

Socioeconomic status does not affect prognosis in patients with glioblastoma multiforme

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Abstract

Background: Glioblastoma multiforme (GBM) is an aggressive malignancy, but there is marked heterogeneity in survival time. Health care disparities have demonstrated significance in oncologic outcomes but have not been clearly examined in this patient population. We investigated the role of sociodemographic variables in the prognosis of adult patients diagnosed with GBM.

Methods: This retrospective analysis included patients with a histologically confirmed diagnosis of GBM, who underwent resection or biopsy at a single institution from 2000 to 2014. Socioeconomic status (SES) was determined by household income according to the US Census zip code tabulation areas and the US national poverty level. Multivariate Cox proportional hazards analysis calculated effects on patient survival.

Results: Thirty percent of 218 subjects were of low SES, 57% mid, and 13% high. Low SES patients tended to be male (62%), Caucasian (92%), unmarried (91%), have dependents (100%), and limited to high school education (55%). SES did not predict insurance or employment status. SES was associated with marital status and number of cohabitants ($P < 0.0001$) but not clinical trial enrollment. Multivariate analysis demonstrated no relationship between SES and survival. Shorter prognosis was associated with history of military service (hazard ratio [HR] 2.06, $P = 0.0125$), elderly patients (HR 1.70, $P = 0.0158$), and multifocal disease (HR 1.75, $P = 0.0119$). Longer prognosis was associated with gross total resection (HR 0.49, $P = 0.0009$), radiation therapy (HR 0.12, $P < 0.0001$), and temozolomide (HR 0.28, $P < 0.0001$).

Conclusions: SES alone does not predict prognosis in patients with newly diagnosed GBM. Sociodemographic variables such as old age, military service record, and insurance type may have a prognostication role.

Key Words: Brain tumor, glioblastoma multiforme, glioma, poverty, prognosis, socioeconomic status

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INTRODUCTION

Gliomas are the most common type of primary brain tumor.^[21] These tumors progress rapidly with a nearly uniformly fatal outcome. Patients frequently have late stage disease at the time of presentation, often Grade IV astrocytoma otherwise termed glioblastoma multiforme (GBM). A few advancements have significantly extended glioblastoma patient survival time in recent years since the breakthrough randomized clinical trial by Stupp *et al.* in 2005. The Stupp study demonstrated 21% increase in median survival time, extending the median overall survival from 12.1 to 14.6 months in patients treated with temozolomide (TMZ) in addition to concomitant radiation therapy (XRT).^[51] Although 14.6 months median survival time provides a strong, evidence-based approximation, there is a wide range of survival times indicative of heterogeneity in the population.^[33] A long-standing question persists regarding the factors that distinguish the short-term from the long-term survivors.

Socioeconomic status (SES) has been previously suggested to affect outcomes in a variety of malignancies.^[4,10,36,45] The prognostic role of SES in glioblastoma patients has been investigated in settings outside of the United States.^[22,23] Many variables have been inconsistently used as a proxy for SES, including zip code, census tracts, Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD), income, and occupation. A major difficulty of socioeconomic research lies in a universal statistical representation of a patient's social position and economic resources.^[8]

The zip code has been frequently used in US-based public health research as a proxy for SES.^[19,40] This was not its original intended use, which was for mail delivery by the US Postal Service.^[28,56] It was not originally meant to accurately depict the living situation and economic status of its residents. Zip code tabulation areas (ZCTAs) were created in 2000 by the US Census Bureau to be smaller, more homogeneous representations of population land areas.^[26] US Census household income statistics are calculated according to ZCTA. Thus, this variable was selected for the purposes of our study as it would provide a means to uniformly analyze patient income.

Using ZCTAs and government-sanctioned national poverty levels, we sought to assess the role of SES and other demographic variables in the prognosis of adult patients diagnosed with GBM.

METHODS

We retrospectively analyzed patients with a histologically confirmed diagnosis of GBM, who underwent resection or biopsy at Vanderbilt University Medical Center from 2000 to 2014. Children and incarcerated patients were

excluded from the study. Two hundred eighteen subjects were included. After approval from the Vanderbilt Institutional Review Board, data were extracted from electronic medical records and cataloged in the Research Electronic Data Capture database.^[25] Specific variables of interest included poverty level, military history, employment, insurance, living situation, education level, race, sex, age, coexisting diagnosis of diabetes mellitus (DM), Karnofsky performance status (KPS), extent of resection, tumor staging at the time of diagnosis, treatment received, and clinical trial enrollment.

