Sex is an important prognostic factor for glioblastoma but not for nonglioblastoma

Haley Gittleman, Quinn T. Ostrom, LC Stetson, Kristin Waite, Tiffany R. Hodges, Christina H. Wright, James Wright, Joshua B. Rubin, Michael E. Berens, Justin Lathia, James R. Connor, Carol Kruchko, Andrew E. Sloan, and Jill S. Barnholtz-Sloan

Central Brain Tumor Registry of the United States, Hinsdale, IL (H.G., Q.T.O., C.K., J.S.B-S.); Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH (H.G., L.S., K.W., J.L., A.E.S., J.S.B-S.); Department of Population Health and Quantitative Sciences, Case Western Reserve University School of Medicine, Cleveland, OH (H.G., K.W., J.S.B-S.); Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX (Q.T.O.); Department of Neurological Surgery, University Hospitals of Cleveland and Case Western University School of Medicine, OH (T.R.H., C.H.W., J.W., A.E.S.); Seidman Cancer Center, University Hospitals of Cleveland, OH (T.R.H., A.E.S.); Washington University School of Medicine, St. Louis, MO (J.B.R.); Translational Genomics Research Institute, Phoenix, AZ (M.E.B.); Cleveland Clinic, Lerner Research Institute, OH (J.L.); Department of Neurosurgery, Penn State Cancer Institute, Penn State, State College (J.R.C.)

Corresponding Author: Jill S. Barnholtz-Sloan, PhD, Case Western Reserve University School of Medicine, Case Comprehensive Cancer Center, 2103 Cornell Rd, WRB 2-526, Cleveland, OH 44106–5065 (jsb42@case.edu).

Abstract

Background. Glioblastoma (GBM) is the most common and most malignant glioma. Nonglioblastoma (non-GBM) gliomas (WHO Grades II and III) are invasive and also often fatal. The goal of this study is to determine whether sex differences exist in glioma survival.

Methods. Data were obtained from the National Cancer Database (NCDB) for years 2010 to 2014. GBM (WHO Grade IV; N = 2073) and non-GBM (WHO Grades II and III; N = 2963) were defined using the histology grouping of the Central Brain Tumor Registry of the United States. Non-GBM was divided into oligodendrogliomas/mixed gliomas and astrocytomas. Sex differences in survival were analyzed using Kaplan–Meier and multivariable Cox proportional hazards models adjusted for known prognostic variables.

Results. There was a female survival advantage in patients with GBM both in the unadjusted (P = .048) and adjusted (P = .003) models. Unadjusted, median survival was 20.1 months (95% CI: 18.7-21.3 months) for women and 17.8 months (95% CI: 16.9-18.7 months) for men. Adjusted, median survival was 20.4 months (95% CI: 18.9-21.6 months) for women and 17.5 months (95% CI: 16.7-18.3 months) for men. When stratifying by age group (18-55 vs 56+ years at diagnosis), this female survival advantage appeared only in the older group, adjusting for covariates (P = .017). Women (44.1%) had a higher proportion of methylated *MGMT* (O^6-methylguanine-DNA methyltransferase) than men (38.4%). No sex differences were found for non-GBM.

Conclusions. Using the NCDB data, there was a statistically significant female survival advantage in GBM, but not in non-GBM.

Gliomas are the most common form of primary brain tumor, representing about 80% of malignant brain and other CNS tumors.[1–11] The World Health Organization (WHO) classification system groups gliomas into 4 histological grades based on level of malignancy; malignant gliomas are defined as Grade II, III and IV tumors.[1–9,12–14]

Nonglioblastoma (non-GBM), WHO Grades II and III gliomas, usually also evolve into high-grade gliomas, which are universally fatal.[1,12,15,16] Glioblastoma (GBM), WHO Grade IV, is the most common, aggressive, and deadly glioma, accounting for approximately 15% of all primary brain and CNS tumors and 50% of all malignant primary brain and CNS tumors.[1–4,17–21] Standard-of-care treatment consists of maximum safe surgical resection followed by radiotherapy in addition to concomitant and adjuvant chemotherapy with the alkylating agent temozolomide (TMZ).[13,17–19] Despite this aggressive therapeutic regimen, patients with GBM have an extremely poor prognosis,[1,3,4,10,13,17,20] with a 5-year survival rate of 5.6%.[2] Non-GBMs generally affect patients at a younger age than GBM, with a peak incidence occurring between age 35 and 44 years in patients with non-GBM, compared with between age 75 and 84 years in those with GBM.[2,12,15] Standard treatment for non-GBM gliomas begins with maximal safe resection with subsequent radiotherapy and/or chemotherapy depending on the tumor lineage and grade.[12,15,16]

Sex disparities in cancer incidence, survival, and prevalence have been well established for a variety of cancers, including oral and oropharyngeal cancer, liver cancer, cloacogenic anal cancer, and brain tumors.[3,5,11,22–28] Previous studies have shown that men not only develop cancers more frequently, they have poorer responses to therapy as measured by progression-free and overall survival compared with women.[5,22] Overall, cancer incidence rates are about 20% higher in men, while mortality rates are about 40% higher.[22] The EUROCARE-2 study analyzed survival in 1 million European cancer cases diagnosed in 1985-1989, finding that sex was a significant predictor of survival and suggesting that women had a biological advantage over men in coping with cancer.[29] In general, gliomas are more common in men than women.[2,5–7,11,13,15,20,23,24,30–32] Primary GBM is about 1.58 times more common in men than in women.[2,17,20,21,25] A study by Ostrom et al found that sex was significantly associated with survival in 2 independent datasets, confirming a female survival advantage among patients with GBM who received standard-of-care treatment.[33] Whether the female survival advantage exists in non-GBM is unclear. Thus, the goals of this study are to confirm the sex differences in survival findings of Ostrom and colleagues in patients with GBM who received standard-of-care and assess this potential sex disparity in survival in primary non-GBM using data from the National Cancer Database (NCDB).

Materials and Methods

This study was approved as an exempt study by the University Hospitals Institutional Review Board. Data were obtained from the NCDB for the diagnosis years of 2010 to 2014, which collects data from more than 1500 hospitals in the United States, covering more than 70% of all newly diagnosed cases of cancer.[34] GBM and non-GBM were defined using the histology grouping scheme for malignant gliomas (WHO Grades II, III, and IV) consistent with that of the Central Brain Tumor Registry of the United States (CBTRUS).[2] GBM was defined using ICD-O-3 codes

9440/3, 9441/3, and 9442/3. Non-GBM was divided into 2 categories: oligodendrogliomas/mixed gliomas and astrocytomas. The oligodendrogliomas/mixed gliomas were defined using the following ICD-O-3 codes: oligodendroglioma (9450/3), anaplastic oligodendroglioma (9451/3, 9460/3), and oligoastrocytic tumors (9382/3). The astrocytomas were defined using the following ICD-O-3 codes: diffuse astrocytoma (9400/3, 9410/3, 9411/3, 9420/3), anaplastic astrocytoma (9401/3), and unique astrocytoma variants (9381/3, 9424/3).

