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Age-stratified comorbid and pharmacologic analysis of patients with glioblastoma

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ABSTRACT

Background: Increased age is a strong and unfavorable prognostic factor for patients with glioblastoma (GBM). However, the relationships between stratified patient age, comorbidities, and medications have yet to be explored in GBM patient survival analyses.

Objective: To evaluate co-morbid conditions, tumor-related symptoms, medication prescriptions, and subject age for patients with GBM and to establish potential targets for prospective studies.

Methods: Electronic health records for 565 patients with IDHwt GBM were evaluated at a single center between January 1, 2000 and August 9, 2021 were retrospectively assessed. Data were stratified by MGMT promoter methylation status when available and were used to construct multivariable time-dependent cox models and intra-cohort hazards.

Results: Younger (<65 years of age) but not older (≥65 years) GBM patients demonstrated a worse prognosis with movement related disabilities ($P < 0.0001$), gait/balance difficulty ($P = 0.04$) and weakness ($P = 0.007$), as well as psychiatric conditions, mental health disorders ($P = 0.002$) and anxiety ($P = 0.001$). In contrast, older but not younger GBM patients demonstrated a worse prognosis with epilepsy ($P = 0.039$). Both groups had worse survival with confusion/altered mental status ($P = 0.023$ vs < 0.000) and an improved survival with a Temozolomide prescription. Older but not younger GBM patients experienced an improved hazard with a prescription of ace-inhibitor medications ($P = 0.048$).

Conclusion: Age-dependent novel associations between clinical symptoms and medications prescribed for co-morbid conditions were demonstrated in patients with GBM. The results of the current work support future mechanistic studies that investigate the negative relationship(s) between increased age, comorbidities, and drug therapies for differential clinical decision-making across the lifespan of patients with GBM.

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1. Introduction

Glioblastoma (GBM) is an aggressive primary brain tumor that can present at any age but is primarily diagnosed in older adults ≥65 years of age. The median age of a GBM diagnosis is 68–70 years old with a peak incidence among individuals who are 70–79 years of age (Kim et al., 2021). Increased age is a negative prognostic factor for patients with GBM. The U.S. Census Bureau estimates that the elderly population will increase to nearly 70 million individuals by the year 2030 (Yancik, 2005) which will enhance the risk for more older adults to develop GBM. Understanding the biological determinants that contribute to the negative relationship between increased GBM patient age and decreased survival is an understudied area of research. Younger and older adults differ with respect to immune competency, number and severity of co-morbid conditions, as well as treatments including medication usage that may influence patient care (Avorn, 1995). Age and age-related changes involving polypharmacy, co-morbid conditions, and frailty affect patient tolerance arising from treatments with therapy. There are a number of studies that have characterized the relationship(s) between GBM patient co-morbidities (Carr et al., 2019), medications (Knudsen-Baas et al., 2021; Caudill et al., 2011; Otto-Meyer et al., 2020) and survival. However, an investigation into the potential enrichment of these considerations by specific age group has not been performed. This study aimed to examine potential relationships between age, co-morbidities, and prescription medications that stratify with survival outcomes in GBM patients for establishing targets that can be mechanistically interrogated in future clinical trials.

2. Materials and methods

2.1. Inclusion criteria

Patient records from the Northwestern Medicine Enterprise Data Warehouse (NMEDW) containing electronic health records for all clinical and research data sources at Northwestern Medicine were retrospectively extracted and analyzed. Data was queried in September 2021, and included all records of patients who were diagnosed with "GBM" between January 1st, 2000, and September 8th, 2021. A diagnosis of GBM was made based on a pathological assessment of surgical specimens per definitions of new molecular classifications introduced in 2021 (Louis et al., 2021). This study was approved by the Northwestern University Institutional Review Board (IRB). Informed consent was not required since all patient data analyzed was de-identified and therefore this work was considered non-human subject research. Inclusion criteria required complete evidence of: (i) ≥18 years of age, (ii) a pathology-confirmed diagnosis of GBM, (iii) extent of tumor resection, and (iv) patient status at time of data collection. Date of pathological diagnosis with GBM was used as the start time. Date of death was used to define event time. Patients that were alive or lost to follow-up were censored to last recorded date. Survival time was calculated as the difference between diagnosis date and event time or censorship (Fig. 1).