To improve internal validity, zip codes were transformed into ZCTA codes in accordance with the 2012 United States Census.^[60] ZCTA-associated household income and the 2012 US Department of Health and Human Services National Poverty Guideline adjusted for the number of occupants were used to represent SES.^[1] Duration of disease was measured from the time of histologic diagnosis to date of death.

All data were de-identified before statistical analysis in Microsoft Excel (Microsoft, Redmond, Washington)^[35] and JMP Pro (SAS Institute Inc. Cary, NC).^[43] Univariate Cox proportional hazard analysis assessed the isolated role of each categorical variable upon the continuous variable, disease duration. A conservative approach was taken and variables with whole model $P < 0.10$ were included in Cox proportional hazards multivariate analysis to control for confounding factors. Statistically insignificant variables were then removed from the multivariate analysis in a stepwise fashion until only significant variables remained ($P < 0.05$). Kaplan–Meier survival curves were used to depict median survival times for the statistically significant multivariate data. All statistical analyses were censored for living study subjects.

RESULTS

The 218 study subjects were stratified according to their income-based socioeconomic profile [Table 1]. Patient income was designated by the average for their ZCTA of residence and compared to the national poverty level for their household size. Income was divided into tertiles: Low, mid, and high. Low SES was designated by a subject grossing $<250\%$ annual income above the associated national poverty level for their ZCTA. Mid and high SES were classified by $250\text{--}500\%$ and $\geq 500\%$ above the national poverty level, respectively. Twenty-two patients (10%) were still alive at the time of statistical analysis.

SES predicted marital status ($P = 0.0003$), number of cohabitants ($P < 0.0001$), and level of education attained ($P = 0.0485$). Our institution makes a concentrated effort to provide healthcare to the underserved, and most patients in this study were of low SES (47%). There was no statistical difference in race, age, or sex across SES. Low

Table 1: Sociodemographic profile of study patients at the time of presentation

	Income-based socioeconomic status (% above poverty level)			P
	Low (<250%)	Mid (250-500%)	High ≥500%	
Overall (%)	65 (30)	125 (57)	28 (13)	-
Age at diagnosis (years) (%)				
<65	39 (60)	77 (62)	12 (43)	0.1847
≥65	26 (40)	48 (38)	16 (57)	
Sex (%)				
Male	40 (62)	70 (56)	13 (46)	0.3988
Female	25 (38)	55 (44)	15 (54)	
Race (%)				
Caucasian	60 (92)	118 (94)	27 (96)	0.7184
Other	5 (8)	7 (6)	1 (4)	
Insurance at presentation (%)				
No	7 (11)	6 (5)	1 (4)	0.2265
Yes	58 (89)	119 (95)	27 (96)	
Primary insurance type (%)				
Medicare	27 (47)	45 (38)	12 (44)	0.2939
Private	26 (45)	59 (50)	15 (56)	
Other (Medicaid, VA, military Tricare)	5 (9)	15 (13)	0 (0)	
Former military (%)				
No	60 (92)	111 (89)	28 (100)	0.1550
Yes	5 (8)	14 (11)	0 (0)	
Employment status (%)				
Full-time	27 (42)	52 (42)	15 (56)	0.6778
Part-time or unemployed	14 (22)	26 (21)	3 (11)	
Retired	23 (36)	46 (37)	9 (33)	
Cohabitants (%)				
Alone	0 (0)	27 (22)	11 (39)	<0.0001#
1+ other person	65 (100)	96 (78)	17 (61)	
Marital status (%)				
Married	6 (9)	41 (33)	12 (43)	0.0003#
Not married	59 (91)	84 (67)	16 (57)	
Living children (%)				
No	8 (12)	20 (16)	6 (22)	0.4851
Yes	57 (88)	104 (84)	21 (78)	
Highest education achieved (%)				
≤High school diploma or equivalent	28 (55)	57 (55)	7 (28)	0.0485#
>High school diploma	23 (45)	48 (45)	18 (72)	
Diabetes mellitus (%)				
No	53 (82)	108 (86)	26 (93)	0.3417
Yes	12 (18)	17 (14)	2 (7)	
Clinical trial enrollment (%)				
No	54 (83)	105 (84)	20 (71)	0.2836
Yes	11 (17)	20 (16)	8 (29)	
Multifocal disease (%)				
No	57 (88)	102 (82)	24 (86)	0.6066
Yes	8 (12)	22 (18)	4 (14)	
Extent of resection (%)				
GTR	16 (25)	17 (14)	7 (25)	0.0891
STR or NTR	41 (63)	80 (64)	13 (46)	

Contd...