For the primary GBM dataset, patients were included if they were diagnosed in 2010-2014, were at least age 18 years at diagnosis, either had subtotal or gross total resection, had radiotherapy (beam or combination) following their surgery, had chemotherapy (defined as chemotherapy administered as first course of therapy, single-agent chemotherapy administered as first course of therapy, or multiagent chemotherapy administered as first course of therapy), had a histologic diagnostic confirmation, had a KPS between 10 and 100 (0 excluded), had known promoter methylation status of O^6-methylguanine-DNA methyltransferase (*MGMT*), and had unifocal GBM. The final dataset included 2073 patients (1250 men and 823 women). A CONSORT diagram depicting the GBM patient selection process is presented in Supplemental Figure 1. For the primary non-GBM dataset, patients were included if they were diagnosed in 2010-2014, were at least age 18 years at diagnosis, had a histologic diagnostic confirmation, had KPS between 10 and 100 (0 excluded), known loss of heterozygosity status of chromosomes 1p/19q (1p/19q codeletion), and had unifocal non-GBM. The final dataset included 2963 patients (1676 men and 1287 women). A CONSORT diagram depicting the non-GBM patient selection process is presented in Supplemental Figure 2. Owing to the level of missing data for *MGMT* in the GBM dataset and 1p/19q in the non-GBM dataset, sensitivity analyses were run to assess any difference in distribution of these variables between men and women. Two methods were used: Pearson's chi-squared test and calculating the area under the receiver operating characteristic (ROC) curve.

The following variables were included in the analyses: sex (men, women), age at diagnosis (continuous; years), primary payer (not insured, private insurance/managed care, Medicaid, Medicare, other government), urban/rural (metro, urban, rural), CBTRUS histology (diffuse astrocytoma, anaplastic astrocytoma, unique astrocytoma variants, oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytic tumors) [non-GBM only], tumor size (continuous; mm), KPS (continuous; score from 0–100 by tens), *MGMT* methylation (yes, no) [GBM only], 1p/19q codeletion (yes, no) [non-GBM only], surgical resection (no surgery, biopsy, subtotal resection, gross total resection), radiation therapy (yes, no) [non-GBM only], chemotherapy (yes, no) [derived from as defined above for "yes" for non-GBM], follow-up time (continuous; months), and vital status (alive, dead). Because of the amount of missing data for KPS (76.2% missing for GBM and 81.3% for non-GBM), this variable was imputed using multivariate imputation by chained equations using the R package "mice."[35] The raw, unimputed values for KPS for GBM and non-GBM are displayed in Supplemental Table 1.

Descriptive statistics were used to assess sex differences in important prognostic variables, using *t*-tests for

continuous variables and chi-squared tests for categorical variables. Sex differences in survival were analyzed using R version 3.5.0[36] by Kaplan–Meier and multivariable Cox proportional hazards models, including adjusted Kaplan–Meier survival curves using the "survival" R package (R code available on request following pages 28–31, 68–70, 98–99, and 119–120).[37] For both GBM and non-GBM, unadjusted Kaplan–Meier survival curves were generated stratified by sex and tested for differences using the log-rank test. *P* values less than .05 were considered statistically significant. For GBM only, adjusted Kaplan–Meier survival curves were generated by sex, controlling for (1) age at diagnosis and surgical resection, (2) age at diagnosis, surgical resection, and KPS, and (3) age at diagnosis, surgical resection, KPS, *MGMT* promoter methylation, primary payer status, urban/rural, and tumor size. The first 2 adjusted curves (1) and (2) were generated to compare the results with past literature.[33] Similarly, multivariable Cox proportional hazards models were developed for the same models. To examine the potential effect of menopause and sex hormones on survival, the GBM dataset was stratified by age (18-55 years and 56+ years). The cutoff of 55 years was chosen because the most common age range at which women experience menopause in the United States is 48-55 years.[38] For non-GBM, the oligodendrogliomas/mixed gliomas and astrocytomas were analyzed separately. Adjusted Kaplan–Meier survival curves were generated stratified by sex, controlling for age at diagnosis, surgical resection, KPS, 1p/19q codeletion, radiotherapy, chemotherapy, primary payer status, urban/rural, tumor size, and CBTRUS histology. Corresponding multivariable Cox proportional hazards models were developed both for oligodendrogliomas/mixed gliomas and astrocytomas.

Results

Patient demographics both for the GBM dataset (N = 2073) and the non-GBM dataset (N = 2963) for the study years of 2010-2014 are described in Table 1. For GBM, the majority of patients were male (60.3%), had unmethylated *MGMT* (59.3%), and had gross total resection of their tumor (54.3%). The average age at diagnosis was 58.56 years. Men were significantly more likely to have private insurance/managed care, and women were significantly more likely to use Medicaid (*P* = .027). Women were more likely to have methylated *MGMT* than men (44.1% women vs 38.4% men) (*P* = .011). No other significant differences between men and women were found on the other prognostic factors examined. For non-GBM, the majority of patients were male (56.6%), did not have the 1p/19q codeletion (54.2%), had gross total resection (38.3%), had radiation therapy (54.5%), and had chemotherapy (56.5%). The average age at diagnosis was 43.71 years. There were no significant differences between men and women in the prognostic factors examined.

Without adjusting for covariates, the Kaplan–Meier curve (Fig. 1A) shows a significant sex difference for GBM patients, with women having better overall survival than men (*P* = .048). The median overall survival for women was 20.1 months (95% CI: 18.7-21.3 months), and 17.8 months for men (95% CI: 16.9-18.7 months). This difference gets larger with additional adjustments for covariates. A past study showed a significant sex difference for GBM patients adjusting for age at diagnosis and surgical resection, as well as adjusting for age at diagnosis, surgical resection, and KPS,[33] so these Kaplan–Meier curves were drawn using NCDB data to see whether this difference still existed. When adjusting for age at diagnosis and surgical resection, the log-rank *P* value assessing the difference between men and women decreased to .018 (Fig. 1B), and adjusting further for KPS decreased the *P* value to .014 (Fig. 1C). After adjusting for all covariates of interest (age at diagnosis, surgical resection, KPS, *MGMT* methylation, primary payer status, urban/rural, and tumor size), the log-rank *P* value decreased to .003 (Fig. 1D). The median overall survival for women was 20.4 months (95% CI: 18.9-21.6 months), and 17.5 months for men (95% CI: 16.7-18.3 months). The corresponding hazard ratios (HRs) for sex, presented as men vs women, along with their 95% confidence intervals (CI) for each of the 4 models, are presented in Fig. 2A. The plot shows that the male:female HR shifts farther away from 1 with more covariates added. The values for the HRs, 95% CIs, and *P* values can be found in Supplemental Table 2. All covariates were statistically significant at the .05 level, except for tumor size. The Cox proportional hazards assumption was not violated (*P* = .308).