2.2. Cohort descriptive variables

Profiled demographic, clinical, and tumor-related information included: the age at diagnosis, days of follow-up time, date of death, date of last follow-up, sex, race, ethnicity, diagnosis, surgical procedure. Information taken at or close to the time of surgery included: Charlson comorbidity index (CCI), Karnofsky Performance Status (KPS), body mass index (BMI), marital status, smoking, depression diagnosis, and anxiety diagnosis. Profiled patient tumor characteristics included: isocitrate dehydrogenase (IDH) mutation status, O (6)-methylguanine-DNA methyltransferase (MGMT) methylation status, anatomical tumor location, ki67 status, and p53 status (Table 1). Patient comorbidities and symptoms were extracted from the electronic health record past medical history based on ICD-10 diagnosis codes and then separated into categories for analysis (Supplementary Table 1) which included arthritis, autoimmune disease, bone disease, cardiovascular disease, diabetes, eye/visual problems, gastrointestinal disease (GI), hypertension (HTN), kidney abnormalities, lipid metabolism, mental health conditions, mood disorder, anxiety disorder, movement related disability including subcategories of gait and balance, hemiparesis, plegia, neurocognitive manifestations with subcategories of confusion-altered mental status (AMS), memory loss + cognitive impairment, weakness, other cancer diagnosis, pulmonary disease, seizure disorder, thyroid abnormalities, and vocal communication problem. If the condition resolved prior to a diagnosis of GBM, patients were censored from the analysis of that condition. Profiled tumor associated and general symptoms included deep venous thrombosis/pulmonary embolism (DVT/PE), fatigue, headache, incontinence, epileptic and non-epileptic seizure, and sleep disturbance. Profiled medications were limited to outpatient prescription orders and included both generic and primary brand names (Supplementary Table 2) reflecting selective norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), atypical antidepressants, tricyclic antidepressants (TCAs)/monoamine oxidate inhibitors (MAOIs), anti-convulsant medications, generalized anxiety medications (Buspar), benzodiazepines, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), beta-blockers, digoxin, diuretics, corticosteroids, and temozolomide (TMZ). Specific medications within each drug class were treated as equal medications (ie. escitalopram and sertraline were grouped together as SSRIs). Start time was identified as the prescription initiation time while the end time reflected the end date for medication usage according to the electronic medical record, date of death, or last follow-up. If prescriptions started before a GBM diagnosis, start time was re-calculated to the date of cancer diagnosis.

2.3. SEER database

Northwestern Memorial hospital is a large tertiary center with a potentially different patient population than is recorded in national

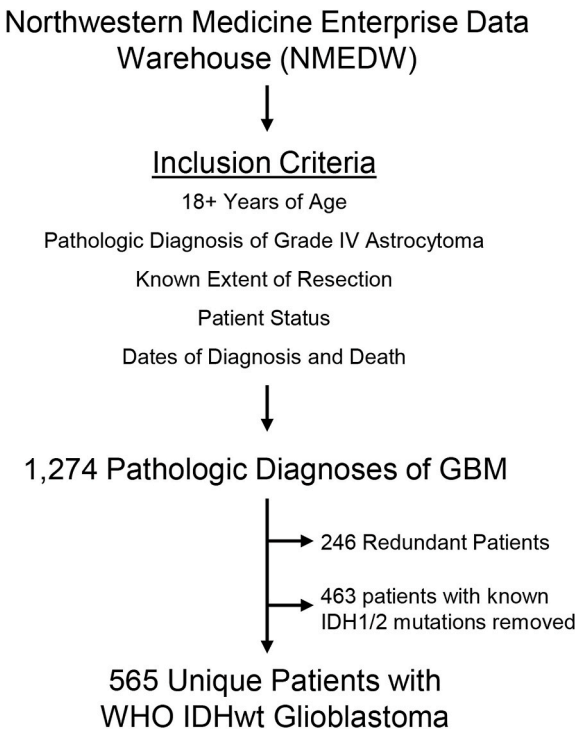

Fig. 1. Inclusion and exclusion criteria for the analysis of human subjects diagnosed with glioblastoma. All patients were pathologically diagnosed in the Northwestern Medicine system.

Table 1
Cohort demographics and tumor characteristics separated by age group. Left column: Combined ages, Middle: 18–64 years, Right: 65+ years. CCI: Charlson Comorbidity Index, KPS: Karnofsky Performance Status, BMI: Body Mass Index, IDH: Isocitrate Dehydrogenase, MGMT: O^6-methylguanine-DNA-methyltransferase.

