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Survival, costs, and health care resource use by line of therapy in US Medicare patients with newly diagnosed glioblastoma: a retrospective observational study

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Abstract

Background. Glioblastoma (GBM) is associated with poor prognosis, large morbidity burden, and limited treatment options. This analysis evaluated real-world treatment patterns, overall survival, resource use, and costs among Medicare patients with GBM.

Methods. This retrospective observational study evaluated Medicare patients age 66 years or older with newly diagnosed GBM using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from 2007 through 2013. Patients were followed from diagnosis to death or end of follow-up. An algorithm defined treatment patterns as lines of therapy (LOTs). The Kaplan-Meier method was used to estimate overall survival for the full sample as well as by LOT, surgical resection, Charlson Comorbidity Index (CCI), tumor size, and age. Resource use and costs during the follow-up period were reported in terms of total and per-patient-per-month (PPPM) estimates.

Results. A total of 4308 patients with GBM were identified (median age, 74 years; CCI of 0, 52%). The most commonly used first LOT was temozolomide (82%), whereas chemotherapy + bevacizumab was most prevalent for second-line (42%) and third-line (58%) therapy. The median overall survival was 5.9 months for resected patients and 3 months for unresected patients, with considerable heterogeneity depending on patient characteristics. A great proportion of patients had claims for an ICU admission (86.2%), skilled nursing facility (76.9%), and home health (56.0%) in the postdiagnosis period. The cumulative mean cost was $95 377 per patient and $18 053 PPPM, mostly attributed to hospitalizations.

Conclusions. Limited treatment options, poor survival, and economic burden emphasize the need for novel interventions to improve care for Medicare patients with GBM.

Keywords

costs | glioblastoma | line of therapy | resource use | survival.

Glioblastoma (GBM), formerly glioblastoma multiforme, is the most common adult malignant primary brain tumor, representing 54% of all gliomas and 45% of malignant primary brain and CNS tumors.[1] About half of patients who are newly diagnosed with GBM are older than 64 years. The annual incidence of GBM is 3.19 cases per 100 000 people in the United States and is greatest in patients age 75 to 84 years (15.03 cases per 100 000 people).[2,3]

Without intervention, patients with GBM die shortly after diagnosis.[4] The median overall survival (mOS) for patients with GBM dramatically increases with standard of care first-line (1L) treatment consisting of maximal safe resection followed by radiotherapy (RT) with concurrent temozolomide (TMZ), followed by adjuvant TMZ.[5] Based on their landmark clinical trial, Stupp et al reported a mOS of 14.6 months with RT plus TMZ and 12.1 months with RT

alone.[5] However, more than 50% of patients with GBM experience disease recurrence within 7 months of initiating 1L treatment.[6] Prognosis is even poorer for recurrent GBM, with a 6-month and 12-month OS rate of 60% to 70%[6–10] and 20% to 30%, respectively.[6,9,11–13] No standard of care has been established in the second-line (2L) setting.

Treatment of GBM in older patients is more challenging because of their poorer prognosis and higher comorbidities. In addition, older patients with GBM may have increased risk of brain toxicity due to RT[14]; however, there have been some studies suggesting reducing the dose and duration of RT, which may reduce toxicity without a significant impact on survival.[15,16] Because the trial by Stupp and colleagues excluded patients 70 years and older, no clear standard of care exists for older patients with GBM. A more recent clinical trial by Perry et al randomly assigned elderly patients with GBM to receive short courses of RT alone or RT with concomitant and adjuvant TMZ. They report a mOS of 9.3 months with RT plus TMZ and 7.6 months with RT alone.[17]

Although the economic burden of GBM has been previously studied,[18–23] the economic trajectories of patients with GBM receiving sequential lines of therapy (LOTs) during their disease have not been previously evaluated. This is relevant because the majority of patients will invariably require several (sequential) LOTs because of disease progression. Furthermore, it will be important to understand the economic impact of the traditional systemic therapies in the context of an evolving treatment landscape, including the evaluation of vaccination therapy, checkpoint inhibitors, T-cell therapies, combinations of immunotherapies, and tumor-treating field therapy.[24,25] This analysis was conducted to assess the real-world treatment patterns, overall survival, health care resource use (HCRU), and direct medical costs in US Medicare patients newly diagnosed with GBM.

Methods

Data Source

This study used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database between 2007 and 2013. The SEER-Medicare database links information from the US National Cancer Institute's 18 SEER cancer registries and Medicare claims data from the Centers for Medicare and Medicaid Services. The SEER program registry collects cancer incidence and mortality rates from 18 tumor registries across the United States covering 28% of the population.[26,27] This registry contains data on patient demographics, primary tumor site, tumor morphology, and follow-up for vital status. Medicare claims provide information on health care services that are provided to and covered for Medicare beneficiaries from the time of Medicare eligibility until death.