To assess whether sex hormones contributed to the female survival advantage in GBM patients, the data were stratified into those age 18–55 years at diagnosis (premenopausal, N = 749) and those 56 years and older at diagnosis (postmenopausal, N = 1324). In the younger age group, without adjustment for any covariates, the log-rank *P* value was not statistically significant (*P* = .116), although the Kaplan–Meier curve does seem to show a favorable outcome for women with long-term survival (Fig. 3A). The median survival for women was 24.3 months (95% CI: 21.7-27.5 months), and 22.5 months for men (95% CI: 21.2-25.7 months). After adjusting for all covariates of interest, the results remained similar (*P* = .182) (Fig. 3B). The median survival for women was 23.7 months (95% CI: 21.3-27.4 months), and 22.1 months for men (95% CI: 20.6-24.3 months). The corresponding HRs and 95% CIs are shown in Fig. 2B (models 1 and 4). The plot shows that the male:female HRs do not change significantly with additional covariates. In the older age group, without adjustment for any covariates, the log-rank *P* value was not statistically significant (*P* = .143) (Fig. 3C). The median survival for women was 17.9 months (95% CI: 16.4-19.6 months), and 15.6 months for men (95% CI: 14.7-16.3 months). After adjusting for all covariates of interest, however, the female survival advantage resurfaced (*P* = .017), although the Kaplan–Meier curves appeared to be similar (Fig. 3D). The median survival for women was 18.4 months (95% CI: 17.0-20.4 months), and 15.5 months for men (95% CI: 14.6-16.2 months). The corresponding HRs and 95% CIs are shown in Fig. 2C (models 1 and 4). The plot shows that the male:female HR shifts farther away from 1 with more covariates added. The values for the HRs, 95% CIs, and *P* values can be found in Supplemental Table 2.

Table 1   Patient characteristics for glioblastoma (GBM) and non-GBM data sets, National Cancer Database 2010-2014

Variable	Glioblastoma (GBM)			Nonglioblastoma (Non-GBM)		
	Male (N = 1250)	Female (N = 823)	*P* Value	Male (N = 1676)	Female (N = 1287)	*P* Value
Age at diagnosis[a] (mean [SD])	58.47 (11.99)	58.71 (12.43)	0.654	43.53 (14.08)	43.96 (14.42)	.412
Primary Payer[b] (N [%])	(Missing N = 18; 0.9%)		0.027	(Missing N = 29; 1.0%)		.266
Not insured	129 (11.0%)	91 (11.9%)		97 (5.9%)	65 (5.1%)	
Private insurance/managed care	211 (18.0%)	121 (15.9%)		1154 (69.6%)	910 (71.3%)	
Medicaid	195 (16.7%)	143 (18.8%)		204 (12.3%)	142 (11.1%)	
Medicare	241 (20.6%)	159 (20.9%)		164 (9.9%)	141 (11.0%)	
Other government	40 (3.4%)	23 (3.0%)		38 (2.3%)	19 (1.5%)	
Urban/Rural[b] (N [%])	(Missing N = 67; 3.2%)		0.279	(Missing N = 88; 3.0%)		.166
Metro	1021 (84.1%)	680 (85.9%)		1356 (83.1%)	1050 (84.4%)	
Urban	171 (14.1%)	104 (13.1%)		244 (15.0%)	181 (14.5%)	
Rural	22 (1.8%)	8 (1.0%)		31 (1.9%)	13 (1.0%)	
CBTRUS Histology[b] (N (%))	NA					.086
Diffuse astrocytoma				179 (10.7%)	172 (13.4%)	
Anaplastic astrocytoma				246 (14.7%)	199 (15.5%)	
Unique astrocytoma variants				3 (0.2%)	6 (0.5%)	
Oligodendroglioma				550 (32.8%)	396 (30.8%)	
Anaplastic oligodendroglioma				264 (15.8%)	177 (13.8%)	
Oligoastrocytic tumors				434 (25.9%)	337 (26.2%)	
Size of Tumor[a] (mm) (mean [SD])	(Missing N = 286; 13.8%)		0.313	(Missing N = 747; 25.2%)		.282
	48.44 (42.76)	46.35 (42.44)		52.45 (59.83)	49.76 (55.69)	
KPS[b] (imputed[c]) (N [%])			0.702			.103
10	7 (0.6%)	4 (0.5%)		6 (0.4%)	8 (0.6%)	
20	5 (0.4%)	4 (0.5%)		3 (0.2%)	7 (0.5%)	
30	5 (0.4%)	2 (0.2%)		8 (0.5%)	9 (0.7%)	
40	18 (1.4%)	20 (2.4%)		12 (0.7%)	6 (0.5%)	
50	27 (2.2%)	23 (2.8%)		14 (0.8%)	25 (1.9%)	
60	81 (6.5%)	47 (5.7%)		58 (3.5%)	51 (4.0%)	
70	150 (12.0%)	113 (13.7%)		221 (13.2%)	170 (13.2%)	
80	376 (30.1%)	236 (28.7%)		367 (21.9%)	296 (23.0%)	
90	438 (35.0%)	276 (33.5%)		665 (39.7%)	489 (38.0%)	
100	143 (11.4%)	98 (11.9%)		322 (19.2%)	226 (17.6%)	
MGMT Promoter Methylation[b] (N [%])			0.011	NA		
Methylated	480 (38.4%)	363 (44.1%)				
Unmethylated	770 (61.6%)	460 (55.9%)				
1p/19q Codeletion[b] (N [%])	NA					.912
Yes codeletion				769 (45.9%)	587 (45.6%)	
No codeletion				907 (54.1%)	700 (54.4%)	
Surgical Resection[b] (N [%])			0.824			.489
No surgery	NA			165 (9.8%)	126 (9.8%)	
Biopsy	NA			344 (20.5%)	263 (20.4%)	
Subtotal resection	574 (45.9%)	373 (45.3%)		387 (30.1%)	543 (32.4%)	
Gross total resection	676 (54.1%)	450 (54.7%)		511 (39.7%)	624 (37.2%)	