Table 1: Contd...

	Income-based socioeconomic status (% above poverty level)			P
	Low (<250%)	Mid (250-500%)	High ≥500%	
Biopsy	8 (12)	28 (22)	8 (29)	
Preoperative KPS (%)				
<70	24 (44)	40 (37)	10 (42)	0.6488
≥70	30 (56)	68 (63)	14 (58)	
Postoperative KPS (%)				
<70	11 (19)	19 (17)	3 (12)	0.7386
≥70	47 (81)	90 (83)	22 (88)	
Chemotherapy (%)				
No	14 (22)	27 (22)	4 (14)	0.8758
Temozolomide (stupp protocol)	47 (73)	92 (74)	22 (79)	
Other	3 (5)	5 (4)	2 (7)	
Concomitant XRT (%)				
No	9 (14)	17 (14)	3 (11)	0.9068
Yes	56 (86)	107 (86)	25 (89)	

-. Excluded from multivariate analysis, *Statistically significant result, GTR: Gross total resection, NTR: Near total resection, STR: Subtotal resection, XRT: Radiation therapy, KPS: Karnofsky performance status, VA: Veterans Affairs

SES patients were more likely to be unmarried, live with at least 1 other person in their home, and have less than or equal to a high school education. SES did not predict presence of insurance or employment status. Low SES patients were not more likely to have Medicaid insurance.

All patients had a histologically confirmed diagnosis of Grade IV astrocytoma. Multifocal disease presentation was uncommon (16%). Most patients (61%) received near total resection or subtotal resection. Extent of resection, KPS, clinical trial enrollment, and type of treatment received were not predicted by SES. Overall patient functional status pre- and post-operatively was high. The preoperative and postoperative KPS scores were at least 70 in 85% and 88% of patients, respectively. Seventy-five percent received TMZ according to the Stupp protocol, and 87% were treated with XRT.

Univariate Cox proportional hazards analysis yielded 12 variables with $P < 0.10$ to meet inclusion criteria for the multivariate analysis [Table 2]. These variables included age, military service, insurance type, employment status, multifocal disease, extent of resection, DM, pre- and post-operative KPS, clinical trial enrollment, XRT, and TMZ. SES was not among them. After stepwise removal in multivariate analysis, seven statistically significant factors remained [Table 2]. After controlling for confounding variables, shorter overall survival time was associated with old age (hazard ratio [HR] 1.70, $P = 0.0158$), history of military service (HR 2.06, $P = 0.0125$), and multifocal disease (HR 1.75, $P = 0.0119$). Longer overall survival time was associated with Veterans Affairs/Tricare/Medicaid insurance (HR 0.42, $P = 0.0028$), gross total resection (HR 0.42, $P = 0.0027$), XRT (0.12, $P < 0.0001$), and

TMZ (HR 0.28, $P < 0.0001$). Individual Kaplan–Meier survival analyses are depicted in Figure 1 with associated median survival time calculations in Table 3.

DISCUSSION

With the rising costs of healthcare and increasing incidence of cancer, oncology patients make up a significant component of the national disease burden in the United States. A patient's ability to access and afford treatment is affected by their social situation and economic resources. In the oncology setting, research calls into question the impact of SES on overall survival after a diagnosis of cancer.^[20] Our study analyzed the interplay of several sociodemographic variables and their impact on median survival time in 218 patients diagnosed with GBM. The SES distribution of our study population appeared to be similar to that of the local county. Approximately 37% of county residents had low SES by study criteria, compared to the 30% in our sample size.^[56] According to our data, SES is not associated with variations in GBM prognosis. However, multivariate analysis demonstrates insurance type, military history, age, multifocal disease, extent of resection, XRT, and TMZ to be statistically significant factors affecting a patient's median survival time.