Sample Selection

Medicare patients age 66 years and older with histologically confirmed GBM, newly diagnosed between 2007 and 2013, were retrospectively identified from the database. Patients were followed from GBM diagnosis to death, Medicare disenrollment, health maintenance organization (HMO) enrollment, or December 31, 2014, whichever occurred first. Patients were included in the sample if they were diagnosed with GBM (*International Classification of Diseases for Oncology, Third Edition* [ICD-O-3] codes: 9440, 9441, 9442) as their primary cancer and with Medicare claims available starting from 12 months prior to diagnosis until the end of their follow-up. Patients were required to be age 66 years or older at the time of diagnosis (ie, 1 year after their Medicare age-based eligibility start) to allow for the 12 months of prediagnosis clinical information, such as baseline comorbidities. Patients were excluded if they 1) had an unknown diagnosis date, 2) received a postmortem GBM diagnosis, 3) had other cancer(s) in the 5 years prior to GBM diagnosis, 4) were not continuously enrolled in Medicare Parts A and B in the 12 months prior to GBM diagnosis, 5) were enrolled in an HMO in the 12 months prior to GBM diagnosis, 6) had more than 1 GBM cancer diagnosis on different dates, or 7) did not receive a diagnostic biopsy or surgery at any point during the study period.

Study Measures and Outcomes

Baseline Characteristics

The following baseline demographics and clinical characteristics were examined: age, sex, race, marital status, census location, urban location, tumor laterality, tumor extension, topographic location, and tumor size. A proxy for poor performance status was created and defined as having a claim indicating a walking aid, oxygen use, wheelchair, or hospice use in the baseline period. Comorbidities were calculated using the Charlson Comorbidity Index (CCI) during the 12-month prediagnosis period. Other comorbidities relevant to GBM but not part of the CCI were also reported, including thromboembolism, pulmonary embolism, Alzheimer disease, epilepsy, cerebral edema, coagulopathy, weight loss, fluid and electrolyte disorders, psychoses, and depression. In addition, the change in CCI and the other comorbidities was examined from baseline to the period following GBM diagnosis to understand the impact of GBM diagnosis on the burden of comorbidities, excluding cancer.

Treatment Patterns

Using Medicare claims data, LOTs were defined according to the following algorithm. The first systemic therapy (1L) was either chemotherapy or bevacizumab with or without concurrent RT use postdiagnosis. A subsequent LOT was defined as: 1) new systemic therapy added more than 30 days after the start date of the prior systemic therapy (if an additional systemic therapy of prior systemic therapy was added within 30 days or less it was considered a combination treatment regimen as part of the original treatment), or 2) the same systemic therapy resumed after a gap of more than 90 days between treatments.[28,29]

Treatment patterns of patients with GBM were analyzed in terms of the following treatment groups: 1) no cancer-related treatment (defined as no systemic therapy and/or radiation), 2) RT alone, 3) systemic therapies. Systemic therapies were evaluated in terms of the number and duration of LOTs designated as 1L, 2L, and 3 or more lines (3L+) of therapy.

Drugs or regimens were reported by LOT based on the following drug groupings: for 1L, TMZ, bevacizumab, systemic combination therapy, and other chemotherapy monotherapy; for 2L: TMZ, bevacizumab, chemotherapy + bevacizumab, other chemotherapy monotherapy, and chemotherapy combination; and for 3L: TMZ, bevacizumab, other chemotherapy monotherapy, bevacizumab + chemotherapy, and chemotherapy combination. Lastly, time from diagnosis to start of treatment, duration of each LOT, and time to next LOT were reported.

Overall Survival

Survival time was reported using the Kaplan-Meier method and stratified with respect to LOT. For patients who did not receive cancer-related treatment, survival time started on the GBM diagnosis date. For patients who received 1L or more, survival time started on the date of 1L initiation. For patients who received 2L or more, survival time started on the date of 2L initiation. The survival time ended at death or censoring for all LOTs. Median and 1-year survival estimates were reported by age, CCI, and tumor size among patients with GBM who had biopsy or resection.

Health Care Resource Use and Direct Medical Costs

HCRU and costs were reported in 3 distinct time periods relative to diagnosis: prediagnosis (12 months to 3 months before GBM diagnosis), peridiagnosis (3 months before GBM diagnosis), and postdiagnosis (GBM diagnosis month to end of follow-up). HCRU were reported in terms of proportion of patients with each HCRU and mean per-patient-per-month (PPPM) estimates. Costs were reported in terms of mean PPPM and cumulative costs over the follow-up period.

HCRU items that were queried included diagnostics (surgical biopsy, surgical resection, CT scan, and MRI scan of the brain), prescription drugs (antianxiety medication, anticonvulsant, antidepressant, antiemetics, proton pump inhibitor, sedatives/hypnotics, systemic steroids, and narcotic opioids), admissions (emergency room [ER], home health, hospice, hospital admission, ICU, and skilled nursing facility [SNF]), and supportive care (occupational therapy, physical therapy, psychological therapy, and speech therapy).

Costs (reimbursed amounts within Medicare claims) were classified in 2 ways. First, costs were reported by setting, that is, inpatient, outpatient, physician, durable medical equipment, home health agency, hospice, and Part D prescription drugs. Second, line-item costs for certain HCRU items (hospitalizations, surgical resection, surgical biopsy, systemic therapy, hospice stay, RT, MRI scan, ER admission, and CT scan) were reported.