Patient Characteristics			Median or n (%)
	Total	**18–64 years of age**	**65 + years of age**
Follow-up time	0.94 (0.01–8.51)	1.06 (0.01–8.51)	0.81 (0.00–6.68)
Deceased	396 (70%)	220 (66%)	176 (76%)
Gender: Male	321 (57%)	198 (60%)	123 (53%)
Female	244 (43%)	134 (40%)	110 (47%)
Race: White	426 (94%)	252 (95%)	174 (94%)
Black or African American	26 (6%)	14 (5%)	12 (7%)
Ethnicity: Hispanic or Latino	481 (95%)	19 (6%)	6 (3%)
Not Hispanic or Latino	25 (5%)	284 (94%)	197 (97%)
Procedure: Biopsy	79 (14%)	48 (15%)	31 (13%)
Resection	485 (86%)	283 (85%)	202 (87%)
CCI: Mild (1–2)	244 (44%)	135 (41%)	109 (48%)
Moderate (3–4)	183 (33%)	108 (33%)	75 (33%)
Severe (>4)	127 (23%)	84 (26%)	43 (19%)
KPS: (10–70)	107 (26%)	64 (24%)	43 (29%)
(80–100)	312 (74%)	205 (76%)	107 (71%)
Median BMI	27.0 (16.6–68.4)	27.3 (16.6–68.4)	26.5 (16.8–55.0)
BMI: Normal	169 (31%)	95 (30%)	74 (33%)
Underweight	6 (1%)	4 (1%)	2 (0%)
Overweight	207 (38%)	119 (37%)	88 (39%)
Obese	168 (30%)	103 (32%)	60 (27%)
Marital Status: Married	384 (76%)	228 (74%)	156 (78%)
Single	103 (20%)	68 (22%)	35 (18%)
Divorced	19 (4%)	11 (4%)	8 (4%)
Smoking: Current	81 (16%)	52 (18%)	29 (14%)
Former	100 (20%)	48 (16%)	52 (25%)
Never	322 (64%)	197 (66%)	125 (61%)
Depression: Yes	141 (25%)	82 (25%)	59 (25%)
Unknown	424 (75%)	250 (75%)	174 (75%)
Anxiety: Yes	124 (2%)	84 (25%)	40 (17%)
Unknown	441 (78%)	248 (75%)	193 (83%)
MGMT Unmethylated	237 (62%)	155 (65%)	82 (57%)
Methylated	145 (38%)	83 (35%)	62 (43%)
Frontal lobe L	86 (24%)	51 (24%)	35 (24%)
R	101 (28%)	66 (31%)	35 (24%)
Temporal lobe L	92 (26%)	55 (26%)	37 (26%)
R	76 (21%)	40 (19%)	36 (25%)
ki67 < 20	134 (28%)	74 (26%)	60 (30%)
≥ 20	350 (72%)	211 (74%)	139 (70%)
P53 < 20	295 (72%)	170 (70%)	125 (76%)
≥ 20	114 (28%)	74 (30%)	40 (24%)

databases. For transparency and comparative purposes, we also queried the GBM patient population, incidence, and mortality data from the Surveillance of Epidemiology and End Results Database (SEER) through SEER * Stat (Version 8.3.5). A rate session was accessed to collect incidence and mortality data and included age, year of diagnosis, histology and the frequency of GBM patients per age group (Fig. 2).

2.4. Statistical analysis

Demographics and baseline clinical features were summarized by major age group that spanned 18–64 years of age and 65+ years of age while using descriptive statistics including median and range for continuous variables, as well as count and percentage for categorical variables. Histogram with percentages were used to compare the age distribution between the NMEDW data and the SEER data for patients with GBM (Louis et al., 2021). We compared the overall survival between different age groups using Kaplan-Meier curves and calculated p-values for pairwise comparisons using the Logrank test. Furthermore, we conducted analyses for baseline clinical factors, co-morbidities, and

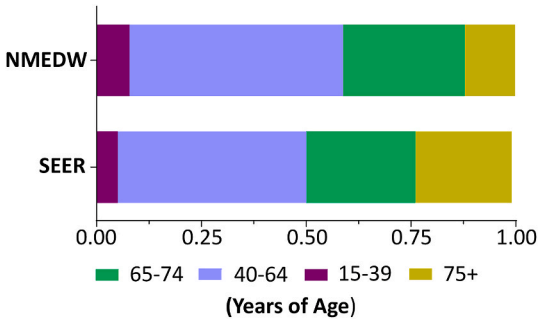

Fig. 2. Comparison of frequency for different age groups among the Surveillance, Epidemiology, and End Results (SEER) database and the Northwestern Medicine Enterprise Data Warehouse (NMEDW) database for patients with a diagnosis of glioblastoma (GBM). Human subjects aged 18–39 years old (purple), 40–64 years old (blue), 65–74 (green), and 75+ (yellow) are represented as different fractions of a total population.

14 types of psychosocial modifier medications for the total cohort and among stratified age groups. For the baseline clinical factor analysis, we utilized Kaplan-Meier curves to determine overall survival and the Logrank test for pairwise comparisons between groups. For the co-morbidity and psychosocial modifier analysis, we treated each co-morbidity or psychosocial modifier as time-dependent variables in a Cox regression that adjusted for baseline covariates and presented hazard ratios with their confidence intervals and p-values from the Cox regression model in forest plots.

3. Results

In total, 565 patients met the inclusion criteria and their data was analyzed (Fig. 1). There were 332 patients (59%) in the younger cohort (18–64 years of age) and 233 patients (41%) in the older cohort (≥65 years of age). The mean age and standard deviation of NMEDW-affiliated GBM patients at the time of diagnosis was 60 ± 13 years of age and patients were followed for a median 0.94 years. The distribution was significantly different than GBM patients analyzed in the SEER database ($P < 0.0001$) and confirms that the NMEDW cohort is primarily younger than a national sample (Fig. 2). At the time of data collection, 30% of GBM patients were alive at last follow-up. (Fig. 3). For the 18–64

