of insurance status remains another potential confounding factor that may influence outcomes in patients with GBM. Previously, it has been demonstrated that healthcare status affects outcomes in patients with brain tumors [38-39]. However, in our study, no clear difference in insurance status was found, which may, largely in part, be due to the presence of a public healthcare provider (Jackson Memorial Hospital), the largest public county hospital in the United States. Within this system, patients without insurance can obtain surgery, radiation, and chemotherapy for GBM. Furthermore, in our study, we were unable to obtain income or other socioeconomic data points from our study group. Therefore, a thorough analysis of other socioeconomic risk factors may be obscured.

Lastly, we recognize an important factor in any discussion on diverse ethnic groups, such as Hispanics, since the Hispanic subset of patients in Miami can be largely variable across every socioeconomic group and nationality. Therefore, comparing socioeconomic classes in a subset of specific Hispanics may be important in teasing out the true prognostic differences among our patient group. In our county hospital, the majority of patients arrive from lower socioeconomic groups; yet, because we remain a tertiary referral center, a significant portion of our patients is private as well. Further epidemiological research in a broader study may be helpful to understand the role of socioeconomic class or ethnicity on GBM prognosis.

Future studies

In order to effectively assess healthcare disparities among the Hispanic adult GBM population, we have begun prospectively enrolling patients into a clinical database that will allow for outcome analyses of select ethnic groups. Using this IRB-approved database, complete patient information, including insurance status, self-reported ethnicity, and postoperative complications, can be directly obtained without the inherent biases of retrospective studies. Additionally, by collecting histological specimens simultaneously, genomic profiles of various ethnic subpopulations could be correlated to patient prognosis.

Conclusions

Based on our retrospective analysis of 140 GBM patients, Hispanic adults (age: 18 - 65 years) may have a decreased survival compared to age-matched controls. However, in this Hispanic adult cohort, the incidence of hypertension and diabetes was markedly higher than other groups; therefore, estimating the risk of ethnicity/comorbidities on patient prognosis might be difficult. This remains one of the first studies in adults to show survival differences in certain ethnic subpopulations for GBM. At present, conclusive evidence on the survival disadvantage of Hispanic adults is not present, and further prospective studies are needed to fully assess the socioeconomic risk factors, comorbidities, and genetic predisposition in certain ethnic subgroups for GBM. Although our study does not definitively verify ethnicity as a negative prognosticator, it suggests the heterogeneous nature of GBM and the need for subpopulation-specific research studies.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. University of Miami Miller School of Medicine Institutional Review Board issued approval IRB# 20110821. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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