Statistical Analysis

Descriptive statistics were used to evaluate baseline characteristics. For categorical variables, frequency and percentage distributions were reported. For continuous variables, mean, SD, median, and ranges were reported as appropriate. The Kaplan-Meier method for survival analysis was used to describe the time-to-mortality comparing different LOT groups, and the log-rank test was used to determine statistical significance. Median (1-year) survival and *P* values based on the log rank test were reported. The 95% CIs were reported using the Brookmeyer and Crowley methodology.[30] A multinomial logistic model was fit to identify patient factors that were predictive of receipt of RT alone, 1L, 2L, and 3L or more therapy (vs no cancer-related treatment) and odds ratios with 95% CI were reported. HCRU were reported in terms of PPPM estimates in each time period. Mean cumulative costs with bootstrapped 95% CI were reported over the entire study period and in each time period. Data analyses were performed using SAS 9.4 software (SAS Institute Inc). All significance tests were 2-sided, with a P value < .05 considered statistically significant.

Results

Baseline Characteristics

We identified 12 067 patients with histologically confirmed GBM as their primary cancer, diagnosed between 2007 and 2013. Among these, 4308 patients met the inclusion criteria (Supplementary Fig. S1). The median age at diagnosis was 74 years, 54.4% of the patients were male, 63.7% were married, 88.1% were non-Hispanic white, and 43.5% were in the West Census region. Prior to diagnosis 52.0% of patients had a CCI score of 0, and 25.5% had a poor performance proxy indicator (Table 1).

Change in Comorbidity Profile

The median CCI at baseline (in the year prior to GBM diagnosis) was 0 for all patients and increased to 2 in the postdiagnosis period (median follow-up time, 5.6 months postdiagnosis). The drivers of this increase in CCI were paralysis and dementia (Supplementary Table S1). Other comorbidities, not captured in the CCI, that increased significantly from baseline include thromboembolism (0.6% vs 6.8%), Alzheimer disease (1.9% vs 4.0%), epilepsy (8.8% vs 56.5%), cerebral edema (5.9% vs 65.3%), coagulopathy (2.1% vs 18.7%), weight loss (1.8% vs 13.8%), fluid and electrolyte disorders (9.0% vs 48.4%), psychoses (3.6% vs 13.1%), and depression (6.2% vs 21.7%).

Treatment Patterns

Among the patients in our sample, 2171 (50.4%) received systemic therapy ± RT, 1188 (27.6%) received RT alone, and 949 (22.0%) did not receive any cancer-related treatment (systemic therapy or RT). Among patients with GBM who received systemic therapy, 712 (32.8%) patients received

Table 1 Baseline Characteristics of Full Cohort and by Lines of Therapy

Patient Characteristics	Category	GBM Cohort (N = 4308)
Age at diagnosis, n (%), y	66-70	1259 (29.2)
	71-75	1175 (27.3)
	76-80	1021 (23.7)
	80+	853 (19.8)
Sex, n (%)	Male	2344 (54.4)
	Female	1964 (45.6)
Race/Ethnicity, n (%)	Non-Hispanic white	3797 (88.1)
	Non-Hispanic black	158 (3.7)
	Hispanic	231 (5.4)
	Other	122 (2.8)
Marital status at diagnosis, n (%)	Single (never married)	302 (7.0)
	Married	2746 (63.7)
	Separated/Divorced/Widowed	1126 (26.1)
	Unknown	134 (3.1)
Census location, n (%)	West	1872 (43.5)
	South	985 (22.9)
	Northeast	905 (21.0)
	Midwest	546 (12.7)
Urban location, n (%)	Rural	476 (11.0)
	Urban	3832 (89.0)
Charlson Comorbidity Index, n (%)	0	2239 (52.0)
	1	1125 (26.1)
	2	492 (11.4)
	3+	452 (10.5)
Poor performance status, n (%)	Yes	1097 (25.5)
Laterality, n (%)	Right side	1873 (43.5)
	Left side	1750 (40.6)
	Unknown or midline	685 (15.9)
Tumor extension, n (%)	Supratentorial tumor confined to 1 side	3069 (71.2)
	Confined to brain or meninges	243 (5.6)
	Confined to ventricles	161 (3.7)
	Tumor crosses the midline	596 (13.8)
	Unknown	83 (1.9)
	Other	156 (3.6)
Topographic location of tumor, n (%)	Frontal lobe	1185 (27.5)
	Temporal lobe	1136 (26.4)
	Parietal lobe	729 (16.9)
	Overlapping sites	613 (14.2)
	Cerebrum (except lobes)	395 (9.2)
	Occipital lobe	223 (5.2)
	Cerebellum	26 (0.6)
Tumor size, n (%)	Less than 50 mm	723 (16.8)
	Between 50 and 70 mm	2713 (63.0)
	Greater than 70 mm	210 (4.9)
	Missing	662 (15.4)
Diagnosis year, n (%)	2007	643 (14.9)

Table 1 Continued

Patient Characteristics	Category	GBM Cohort (N = 4308)
	2008	584 (13.6)
	2009	619 (14.4)
	2010	592 (13.7)
	2011	581 (13.5)
	2012	637 (14.8)
	2013	652 (15.1)

Abbreviation: GBM, glioblastoma.