Sociodemographic variables are relevant to both the developing and developed world. They have an established role in many different types of malignancies and various stages throughout the disease course.^[4,10,36,45] SES is a limiting factor in access to oncologic surgical care^[24] and clinical trials.^[46,55] It is associated with increased postoperative complications,^[40] including

Table 2: Univariate and multivariate analysis of prognostic variables

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Male sex	1.23	0.93-1.64	0.1470	-	-	-
Non-caucasian	0.79	0.42-1.36	0.4227	-	-	-
Age ≥65 years at diagnosis	2.14	1.60-2.86	<0.0001 [#]	1.70	1.11-2.61	0.0158 [#]
Insurance at presentation	1.30	0.74-2.55	0.3842	-	-	-
Former military	1.83	1.08-2.89	0.0254 [#]	2.06	1.18-3.41	0.0125 [#]
Insurance type (vs. private)	-	-	0.0009 [#]	-	-	0.0009 [#]
Medicare	1.79	1.31-2.43	0.0002 [#]	1.31	0.83-2.05	0.2438
Other	1.08	0.62-1.77	0.7781	0.42	0.22-0.75	0.0028 [#]
Employment (vs. full-time)	-	-	<0.0001 [#]	*	*	*
Retired	2.05	1.49-2.82	<0.0001 [#]			
Part-time/unemployed	1.19	0.80-1.74	0.3904			
Poverty level (vs. low)	-	-	0.4867	-	-	-
Mid	1.05	0.77-1.45	0.7420			
High	0.81	0.50-1.28	0.3756			
Cohabitants	1.14	0.79-1.68	0.4990	-	-	-
Married	1.03	0.77-1.43	0.8625	-	-	-
Living children	1.09	0.75-1.64	0.6628	-	-	-
≤high school education	1.10	0.81-1.50	0.5338	-	-	-
Multifocal disease	1.43	0.96-2.05	0.0748	1.75	1.14-2.63	0.0119 [#]
Resection extent (vs. biopsy)	-	-	0.0004 [#]	-	-	0.0019 [#]
GTR	0.46	0.28-0.73	0.0012 [#]	0.42	0.24-0.74	0.0027 [#]
NTR/STR	0.94	0.67-1.36	0.7401	0.48	0.57-1.32	0.4773
Preoperative KPS ≥70	0.74	0.54-1.00	0.0531	*	*	*
Postoperative KPS ≥70	0.47	0.33-0.71	0.0004 [#]	*	*	*
Diabetes mellitus	1.73	1.13-2.56	0.0124 [#]	*	*	*
No clinical trial enrollment	1.78	1.20-2.74	0.0033 [#]	*	*	*
No TMZ	4.21	2.93-5.96	<0.0001 [#]	3.56	2.17-5.73	<0.0001 [#]
No concomitant XRT	4.61	3.01-6.83	<0.0001 [#]	8.42	4.22-16.58	<0.0001 [#]

[#]Included in multivariate analysis but insignificant with $P>0.05$. -: Excluded from multivariate analysis. *Statistically significant result. CI: Confidence interval, GTR: Gross total resection, NTR: Near total resection, STR: Subtotal resection, XRT: Radiation therapy, TMZ: Temozolomide, KPS: Karnofsky performance status, HR: Hazards ratio

higher postoperative mortality.^[32] Furthermore, treatment advances do not appear to affect all social classes equally.^[38]

Race is a frequently studied demographic variable in oncology. African-American patients have decreased overall survival in non-central nervous system (CNS) adult and pediatric malignancies compared to their Caucasian counterparts.^[3,4,26,30,52] CNS malignancies are commonly excluded from the large scale sociodemographic studies, so focused statistical analyses have been warranted. Over 90% of patients were Caucasian across all SES strata in our study which is indicative of the predominance of GBM in the white population. Race was not associated with prognosis in our GBM study which is congruent with many studies^[16,34,41,47,50] yet may be inconsistent with others.^[6] Nevertheless, the race has been linked to lower clinical trial enrollment. We did not demonstrate an association between clinical trial enrollment and median survival time; however, there has been a suggested link in others.^[22]

Socioeconomic data specific to CNS malignancy incidence and outcomes have yielded mixed results.^[45,47] Specific to the pathogenesis of GBM, incidence is higher in elderly, male, and Caucasian patients and possibly linked to SES.^[12,58] Consistent with prior research, our study reported shorter prognoses for elderly patients. The shorter life expectancy is believed to be related to the elderly's decreased likelihood to undergo surgical resection after biopsy and receive multimodal therapy, given the compromised quality of life.^[7] Some suggest certain occupations be at increased risk for glioma given their environmental exposure^[18] while others negate this finding.^[42,44] Investigators have found higher GBM incidence in populations with higher SES^[39] as well as with lower SES when Medicaid insurance is used as a proxy.^[48]

ZCTA codes served as a useful representation of income and proxy for SES in our study. Other studies in and outside of neurosurgery have used zip codes as an SES