Table 1 Continued

Variable	Glioblastoma (GBM)			Nonglioblastoma (Non-GBM)		
	Male (N = 1250)	Female (N = 823)	P Value	Male (N = 1676)	Female (N = 1287)	P Value
Radiation Therapy[b] (N [%])	NA—all GBM patients had radiotherapy because of inclusion criteria					.603
Yes				921 (55.0%)	694 (53.9%)	
No				755 (45.0%)	593 (46.1%)	
Chemotherapy[b] (N [%])	NA—all GBM patients had chemotherapy because of inclusion criteria					.214
Yes				964 (57.5%)	710 (55.2%)	
No				712 (42.5%)	577 (44.8%)	

Abbreviation: CBTRUS, Central Brain Tumor Registry of the United States; *MGMT*, O^6-methylguanine-DNA methyltransferase; NA, not available.
[a]*P* value calculated by *t*-test.
[b]*P* value calculated by chi-squared test.
[c]KPS had 2410 (76.2%) missing values for the GBM data set and 1580 (81.3%) missing values in the non-GBM data set. Therefore, KPS was imputed using multivariate imputation by chained equations using the "mice" R package.[33]

Kaplan–Meier analysis was performed for non-GBM patients, stratified by histology (oligodendroglioma/mixed glioma and astrocytomas), unadjusted and adjusted for covariates. For oligodendroglioma/mixed glioma, the unadjusted log-rank *P* value was .413 (Fig. 4A), and the adjusted log-rank *P* value was .904 (Fig. 4B), showing no sex difference in overall survival. Unadjusted, the median overall survival for women and men could not be obtained, since the proportion of patients who died did not reach 0.5; however, the 95% CI lower bound was 78.5 months for women and 81.1 months for men. Adjusted, the 95% CI lower bound stayed the same for women (78.5 months), but could not be calculated for men, as their overall survival improved after adjustment. For astrocytomas, the unadjusted log-rank *P* value was .739 (Fig. 4C), and the adjusted log-rank *P* value was .227 (Fig. 4D), again demonstrating no sex difference in overall survival. Unadjusted, the median overall survival and corresponding 95% CI for women could not be obtained; however, the median overall survival for men was 72.2 months, with a 95% CI lower bound of 60.6 months. Adjusted, none of the median survival estimates could be obtained, which could be because of the short period of follow-up. The corresponding values for the HRs, 95% CIs, and *P* values from the Cox proportional hazards models can be found in Supplemental Table 3. The Cox proportional hazards assumption was not violated (*P* = .687).

The mean ages at diagnosis were about the same for men and women both for GBM (men: 58.47 years; women: 58.71 years) (*P* = .654) and non-GBM (men: 43.53 years; women: 43.96 years) (*P* = .412). Similarly, the mean tumor sizes at diagnosis were about the same for men and women both for GBM (men: 48.44 mm; women: 46.35 mm) (*P* = .313) and non-GBM (men: 52.45 mm; women: 49.76 mm) (*P* = .282). To determine any differences in the underlying distributions of patient age at diagnosis by sex and tumor size by sex, plots of these distributions were generated both for GBM and non-GBM. For GBM, women were diagnosed at later ages than men (Fig. 5A), and women had smaller tumor sizes at diagnosis than men (Fig. 5B). Conversely, in non-GBM, there was no significant difference in age (Fig. 5C) or tumor size (Fig. 5D) by sex at the time of diagnosis.

Discussion

We have described overall survival by sex in patients with GBM and non-GBM (malignant gliomas, WHO Grades II, III, and IV) for the diagnosis years 2010-2014 using NCDB data. There is a notable female survival advantage in GBM, but not in non-GBM. Our study validates a previous study by Ostrom et al that reported a significant female survival advantage in patients with GBM diagnosed in 2007 or later who received standard-of-care using 2 data sources: (1) the Ohio Brain Tumor Study (OBTS), a multicenter study in Ohio, and (2) the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[33] The study reported a significant log-rank *P* value, with women having better overall survival than men when adjusting for age at diagnosis and extent of resection (*P* = .0017) using the SEER 18 data, and adjusting for age at diagnosis, extent of resection, and postsurgical KPS (*P* = .0006) using the OBTS data.[33] Our study built on the previous analyses by including a more robust sample size (N = 2073) than that of OBTS (N = 228), and including additional prognostic factors in our survival models, such as *MGMT* methylation status, primary payer status, urban/rural location, and tumor size. Moreover, the cohort of patients with GBM from NCDB is more comprehensive across the United States (covering more than 70% of cancer diagnoses in the United States), as the SEER cohort represents patients from the 18 SEER registries (covering ~30% of the United States), and the OBTS cohort represents patients from Ohio only. It is important to note that the analyses by Ostrom and colleagues did not include biopsy-only patients with GBM; therefore, to directly compare our results with those of Ostrom et al, we limited our cohort to patients who received either subtotal or gross total surgical resection.