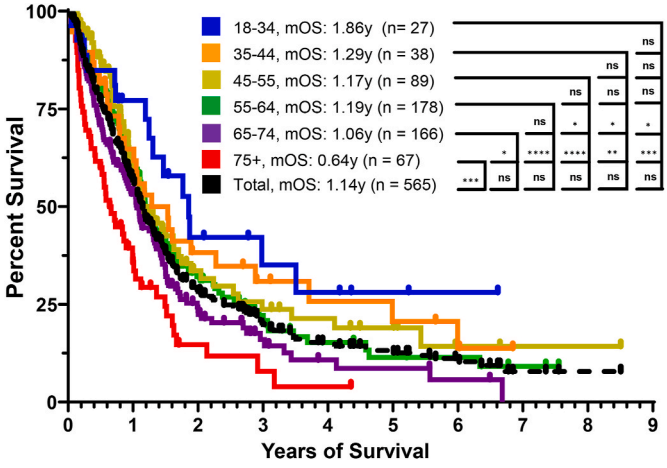

Fig. 3. Age-stratified survival of pathologically diagnosed patients with glioblastoma based on data in the Northwestern Medicine Enterprise Data Warehouse. Patients shown as Kaplan-Meier curves are 18–34 years old (blue), 35–44 years old (orange), 45–55 years old (yellow), 55–64 years old (green), 65–74 years old (purple), 75+ years old (red), and the total population (black). mOS: Mean Overall Survival. ns: not significant. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

years of age GBM patient cohort, six-month, 1-year, and 5-year survival was 75.3%, 52.4%, and 5.4%, respectively. These numbers were reduced at the six-month, 1-year, and 5-year survival for GBM patients ≥65 years of age and were 58.3%, 39.9%, and 2.1%, respectively.

As expected, patient survival followed the known trends associated with MGMT promoter methylation. While resection demonstrated improved short- and long-term survival in younger patients, this was not significantly demonstrated in older patients. (Fig. 4A–D). A baseline KPS of >70 is a positive predictor for longer survival in older, but not younger adults (Fig. 4E and F). (Bruno et al., 2022) Functional status was evaluated and dichotomized into KPS of 10–70 and KPS of 80–100.76% of patients with known KPS scores were 80–100. When