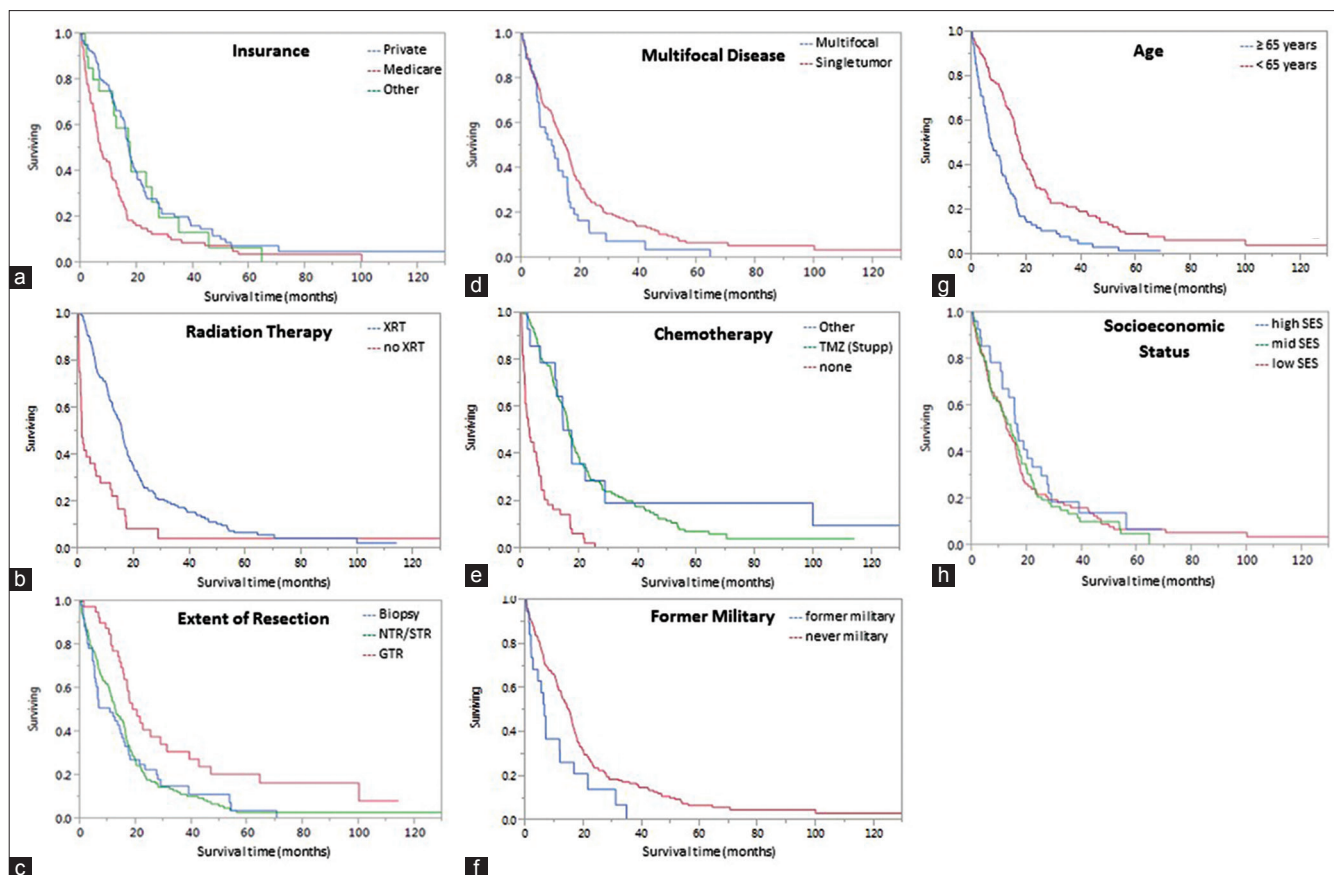


Figure 1: Kaplan–Meier survival curves for (a-g) statistically significant variables in the multivariate analysis and (h) the nonsignificant role of income-based socioeconomic status

marker as well.^[19,40] Yet, direct patient-reported incomes would provide a more accurate measure of individual economic standing. Several different markers of SES have been used in the GBM literature without consistency. In Australia, different IRSAD scores did not affect long-term survival^[22] or the number of surgical resections a patient underwent.^[49] British studies reported poorer prognoses for patients treated in public hospitals as opposed to private institutions^[31] and for patients of lower SES determined by Carstairs index for social deprivation.^[54] SES did not impact median survival time according to our US-based study using ZCTA codes. We considered the 2012 US ZCTA codes to be an appropriate representation of a patient's SES when household size and the national poverty level were accounted for in the analysis. Although individual patient income was unavailable, census tracts represent wealth and resources from a regional standpoint.