2L or more, and 183 (25.7%) patients received 3L or more (Supplementary Fig. S2). The most commonly used 1L therapy was TMZ (83.2%). The most commonly used 2L and 3L was chemotherapy + bevacizumab (41.0% of 2L; 56.5% of 3L) followed by bevacizumab (35.7% of 2L; 22.6% of 3L; Fig. 1).

Patients with GBM initiated systemic treatment soon after diagnosis (median, 1.5 months). This median time was longer for patients who had resection compared with biopsy (1.1 vs 1.7 months). The median (interquartile range) duration of 1L, 2L, and 3L or more therapies was 2.4 (1.4-5.7), 3.2 (1.4-6.5) and 2.8 (1.4-4.8) months, respectively. The mean (SD) duration of 1L, 2L, and 3L or more therapies was 4.2 (4.5), 4.9 (5.5), and 3.8 (3.7) months, respectively. The median time from end of 1L to start of 2L was 6.4 months, and median time from end of 2L to start of 3L was 5.6 months. Beyond 1L, there was no clear treatment pathway with patients receiving various combinations of systemic therapy (Supplementary Fig. S3).

In terms of predictors of receipt of LOT, patients were more likely to get additional lines if they were younger at diagnosis, married, had a lower CCI score, did not have a poor performance status indicator, or had smaller tumor size at diagnosis (Supplementary Table S3).

Overall Survival

The mOS varied depending on whether patients received surgical resection, number of LOTs, age, CCI, and tumor size (Table 2). Resected patients had a mOS of 5.9 months from diagnosis compared with 3 months for patients who had a biopsy only. In patients without any cancer-related treatment, mOS was similar between resected (2.0) and biopsy (2.6) groups. In patients receiving RT alone, resected patients had a mOS of 3.6 months compared with 2.3 months for patients who had a biopsy. Among patients who received systemic therapy, resected patients had a mOS of 8.8 months from the start of 1L compared with 3.6 months for patients who had a biopsy only. From the beginning of 2L, resected patents had a mOS of 8 months compared with 6.5 months for patients who had a biopsy only. Tumor size, age, and CCI played an important role in the heterogeneity of mOS in resected patients through the first 2 lines of treatment.

Health Care Resource Use

In all patients, 71.8% of patients had a surgical resection and 28.2% had a biopsy (including 7.3% of patients who were coded both for biopsy and surgical resection the same day). Most patients used MRI and CT scans in the postdiagnosis period, with MRI scans being used more frequently on a PPPM basis (0.539 vs 0.379). However, the use of CT scans PPPM was lower because patients received more lines (0.29 for ≥1L, 0.21 for ≥2L, 0.17 for ≥3L). In contrast, PPPM MRI use remained relatively consistent (0.53 for ≥1L, 0.53 ≥ 2L, 0.55 for ≥3L) by the number of lines received, implying that MRIs are used routinely in clinical practice to monitor for progression (Fig. 2).

The proportion of patients who had an ER admission in the postdiagnosis period was 89.8% in all patients and was highest (97.3%) in patients who received at least 3L and lowest in patients who did not receive any LOT. Many (71.8%) patients went into hospice and most (98%) had a hospitalization in the postdiagnosis period. A great proportion of patients had ICU admission (86.2%), SNF (76.9%), and home health (56.0%) claims in the postdiagnosis period. It is also worth noting that the majority of ICU admissions (85%) and SNF admissions (49%) occurred during the month of diagnosis. Generally, across all admissions, the PPPM use went down as patients received additional LOTs.

In terms of supportive care, in descending order, many patients had physical (93.1%), occupational (84.4%), speech (71.7%), and psychological (11.7%) therapy in the postdiagnosis period. The use of prescription drugs in the postdiagnosis period was also prevalent in our sample. The most commonly used supportive prescription drug class was antiemetics (40.1%) followed by steroids (24.2%). As patients received more LOTs, the proportion of patients using prescription drugs in the postdiagnosis period increased. (Supplementary Table S2).

Direct Medical Costs

The mean cumulative (PPPM) cost for a Medicare GBM patient was $98 710 ($17 800) in the peri- and postdiagnosis periods, of which 58% was incurred in the inpatient setting. Among 1L+ patients, the postdiagnosis mean cumulative