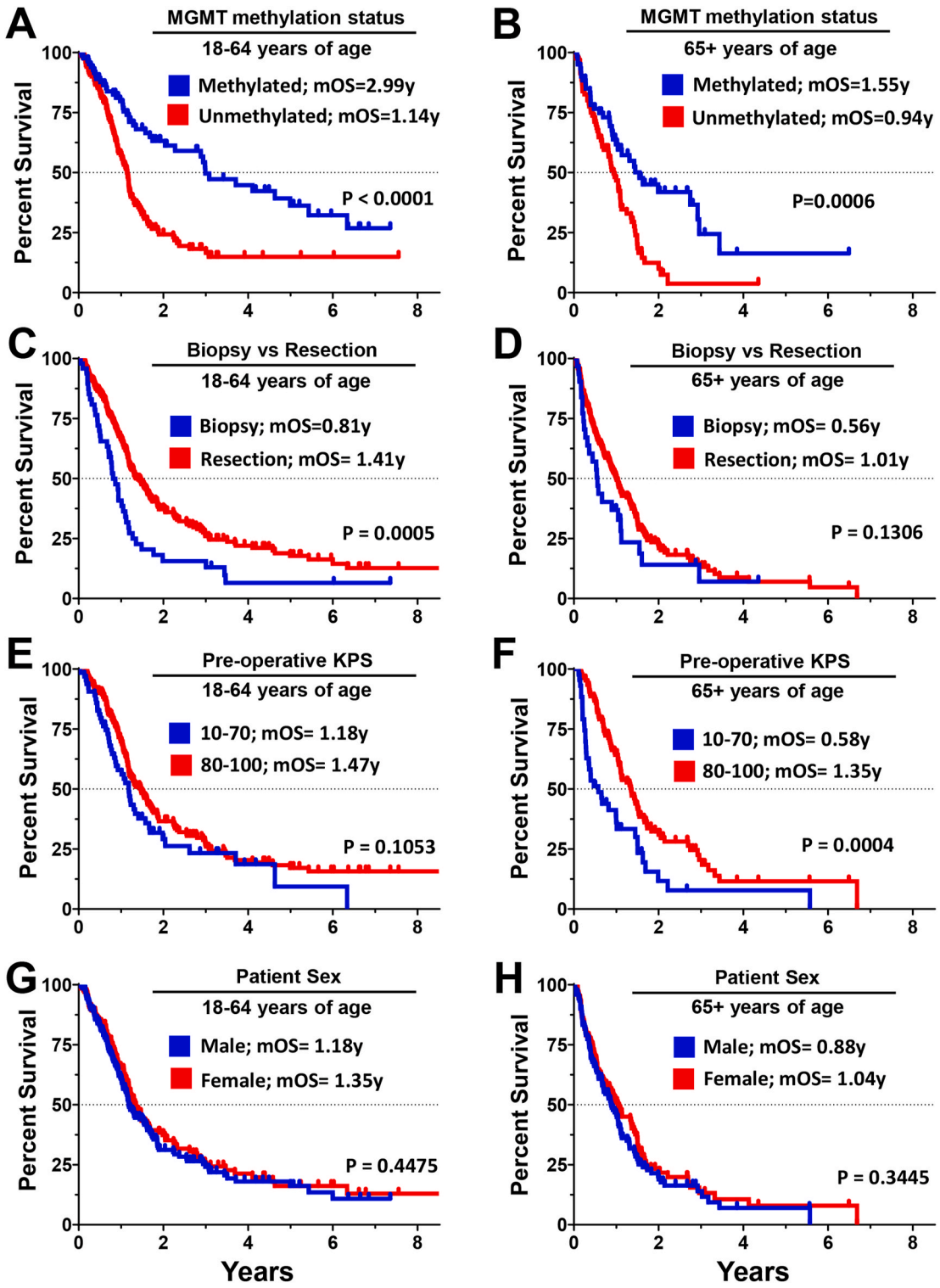

Fig. 4. Kaplan-Meier survival analysis of glioblastoma patients for MGMT methylation status, biopsy vs resection status, and pre-operative KPS stratified by age. (A) 18–64 years of age and **(B)** 65+ years of age for glioblastoma patients with MGMT methylated (blue) or unmethylated (red) tumor. **(C)** 18–64 years of age and **(D)** 65+ years of age for glioblastoma patients that received a tumor resection (blue) vs biopsy (red). **(E)** 18–64 years of age and **(F)** 65+ years of age for glioblastoma patients with a pre-operative KPS of 80–100 (blue) and 10–70 (red). mOS: Mean Overall Survival.

stratified by age, 76% of younger GBM patients had a KPS of 80–100 as compared to 71% of older adults. There was no difference in survival when stratified by patient sex regardless of age (Fig. 4G and H).

Using the Charlson Comorbidity Index (CCI), a tool that predicts the 10 year-long survival for patients with 19 potential types of co-morbidities, (Charlson et al., 1987) younger and older GBM patients had similar 1–2 CCI scores of 41% and 48%, respectively. Younger and older GBM patients also had similar >4 CCI scores of 26% and 19%, respectively. Figs. 5 and 6 show age-stratified survival associations with co-morbidities and tumor-related symptoms, respectively, while controlling for age, sex, race, CCI, anatomic location of cancer, MGMT promoter methylation status, IDH mutation status, Ki67 status, p53 status, body mass index (BMI), smoking status, marital status, depression and anxiety, biopsy vs. resection, and KPS in a multivariable model.

Among the total cohort of GBM patients, there was a poorer prognosis associated with mental health disorders (HR 1.53, 95% CI 1.06–2.20, P = 0.022) including anxiety disorders (HR 1.86, 95% CI 1.09–3.17, P = 0.024), movement related disability (HR 1.71, 95% CI 1.32–2.20, P < 0.000) including hemiparesis (HR 1.64, 95% CI (1.17–2.32), P = 0.004), Plegia (HR 5.17, 95% CI (1.84–14.53), P = 0.002), gait imbalance (HR 1.50, 95% CI (1.05–2.15), P = 0.025), and weakness (HR 2.02, 95% CI (1.29–3.16), P = 0.002), as well as and neurocognitive manifestations (HR 1.46, 95% CI 1.04–2.05, P = 0.027), which included confusion/altered mental status (HR 2.98, 95% CI 1.78–4.97, P < 0.000). A poorer prognosis trended towards an association with eye/vision problems (HR 1.37, 95% CI 1.10–1.71, P = 0.005).

Overall, there was a similar trend for co-morbidities and tumor-related symptoms among both younger and older adult patients with GBM with some select differences. The younger- but not the older-patients had a significantly poorer prognosis associated with the co-diagnosis of mental health disorder(s) (HR 2.09, 95% CI 1.3–3.35, P = 0.002) including anxiety disorder(s) (HR 2.83, 95% CI 1.5–5.32, P = 0.001), neurocognitive manifestations (HR 1.79, 95% CI 1.16–2.77, P = 0.009), movement disorders (HR 2.09.95% CI 1.48–2.96, P < 0.000), including hemiparesis (HR 2.5, 95% CI 1.62–3.88, P < 0.000), gait/balance difficulty (HR 1.66, 95% CI 1.02–2.68, P = 0.040), generalized weakness (HR 2.25, 95% CI 1.25–4.07, P = 0.007), and developing a DVT or PE (HR 1.51, 95% CI 1.01–2.27, P = 0.046). In contrast, the older- but not the younger-patients showed a worse prognosis for epileptic seizures (HR 2.26, 95% CI 1.04, 4.90, P = 0.039). Both younger and older groups showed a strikingly worse prognosis for confusion/altered mental status (HR 2.30, 95% CI 1.12–4.71, P = 0.023) vs (HR 5.13, 95% CI 2.28–11.52, P < 0.000). Interestingly, the HR for confusion/altered mental status was substantially higher among older GBM patients as compared to younger counterparts. This latter metric is notable since this is a parameter that's also predominant in age-related neurodegenerative Alzheimer's disease and age-related dementia(s).