Patient resources were further analyzed in our study of military background and insurance status at the time of diagnosis. While lack of insurance did not affect prognosis, a patient's insurance type was statistically significant in the multivariate model [Table 2]. Notably, our institution is committed to treating all patients with brain tumors regardless of insurance type, which

likely affected outcomes. Patients who had served in the military had shorter survival times than those who had not. Certain military occupational exposures, for example, agent orange, have a suggested association with increased incidence of multiple non-CNS cancers^[59] and more aggressive types,^[2] yet further research is warranted. Despite the shorter survival prognosis for veterans, the patients who possessed military insurance or Medicaid at the time of diagnosis had significantly longer survival times than those with private plans.

Glioblastoma has been studied extensively in search of predictors separating the short from long-term survivors. No factor has been found to more strongly affect tumor prognosis than the addition of TMZ to XRT since the 2005 Stupp trial;^[51,53] evidence corroborated by our study. Yet, type 2 DM,^[14] performance status,^[9,13] tumor location,^[11] age,^[27] multifocal tumors,^[37] and extent of tumor resection^[9,27] also have an apparent role in prognostication. Researchers have used this information to create a glioma prognostication score based upon evidence that periventricular location, presence of language or motor deficit, postoperative KPS, and old age negatively affect median survival time.^[11] Genetics also offers promising insight regarding varied treatment response^[15,57] and more aggressive tumor behavior.^[5]

Table 3: Median survival times for statistically significant multivariate results

	Median survival time (months)	95% CI	Log-rank P value
Age at diagnosis (years)			
≥65	7.22	5.67-10.77	<0.0001#
<65	17.70	15.67-20.00	
Former military			
Yes	6.50	1.97-11.87	0.0140#
No	15.03	12.37-16.23	
Insurance type			
Medicare	6.95	5.47-10.77	0.0006#
Private	17.1	15.67-19.60	
Other - Medicaid, military	17.43	6.40-25.27	
Chemotherapy			
TMZ - Stupp	16.23	15.03-18.53	<0.0001#
None	2.83	1.40-5.33	
Other	13.2	2.17-21.93	
XRT			
Yes	15.97	13.50-17.10	<0.0001#
No	1.40	0.83-3.03	
Resection extent			
GTR	20.23	15.37-31.03	0.0010#
NTR/STR	12.60	10.77-15.97	
Biopsy	6.55	5.00-15.53	
Multifocal disease			
Yes	11.09	5.90-15.60	0.0624
No	14.93	11.87-16.70	

#Statistically significant result (P<0.05). CI: Confidence interval, GTR: Gross total resection, NTR: Near total resection, STR: Subtotal resection, XRT: Radiation therapy, TMZ: Temozolomide

Despite new evidence, the question regarding short-versus long-term glioma survivors remains unanswered.

We disproved our hypothesis and found SES to not be associated with GBM prognosis in a sample size whose demographics were similar to the local population. This is notably different from several other malignancies; in which, authors have presented a prognostic role for sociodemographic variables.^[10,17,38] This may be in part due to our institution’s pledge to serve patients with limited resources. It is our departmental policy to treat all new brain tumor diagnosed with equal care, regardless of insurance and income status. Another hypothesis could be that SES is less significant in GBM given the late presentation of most patients and limited efficacy of the current treatment regimen. A malignancy with similarly poor survival statistics is pancreatic cancer. However, one retrospective study contradictory to this theory shows that SES may be associated with survival of elderly pancreatic cancer patients.^[29] In general, several etiologies are likely intermingled, and a multi-institutional epidemiological study of GBM prognosis is warranted to validate our study results.

CONCLUSIONS

In our US-based study using ZCTA codes as a proxy for SES, we present new data demonstrating that SES does not affect GBM prognosis. However, sociodemographic variables such as a military service record and insurance type have a suggested prognostication role. Consistent with prior studies, old age, multifocal tumors, XRT, and chemotherapy affected outcomes. XRT has the largest impact on median survival time. Although a small, single-institution, retrospective study, this research presents a formative opportunity for physicians to consider a patient’s socioeconomic profile when treating GBM.

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Conflicts of interest

There are no conflicts of interest.

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