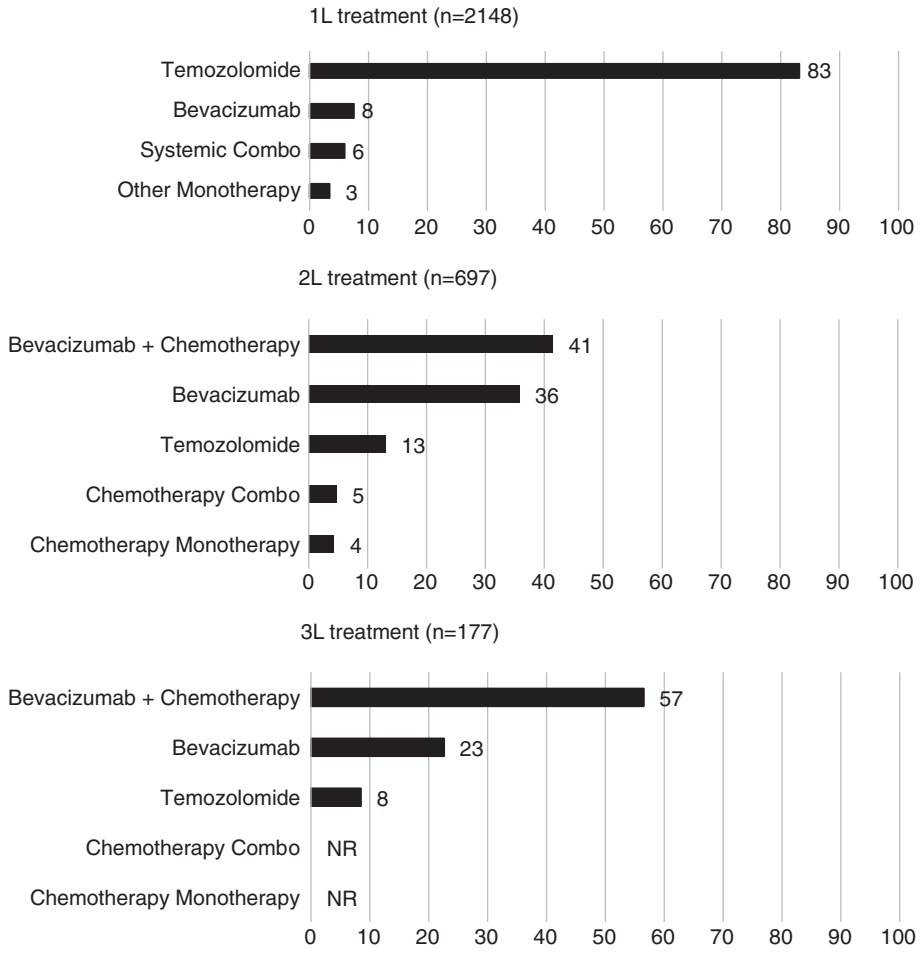

Fig. 1 Most commonly used treatments at each line of therapy (proportion of patients, %, in each line of therapy). NR indicates not reported because number of patients was either less than 11 or could be used to derive patient numbers less than 11.

(PPPM) cost was $124 138 ($13 041), of which 50% was in the inpatient setting. Patients receiving RT only had lower costs compared with patients receiving more than 1L systemic therapies ± RT ($79 009 vs $124 138; Table 3, Supplementary Fig. S4).

For all patients, the most costly resources from Medicare's perspective in terms of PPPM costs postdiagnosis were hospitalizations $10 698, surgical resection $5527, surgical biopsy $2138, systemic therapy $975, hospice stay $891, RT $685, MRI scan $153, CT scan $51, and ER admission $111.

Discussion

This large, real-world analysis of Medicare patients with GBM reveals several key findings. First, only one-half of Medicare GBM patients received at least 1L systemic therapy, and about one-third of those received a subsequent LOT. Second, this analysis also shows that there is heterogeneity in OS, with unresected patients having the worst survival. Although survival improves with the initiation of 1L systemic therapy, median OS remains less than 12 months. Third, GBM is a costly and resource-intensive disease. The mean cumulative costs for a Medicare GBM patient who received 1L systemic therapy was $124 138, of which 50% was incurred in the inpatient setting. Most of the costs were incurred during the month of diagnosis mostly because of inpatient costs (ie, surgical resection) involved at diagnosis. Many (72%) patients went into hospice, and most (98%) had a hospitalization in the postdiagnosis period. The proportion of patients having claims for physical therapy (93%), occupational (84%), and speech (72%) therapy was also high. Lastly, the comorbidity profile of patients with GBM worsens after a diagnosis of GBM, thus adding to the clinical burden of the disease.

The findings from the treatment patterns analysis were consistent with previous reports.[22,23,31–33] For example, a previous analysis using the same database found that 29% of patients with GBM did not receive TMZ and/or RT (compared with 28% in our analysis).[22] Another analysis in a commercially insured population showed that 59% of patients with GBM did not receive TMZ after brain surgery.[23] Our analysis showed that 50% of our sample did not

Table 2 Median Overall Survival (1-Year, Survival %) by Lines of Therapy and Surgical Resection/Biopsy