Previous literature has suggested that endogenous hormones may play a role in cancer incidence and survival.[22,29] A study of liver cancer found that estrogens, at concentrations present in women but not in men, suppressed IL-6 production, thereby inhibiting chemically induced liver carcinogenesis.[26] To determine the potential role of menopause
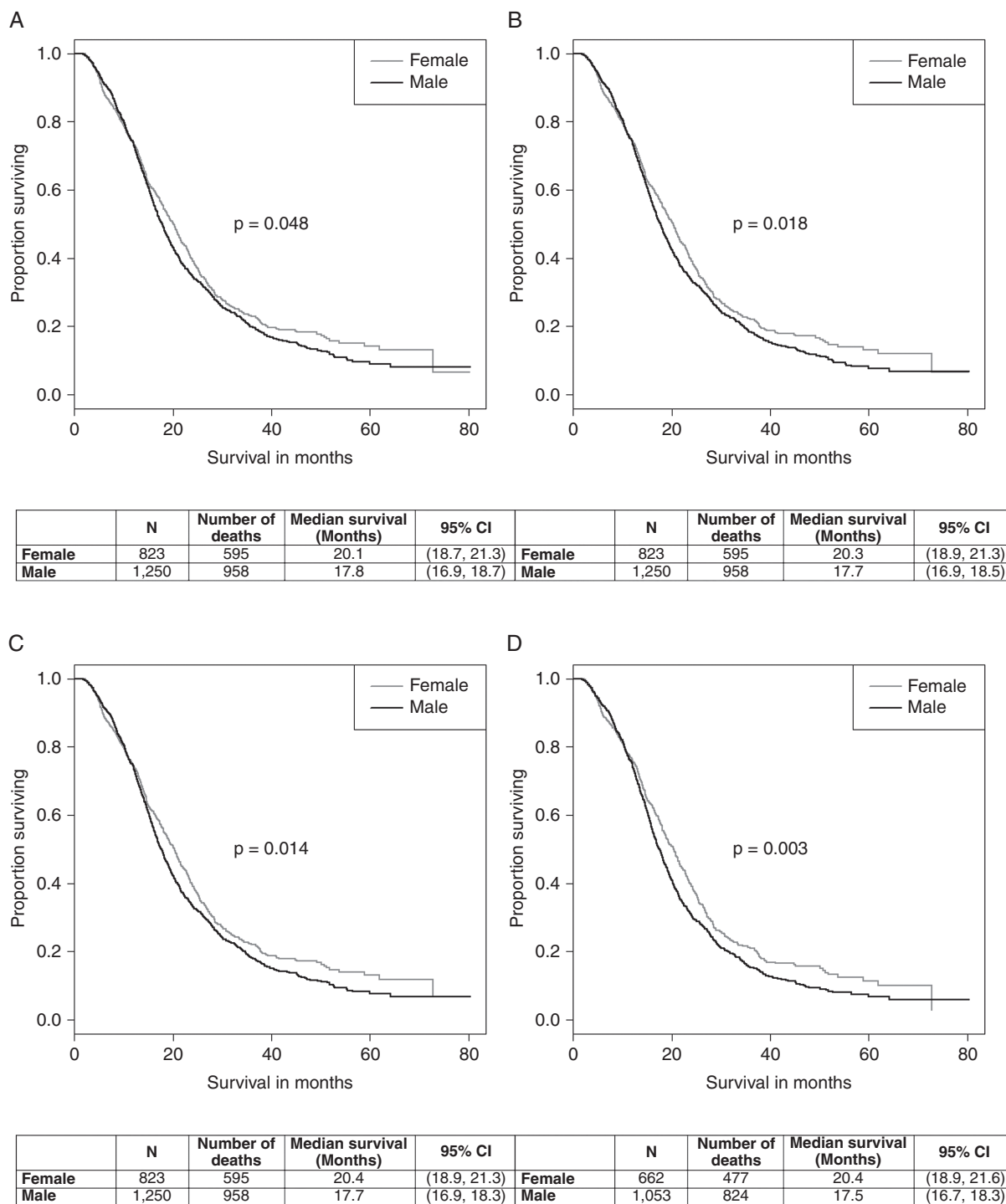
	N	Number of deaths	Median survival (Months)	95% CI
Female	823	595	20.1	(18.7, 21.3)
Male	1,250	958	17.8	(16.9, 18.7)

	N	Number of deaths	Median survival (Months)	95% CI
Female	823	595	20.3	(18.9, 21.3)
Male	1,250	958	17.7	(16.9, 18.5)

	N	Number of deaths	Median survival (Months)	95% CI
Female	823	595	20.4	(18.9, 21.3)
Male	1,250	958	17.7	(16.9, 18.3)

	N	Number of deaths	Median survival (Months)	95% CI
Female	662	477	20.4	(18.9, 21.6)
Male	1,053	824	17.5	(16.7, 18.3)

Fig. 1 Kaplan–Meier curves for glioblastoma survival by sex A, unadjusted, B, adjusted for age at diagnosis and surgical resection, C, adjusted for age at diagnosis, surgical resection, and KPS, and D, adjusted for age at diagnosis, surgical resection, KPS, O^6-methylguanine-DNA methyltransferase (*MGMT*) methylation, primary payer, urban/rural, and tumor size, National Cancer Database 2010-2014.

and sex hormones in survival in our GBM patient population, patients were stratified into 2 age groups: 18-55 years at diagnosis and 56+ years at diagnosis. Within the younger group, there were no sex differences in survival. The older group demonstrated a female survival advantage on multivariable analysis, contradicting the hypothesis that the female survival advantage in GBM patients is due to elevated estrogen or other sex hormones alone.

There is a paucity of literature assessing sex differences in survival in patients with non-GBM (WHO Grades II and
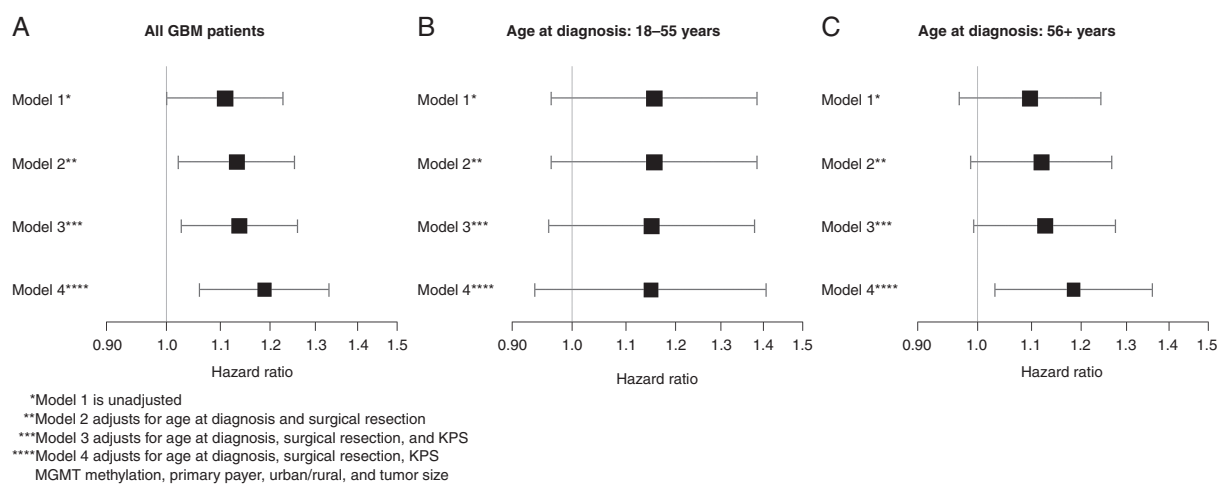
Fig. 2 Cox proportional hazards models' hazard ratios with corresponding 95% CIs for glioblastoma patients A, overall, B, in those age 18–55 years, and C, in those age 56+ years, National Cancer Database 2010-2014.

III), and the results have been inconclusive thus far. One study found that men were 1.18 times more likely than women to die of their non-GBM,[10] while another study found that sex did not significantly influence survival in non-GBM (log-rank test P value >.09).[39] Our study results agree with the latter finding. We did not find a significant sex difference in survival for patients with non-GBM both in the oligodendroglioma/mixed glioma patients and astrocytoma patients, even after adjusting for known prognostic factors. The current study used the most up-to-date data available at the population-level in the United States, as previous studies of sex differences in non-GBM used data from 1979 to 2001[10] and from 1980 to 1995[39]. Because the definition of non-GBM has likely changed since those studies were conducted, our results are most relevant to current diagnosis of non-GBM.