The prevalence of prescribed medications by drug type and age-stratified hazard ratios are shown in Fig. 7. The most common medications prescribed in the outpatient setting by number of patients included steroids (n = 461; 83%), temozolomide (TMZ, n = 400; 75%), and benzodiazepines (n = 199; 39%). Temozolomide and benzodiazepines were more commonly prescribed in younger patients (80% and 45%, respectively) as compared to the older adults (70% and 30%, respectively), but steroid prescriptions were had a similar rate of prescription for young and older adults (85% and 79%, respectively). There was no difference in prescription of mood-altering medications including SNRIs, SSRIs, atypical antidepressants, TCAS and MAO inhibitors (Fig. 7). There were some similarities for overall adult GBM patients prescribed outpatient medications such that Cox modeling showed evidence for a protective effect after prescription with ARBs (HR 0.29, 95% CI 0.12–0.73, P = 0.009) and TMZ (HR 0.12, 95% CI 0.07–0.21, P=<0.000).

Although TMZ was consistently associated with an improved hazard ratio for both young (HR 0.14, 95% CI, 0.06–0.31, P < 0.000) and older GBM patients, (HR 0.1, 95% CI 0.04–0.23, P < 0.000), there was an unexpected age-dependent disparity for Ace-Inhibitors whereby older GBM patients had a better associated outcome (HR 0.47; 95% CI, 0.22–0.99, P = 0.048).

4. Discussion

This study identified age-dependent co-morbidities and pharmacologics that are associated with differences in associated hazard ratios for patients with IDHwt glioblastoma. To our knowledge, this is the first time that a GBM-focused analysis for co-morbidities has been stratified by age. It has been suggested that systemic co-morbidities have less of an effect on GBM patient survival since the disease progresses rapidly and since co-morbid conditions often occur during longer chronic periods of time (Carr et al., 2019). Our results demonstrate that overall survival is

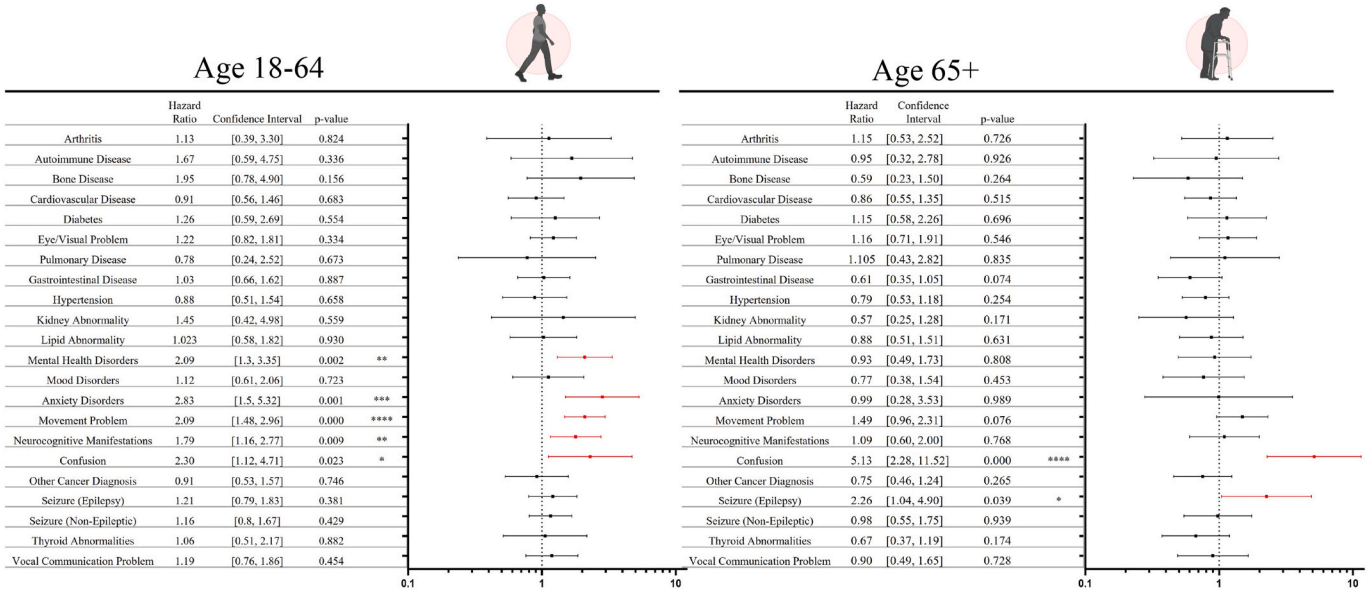

Fig. 5. Results of Cox proportional hazard analysis of glioblastoma patient co-morbidities that were stratified by age. Co-morbid hazard ratios were analyzed for younger 18–64 years of age and older 65+ years of age patients with glioblastoma. GI: Gastrointestinal, HTN: Hypertension, AMS: Altered Mental Status. Red bars indicate significant increases in the hazard ratio. *P < 0.05, **P < 0.01, ***P < 0.001.