	All		No Cancer-Related Treatment		Radiation Alone		1L+		2L+	
	(n = 3646)		(n = 748)		(n = 1032)		(N = 1866)		(N = 609)	
	R	B	R	B	R	B	R	B	R	B
	n = 2660	n = 986	n = 414	n = 334	n = 787	n = 245	n = 1496	n = 370	n = 530	n = 79
Median follow-up time from diagnosis, mo	7.4	3.6	2.6	2.1	5.0	3.7	11.9	5.4	18.0	13.4
All patients	5.9 (26)	3.0 (8)	2.0 (0)	2.6 (3)	3.6 (13)	2.3 (4)	8.8 (38)	3.6 (16)	8.0 (31)	6.5 (22)
Tumor size (cm)										
<5	6.5 (32)[a]	3.6 (14)[a]	2.8 (4)[a]	2.3 (0)[a]	3.7 (17)[a]	2.5 (7.4)	10.1 (43)[a]	6.6 (25)[a]	8.4 (35)	8.1 (19)
5-7	5.9 (26)[a]	3.0 (7)[a]	2.7 (4)[a]	2.1 (0)[a]	3.8 (13)[a]	2.3 (3.5)	8.6 (37)[a]	3.2 (14)[a]	7.9 (30)	6.3 (26)
>7	3.8 (13)[a]	2.2 (4)[a]	2.0 (0)[a]	1.6 (0)[a]	2.7 (4)[a]	1.9 (0)	6.0 (26)[a]	2.5 (6)[a]	6.0 (25)	1.7 (0)
Age, y										
66-70	8.1 (36)[a]	3.1 (11)[a]	2.7 (7)	1.8 (0)	4.7 (19)[a]	3.1 (5)[a]	10.3 (44)[a]	3.8 (21)	8.1 (32)	6.9 (28)
71-75	6.4 (27)[a]	3.4 (8)[a]	2.7 (5)	2.3 (0)	4.3 (18)[a]	2.9 (7)[a]	8.4 (36)[a]	3.9 (13)	8.0 (30)	6.2 (19)
76-80	5.0 (21)[a]	3.1 (11)[a]	2.6 (0)	2.0 (0)	3.2 (10)[a]	2.2 (1)[a]	7.0 (32)[a]	3.9 (23)	7.3 (29)	7.6 (21)
≥80	4.0 (13)[a]	2.8 (4)[a]	2.5 (0)	2.0 (0)	2.6 (5)[a]	2.0 (3)[a]	6.6 (31)[a]	3.2 (10)	8.5 (38)	6.5 (14)
CCI										
0	6.8 (31)[a]	3.2 (10)	2.7 (4)	2.1 (0)	4.2 (15)[a]	2.8 (5)	10.1 (43)[a]	3.6 (19)	7.8 (30)	8.2 (29)[a]
1	5.9 (25)[a]	2.8 (6)	2.5 (0)	2.1 (0)	3.4 (13)[a]	1.9 (1)	8.1 (34)[a]	3.0 (14)	8.5 (35)	3.9 (0)[a]
≥2	4.2 (17)[a]	3.1 (6)	2.4 (4)	2.0 (0)	2.7 (9)[a]	2.0 (4)	6.4 (26)[a]	4.9 (14)	7.6 (27)	4.5 (21)[a]

Abbreviations: R, surgical resection; B, biopsy only; CCI, Charlson Comorbidity Index; 1L+, received first line of systemic therapy; 2L+, received second line of systemic therapy. Time starts from diagnosis date from the untreated and from the start of the line in the treated (1L+ starts from start of first line; 2L+ starts from start of second line).
[a]Statistical significance ($P < .05$) among categories of tumor size, age, and CCI.

receive *any* systemic therapy, although results should not be directly compared because the authors of the prior analysis examined only TMZ receipt in a commercially insured patient population whereas the current analysis is specifically focused on Medicare patients with GBM. Future research is needed to explain why 1 in 2 Medicare patients with GBM does not receive any systemic therapy. It will be interesting to see whether the proportion of untreated patients and the patterns of treatments in the real-world setting evolve as more evidence about the role of novel therapies in the overall management of GBM becomes available. Of note, this analysis found that the median duration of 1L (mostly TMZ) therapy was 2.4 months, which is shorter than the conventional (6 cycles of 28 days) or extended (12 cycles of 28 days) adjuvant TMZ regimen. There are 2 potential reasons for this. First, as documented by our analysis, older patients have poor survival and therefore may not live long enough to finish their treatment. Second, a prior analysis has shown that 75% of older patients discontinued adjuvant TMZ therapy because of progression, bone marrow toxicity, or fatigue.[34] The same analysis shows that only 25% of older patients get to complete all 6 cycles.[34] Similarly, 2 prior analyses in the older population have found the median number of TMZ cycles received were 2[35] and 4,[36] respectively. The median duration of 2L (mostly bevacizumab) therapy was 3.2 months, which is longer than 1L. There could be 2 reasons for this. First, bevacizumab has not been shown to improve survival[37,38] and is given mostly for palliation. Second, pseudoresponse from bevacizumab-based therapies could potentially mean that patients stay on bevacizumab longer.[39]

Survival in GBM has always been poor; however, real-world studies have compared survival rates in the eras pre– and post–TMZ approval and pre– and post–bevacizumab approval. These analyses found that the timing of survival improvement overlapped with the approval of TMZ and bevacizumab.[10,40,41] Our survival estimates closely resemble previous reports and prognostic studies.[22,32,33]

The economic burden of GBM has been examined previously both in commercial and Medicare claims. A prior analysis using commercial claims demonstrated that the average total costs in the 6 months postsurgery were $106 896, ranging from $79 099 for patients who received neither TMZ nor radiation to $138 767 for those who received both therapies.[23] In another analysis that used commercial claims, mean total cumulative costs per patient from 3 months prediagnosis to 12 months and to 5 years postdiagnosis were $201 749 and $268 031, respectively.[18] In a third analysis by Burton et al that focused on Medicare patients, the mean payer-reported treatment cost following diagnostic surgery for all patients was $60 380, and ranged from $38 600 in patients who did not receive RT or TMZ as initial treatment following diagnostic surgery to $103 762 for patients treated after surgery with RT plus TMZ.[22] Our