The female survival advantage in cancer has been previously attributed to a variety of explanations, including lower prevalence of comorbidity, earlier diagnosis, greater resistance to disease, more attentiveness to health, and a lower incidence in risky behaviors in women relative to men.[28,29,40] Another study found that adult height was positively associated with cancer incidence and death both in men and women and accounts for about one-third of the sex disparity in cancer risk by sex.[22] Although height and certain environmental or behavioral risks are not included in the NCDB and thus cannot be addressed in this study, the covariates chosen for our survival models were chosen strategically to account for some of these potential explanations. Assessment of primary payer status and urban/rural location were added to control for patient access to care and to serve as a marker of socioeconomic status, and both of these variables were found to be significant predictors of glioma survival (urban/rural was not significant in non-GBM).

A genetic component may contribute to the female survival advantage found in patients with GBM. Numerous studies have confirmed that *MGMT* promoter methylation is correlated with an improved overall survival

benefit in response to TMZ, irrespective of other treatment choices.[2,3,7,13,18–20] Methylation of the *MGMT* promoter has been demonstrated in 30% to 60% of patients with GBM.[19,20] In our GBM dataset, women had a significantly greater proportion of *MGMT* methylation (women: 44.1% methylated *MGMT*; men: 38.4% methylated *MGMT*; P = .011), which may contribute to their improved survival. One study found that *MGMT* methylation was significantly associated with longer survival in the entire cohort of patients with GBM (P = .009), but was significantly associated with longer survival only in female patients (P = .003) and not in male patients (P = .603).[17] For patients with non-GBM, the most common genetic mutation and characteristic is loss of heterozygosity at chromosomes 1p and 19q.[2,3,13] Like *MGMT* promoter methylation, 1p/19q codeletion is associated with sensitivity to chemotherapy with alkylating agents and improved survival.[7,15,16,41] Codeletion of 1p/19q is also far more common in oligodendrogliomas than in astrocytic gliomas.[3,9] In our oligodendroglioma/mixed glioma dataset, women had a higher proportion of 1p/19q codeletion (61.5%) than men (59.2%), though this difference was not significant (P = .296). In our astrocytoma dataset, women had the same proportion of 1p/19q codeletion (7.2%) as men (7.0%) (P = 1.000).

There are several limitations to this study. First, the NCDB data are not population based, as the results cannot be generalized beyond the 1500 US hospitals included in the data collection. Nonetheless, because more than 70% of new patients with cancer are captured in the dataset, the results are representative across the United States and cover a higher proportion of the country than SEER. Second, there was a fair amount of missing data on important variables, such as KPS, *MGMT* promoter methylation status, and 1p/19q codeletion in the overall NCDB dataset. Thus GBM and non-GBM analyses were limited to patients with complete *MGMT* methylation and 1p/19q codeletion information, respectively, which restricted the sample sizes of both datasets. However, sensitivity
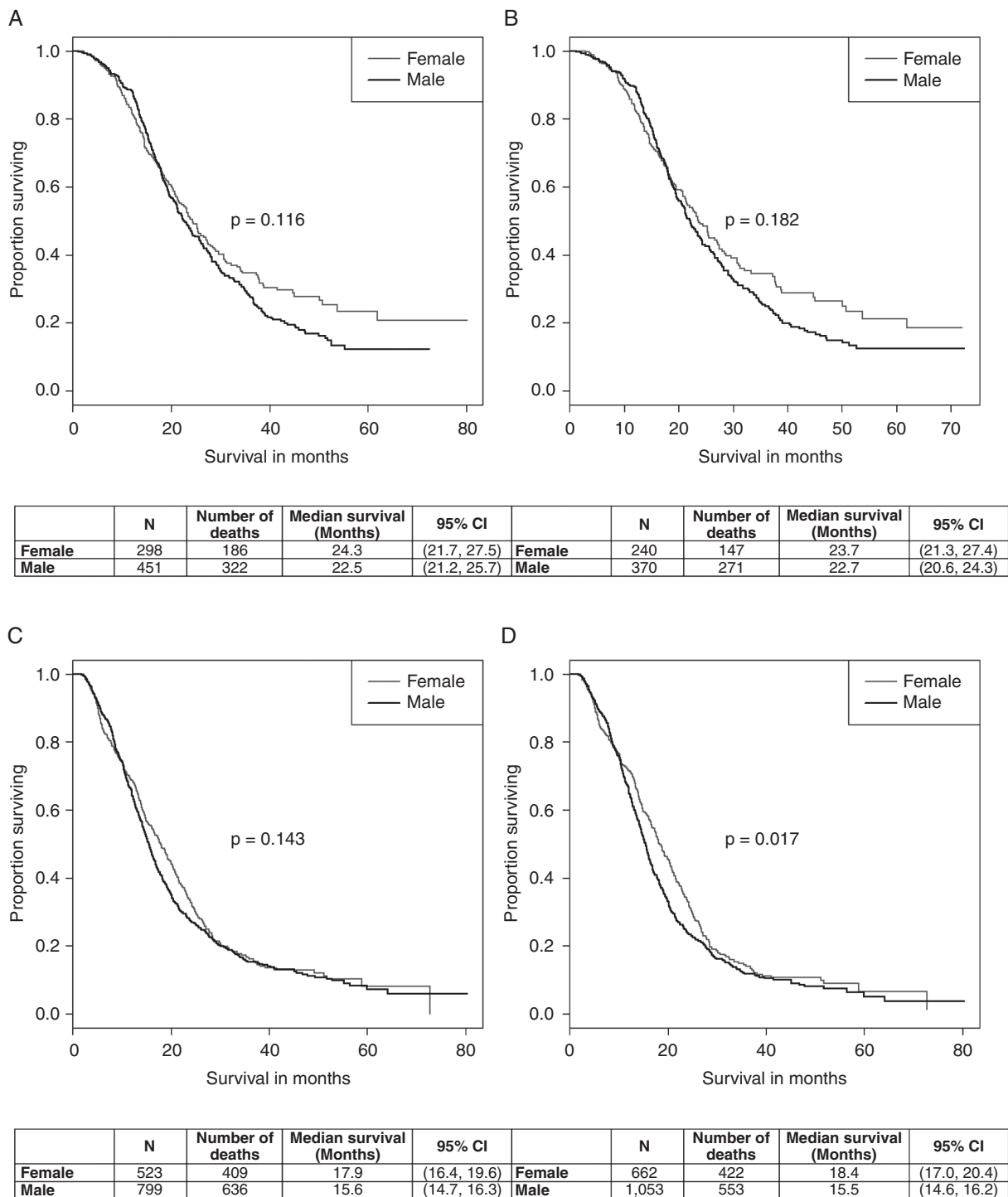
Fig. 3 Kaplan–Meier curves for glioblastoma survival by sex and stratified by age at diagnosis A, unadjusted (age 18-55), B, adjusted for age at diagnosis, surgical resection, KPS, O⁶-methylguanine-DNA methyltransferase (*MGMT*) methylation, primary payer, urban/rural, and tumor size (age 18-55), C, unadjusted (age 56+), and D, adjusted for age at diagnosis, surgical resection, KPS, MGMT methylation, primary payer, urban/rural, and tumor size (age 56+), National Cancer Database 2010-2014.