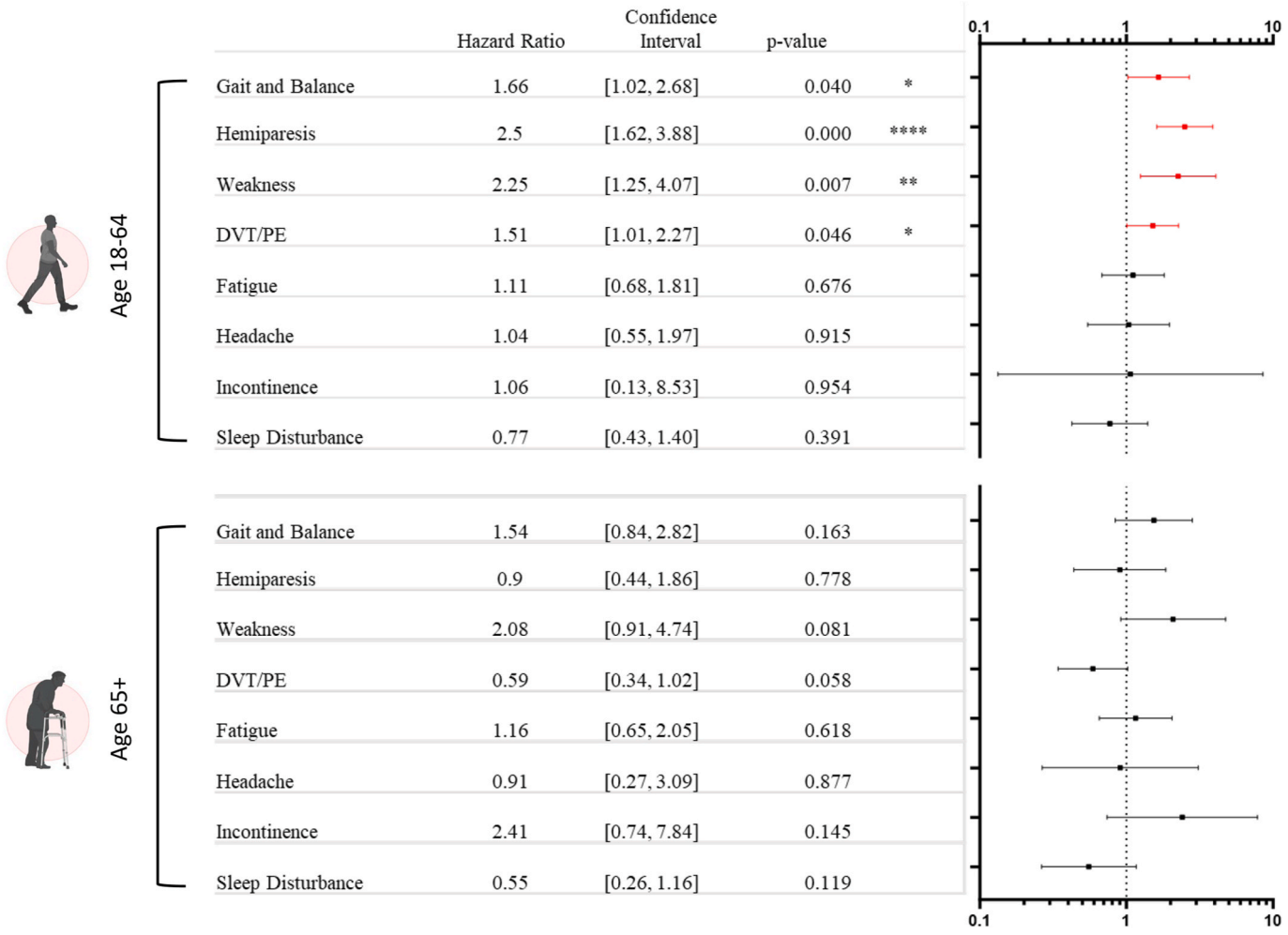

Fig. 6. Results of Cox proportional hazard analysis of glioblastoma patient tumor survival for related symptoms that were stratified by age. Co-morbid hazard ratios were analyzed for younger 18–64 years of age and older 65+ years of age patients with glioblastoma. DVT: Deep Venous Thrombosis, PE: Pulmonary Embolism. Red bars indicate significant increases in the hazard ratio. *P < 0.05, **P < 0.01.