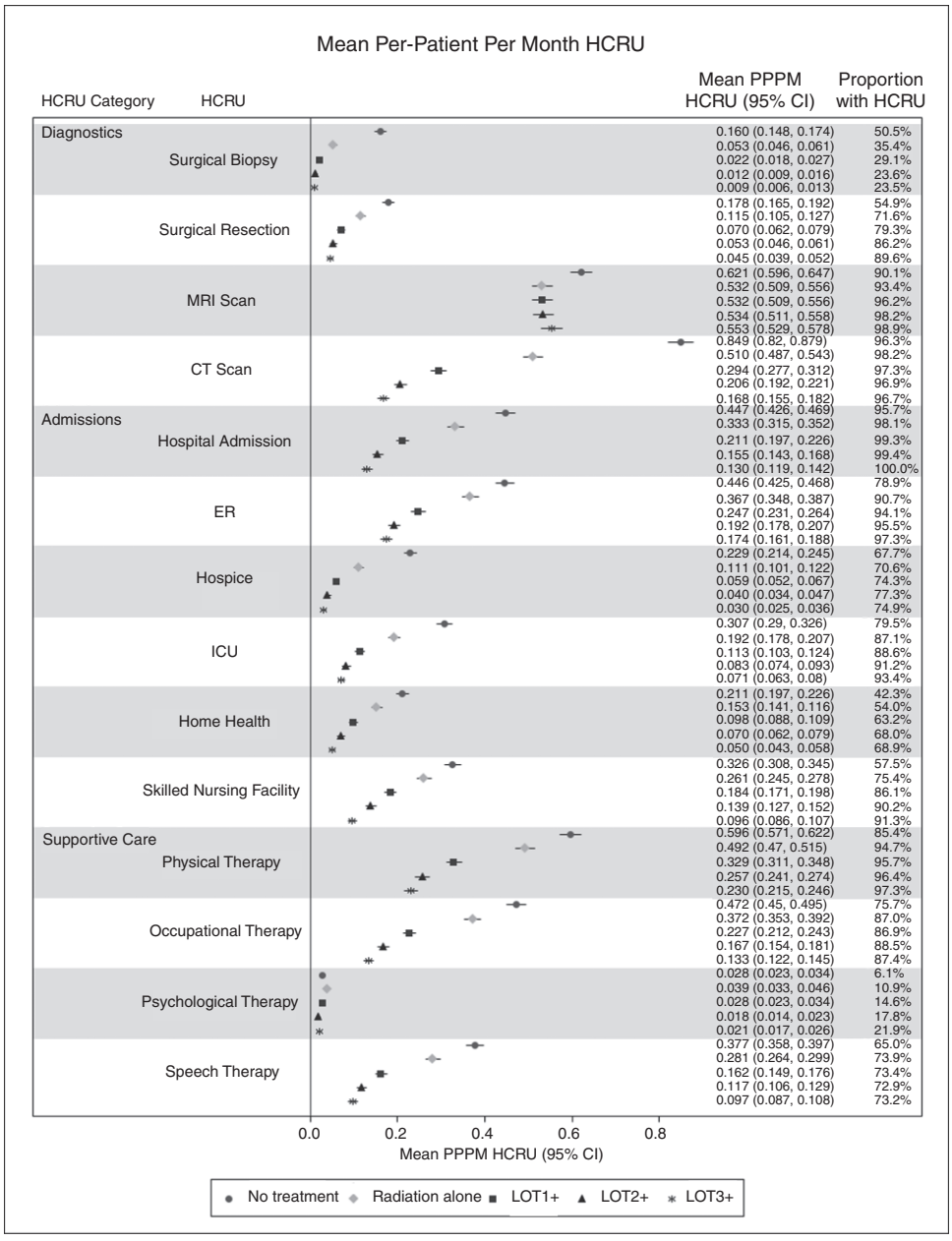

Fig. 2 Per-patient-per-month HCRU of diagnostics, admissions, and supportive care in patients with glioblastoma receiving no systemic therapy, 1 or more lines, 2 or more lines, and 3 or more lines. ER indicates emergency room; HCRU, health care resource use; ICU, intensive care unit; PPPM, per-patient-per-month.

cumulative mean cost estimate for our analysis was higher than Burton and colleagues ($95 377 vs $60 380). There may be 2 possible reasons for this. First, the prior analysis' timing spanned a period during which bevacizumab was not yet approved (1997 to 2009). Second, the proportion of untreated patients was higher compared with our analysis (29% vs 25%), which will cause the mean cost to increase as more patients receive some form of treatment.

The use of certain supportive prescription drugs in Medicare patients underscored the resource-intensive nature of GBM. Previous reports did not provide consistent estimates around supportive care use.[20,42] A 2015 United States–based analysis of chart data in patients who received 1L and 2L therapy reported a somewhat higher proportion of patients receiving prescription drugs compared with our estimates: corticosteroids (85% vs 61%), antiepileptics (51% vs 23%), narcotic opioids (49% vs 35%), proton pump inhibitors (48% vs 8%), and antidepressants (26% vs 16%).[20] The Glioma Outcomes Project conducted in academic and community practices in 2005 has reported higher corticosteroid use, antiepileptic use, and lower antidepressant use.[42] Owing to the differences in time periods, age groups studied, and data sources, it would be challenging to compare these estimates.