Panel A / B table:

	N	Number of deaths	Median survival (Months)	95% CI		N	Number of deaths	Median survival (Months)	95% CI
Female	298	186	24.3	(21.7, 27.5)	Female	240	147	23.7	(21.3, 27.4)
Male	451	322	22.5	(21.2, 25.7)	Male	370	271	22.7	(20.6, 24.3)

Panel C / D table:

	N	Number of deaths	Median survival (Months)	95% CI		N	Number of deaths	Median survival (Months)	95% CI
Female	523	409	17.9	(16.4, 19.6)	Female	662	422	18.4	(17.0, 20.4)
Male	799	636	15.6	(14.7, 16.3)	Male	1,053	553	15.5	(14.6, 16.2)

analyses were conducted to assess any potential difference in the distribution of missing data between men and women in the *MGMT* and 1p/19q variables. For GBM, the level of missingness in *MGMT* was not differentially distributed by sex (Pearson's chi-squared test P = .824 and area under the ROC curve 0.499 [95% CI: 0.492-0.507]). For non-GBM, the level of missingness of 1p/19q deletions was not differentially distributed by sex (Pearson's chi-squared
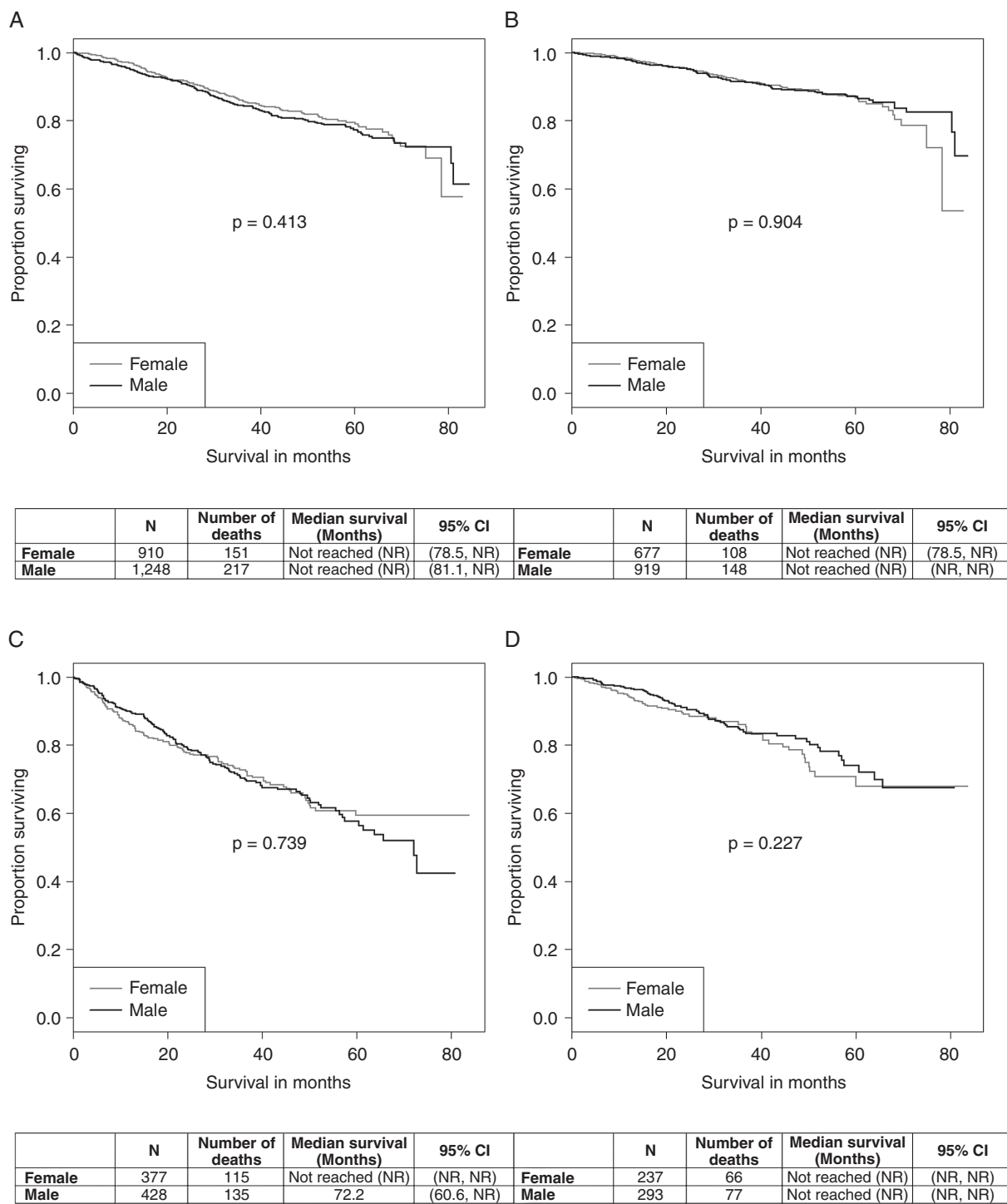
Fig. 4 Kaplan–Meier curves for nonglioblastoma survival by sex A, unadjusted (oligodendroglioma/mixed glioma), B, adjusted for age at diagnosis, surgical resection, KPS, 1p/19q codeletion, radiotherapy, chemotherapy, primary payer, urban/rural, tumor size, and Central Brain Tumor Registry of the United States (CBTRUS) histology (oligodendroglioma/mixed glioma), C, unadjusted (astrocytoma), and D, adjusted for age at diagnosis, surgical resection, KPS, 1p/19q codeletion, radiotherapy, chemotherapy, primary payer, urban/rural, tumor size, and CBTRUS histology (astrocytoma), National Cancer Database 2010-2014.