Table 3 Cumulative Per-Patient and PPPM Costs in US$ (% Total) in the Pre-, Peri, and Postdiagnosis Periods

	Prediagnosis		Peridiagnosis		Postdiagnosis									
	All Patients (n = 4308)		All Patients (n = 4308)		No Cancer-Related Treatment (n = 949)		Radiation Therapy Alone (n = 1188)		1L+ (n = 2171)		2L+ (n = 712)		3L+ (n = 183)	
Cost Category	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%	Cost	%
Cumulative Costs														
Total costs	$4887	100	$3505	100	$50 072	100	$79 009	100	$124 138	100	$165 801	100	$208 665	100
Inpatient	$2036	42	$2101	60	$40 668	81	$55 414	70	$61 583	50	$67 230	41	$74 987	36
Outpatient	$736	15	$373	11	$765	2	$6370	8	$22 334	18	$41 580	25	$65 496	31
Physician	$1028	21	$555	16	$2877	6	$7491	9	$13 159	11	$19 195	12	$23 050	11
DME	$128	3	$49	1	$184	0	$533	1	$13 106	11	$20 256	12	$25 789	12
Hospice	$0	0	$0	0	$4373	9	$6096	8	$6617	5	$7260	4	$5695	3
Home health	$178	4	$116	3	$668	1	$2412	3	$4470	4	$5729	3	$6136	3
Prescription drugs	$782	16	$311	9	$537	1	$692	1	$2870	2	$4552	3	$7511	4
PPPM Costs														
Total costs	$543	100	$1168	100	$21 617	100	$17 760	100	$13 041	100	$9821	100	$8332	100
Inpatient	$226	44	$700	60	$18 217	84	$13 631	77	$7396	57	$4229	43	$3290	39
Outpatient	$82	14	$124	11	$293	1	$1108	6	$1798	14	$2238	23	$2617	31
Physician	$114	23	$185	16	$1231	6	$1445	8	$1341	10	$1301	13	$1162	14
DME	$14	3	$16	1	$74	0	$109	0	$1266	10	$1128	11	$1003	12
Hospice	$0	0	$0	0	$1978	9	$1020	6	$604	5	$394	4	$247	3
Home health	$20	4	$39	3	$190	1	$379	2	$461	4	$355	4	$282	3
Prescription drugs	$87	12	$104	9	$121	1	$68	0	$175	1	$177	2	$232	3

Abbreviations: 1L, first line; 2L, second line; 3L, third line; DME, durable medical equipment; PPPM, per-patient-per-month.

This analysis has several key strengths. First, it used a nationally representative database that represents the older US population with GBM. Second, our analysis is unique in that it provided a range of survival estimates that represented the heterogeneity of GBM survival outcomes. Third, this analysis estimated the costs of common health care resources used by patients with GBM and quantified the costs incurred, identifying the major cost drivers. Previous analyses using commercial claims focused on characterizing HCRU and costs among TMZ-treated patients.[18,23] Our study, on the other hand, has also quantified the economic burden of patients who did not receive systemic therapy, which represents one-half of Medicare patients presenting with GBM. This was possible because we used the ICD-O-3 coding system available from SEER (as opposed to the nonspecific ICD-9-CM coding system available in claims). Fourth, because costs for GBM treatment were established in the literature, we wanted to describe the resources used by these patients relative to their diagnosis from a payer's perspective. Our analysis is unique in that we observed a significant amount of costs incurred before patients were diagnosed with GBM.

Some of the potential limitations of the analysis include the possibility of misclassification of treatments when defining LOT. This analysis used Medicare payer claims, which are generated for the purposes of provider reimbursement and not necessarily for research purposes. For example, a combination of algorithms and clinical expertise was used to define LOT and as a result, certain patients may have been misclassified. Similarly, use of claims to define clinical events are not ideal. For example, the increased Alzheimer disease from pre- to postdiagnosis may be miscoded as cognitive decline related to therapy and/or tumor. In addition, some of the results presented here may not be generalizable to younger patients with GBM given that the population studied was younger than 66 years. Additionally, O6-methylguanine–DNA methyltransferase (*MGMT*) promoter methylation was not analyzed because it was not available in the dataset.[43] *MGMT* promoter methylation has been associated with longer survival in patients with GBM who receive TMZ. It is a major consideration in treatment decision making based on NOA-08, NORDIC, and post hoc analyses of the Stupp and Perry trials.[17,44–46] Lastly, we were able to highlight treatment patterns only through December 2014, the latest year of data availability at the time of the analysis.

As the GBM treatment landscape evolves with the initiation of clinical trials to study novel treatment options, this analysis can provide a benchmark for the current standards of care and relative costs associated with GBM treatment across different lines of systemic therapy in the United States. The limited treatment options, poor survival outcomes, and substantial economic burden demonstrate the importance of identifying new innovative treatment options for patients with GBM, especially for the older population.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. AA and YLL were employees of Pharmerit International during this study. MB and HPK are current employees of Pharmerit International; MFB is also a shareholder of Pharmerit International. PS, BK, Y-LL, and HD are employees of and have stock options in BMS. AN is an employee of and has stock options in Cota Healthcare, Inc, New York, NY.

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