test *P* = .796 and area under the ROC curve 0.501 [95% CI: 0.493-0.509]). KPS had 76.2% missing data in the GBM set and 81.3% in the non-GBM set. We imputed KPS using multivariate imputation by chained equations using the "mice" R package,[35] which is powerful enough to handle this level of missing data in 1 variable. Third, unfortunately,
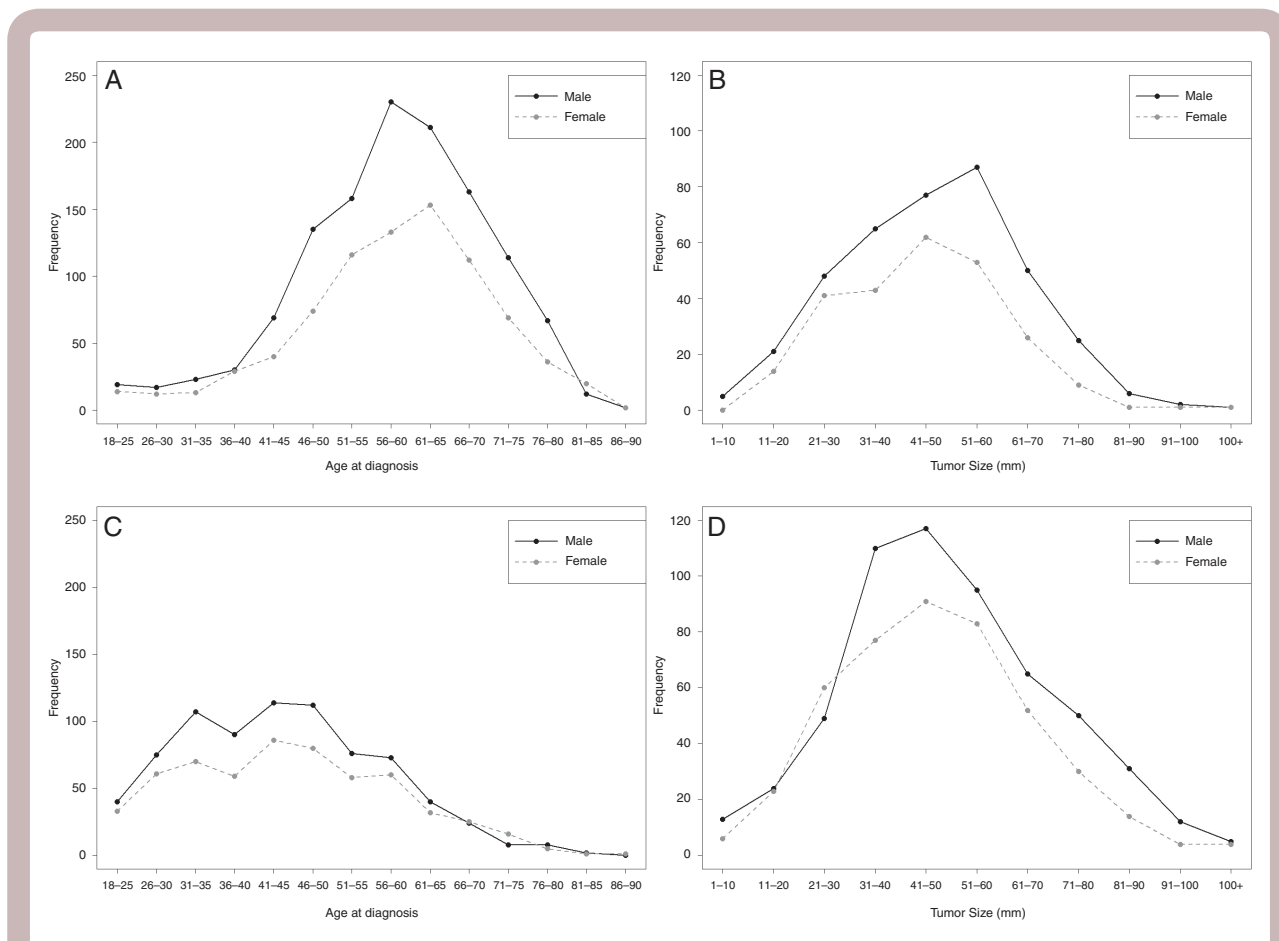
Fig. 5 Distribution by sex of A, glioblastoma (GBM) patient age at diagnosis, B, GBM patient tumor size, C, non-GBM patient age at diagnosis, and D, non-GBM patient tumor size, National Cancer Database 2010-2014.

we do not have information as to which agents (such as TMZ) were given; however, because the patients were all treated between 2010 and 2014, we assume the vast majority of these patients were given TMZ since this is the standard chemotherapy given for glioma. We do not know based on the coding of these data whether radiation therapy and chemotherapy were given concomitantly; however, they were both given as part of first course of treatment so we assume standard-of-care guidelines for glioma were followed for the majority of patients. Fourth, the biggest study limitation is that the NCDB does not provide any data on isocitrate dehydrogenase (*IDH*) mutation, which is an important prognostic variable. The 2016 CNS WHO restructured the definition of diffuse gliomas, incorporating new entities that are defined both by histology and molecular features, including GBM as either GBM *IDH*-wild type or GBM *IDH*-mutant.[42] However, although *IDH* mutations are associated with favorable outcome,[2,3,7,8,16,20] even *IDH*-mutant tumors show notable variability in overall survival, suggesting the likely contribution of additional influential molecular markers.[9] Moreover, *IDH* mutations have fairly low prevalence in GBM, with estimates ranging from about 5% to 12%,[1,3,9,13,15,20] so the vast majority of patients in our GBM dataset are likely *IDH*-wild type. For non-GBM, on the other hand, *IDH* mutations are found in a substantial majority of these cases,[1,9] presenting in approximately

50% to 80% of patients with non-GBM.[3,7,13,20] It is possible that adding *IDH* mutation to the non-GBM survival models would have changed the null results. It is also important to note that these hallmark genetic markers are neither mutually exclusive nor entirely independent.[13] For example, patients who have *IDH* mutations tend to be younger individuals.[3] *MGMT* methylation has been found to be highly associated with 1p/19q codeletion and *IDH* mutations.[13,20] To what extent the interaction of these molecular markers predict responsiveness to specific therapies or overall prognosis remains unclear.

In conclusion, the NCDB data demonstrate a notable female survival advantage in GBM, but not in non-GBM. Since the survival advantage occurred in the patients age ≥56 years, female survival advantage is not likely due to estrogen levels at the time of diagnosis. The reasons for this sex difference in survival for GBM are beyond the scope of this study, but will hopefully provoke future research into these devastating tumors.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice*.

Conflict of interest statement. None declared.

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