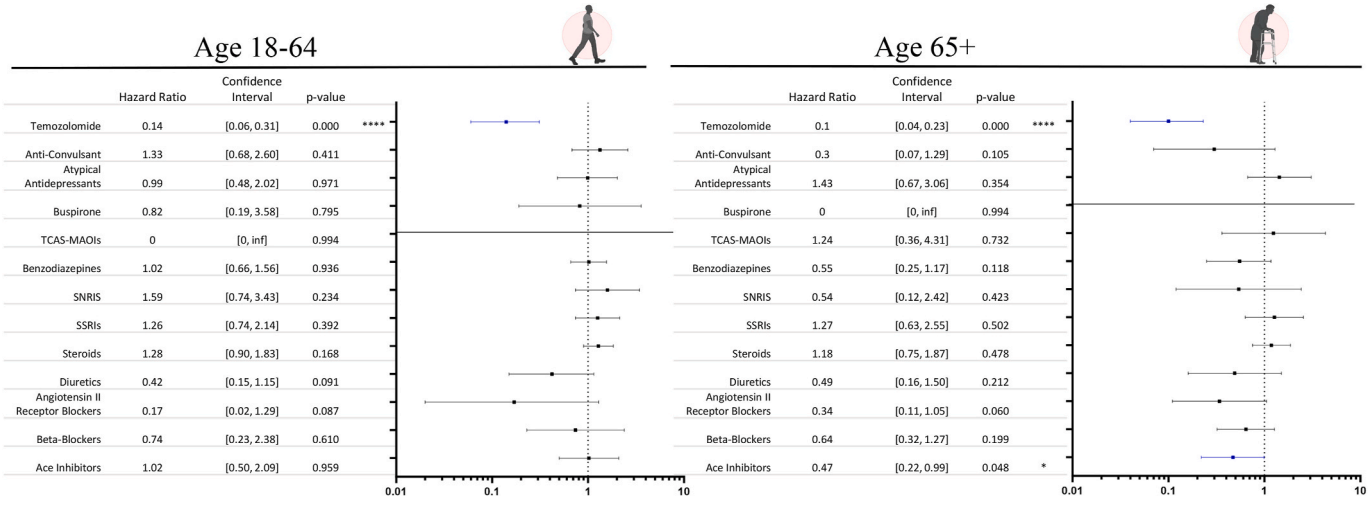

Fig. 7. Results of Cox proportional hazard analysis of glioblastoma patient tumor survival for medication prescription that were stratified by age. Co-morbid hazard ratios were analyzed for younger 18–64 years of age and older 65+ years of age patients with glioblastoma. SSRI: Selective Serotonin Reuptake Inhibitors, SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors, TCAs: Tricyclic Antidepressants, GAD: Generalized Anxiety Disorder medications, ACE: Angiotensin-Converting Enzyme, ARBs, Angiotensin II Receptor Blockers, TMZ: Temozolomide. Blue bars indicate significant decreases in hazard ratio. Red bars indicate significant increases in the hazard ratio. *P < 0.05, **P < 0.01, ****P < 0.0001.

less associated with physical disability-related symptoms in older patients with GBM as compared to younger counterparts. While younger patients had an increased hazard in movement related disability (HR 2.09, $P < 0.000$), older adults did not share this trend (HR 1.49, $P = 0.076$). Given that older adults tend to have a lower functional baseline, younger adults may be more impacted by dramatic changes in function. However, more studies are necessary to explore the impact of pre- and post-operative changes in functional score. Along with younger adults, older patients were negatively affected by changes in cognitive function that's represented by confusion and included altered mental status (AMS) (HR 5.13, $P < 0.000$). This population had a greater hazard ratio compared to younger patients (2.30, $P = 0.023$) that may be attributed to the effect of age with declining cognitive performance (Zaninotto et al., 2018) and/or greater risk for developing delirium (Robinson and Eiseman, 2008). Delirium is an acute state of confusion with changes in arousal and attention that's common in hospitalized patients (Whitlock et al., 2011). Within the post-operative hospital setting, delirium has been reported to affect up to 50% of individuals that are ≥65 years of age and is associated with a high rate of 1 year mortality (Inouye et al., 2014). The poorer prognosis for older patients can be attributed to a lower cognitive reserve and baseline neurologic function as compared to their younger counterparts and a greater susceptibility to hospital acquired complications that can include falls, pressure ulcers, urinary tract infections, aspiration pneumonias, and cardiac complications (Whitlock et al., 2011; Bagri et al., 2008). The underlying biological mechanism(s) associated with an increased hazard ratio and AMS in younger adults with GBM is unknown, but may be due to the timeline between developing confusion/delirium and mortality near death, but this is not established. It's possible that the aging brain is particularly sensitive to inflammation-driven mechanisms that contribute to confusion and/or AMS. It has long been suggested that inflammation contributes to the cognitive deficits in older adults with Alzheimer's disease – a condition defined by the presence of confusion/AMS (Akiyama et al., 2000). An intriguing and untested hypothesis is that the mechanisms contributing to worse outcomes in older adult GBM patients with confusion/AMS may be similar to those in patients with Alzheimer's disease.

Mental health disorders including depression, stress, and anxiety are common among patients with a brain tumor (Ryden et al., 2021; Hartung et al., 2017; Otto-Meyer et al., 2019) and depression-like symptoms are reported to be as high as 38% within the general cancer population (Rabin et al., 2022). Brain tumor patients with depression have been shown to have worse outcomes regardless of the time at diagnosis (Jutte et al., 2015) or time of surgery, (Oh et al., 2021) with an increased prevalence of extensive tumor necrosis on Magnetic Resonance Imaging (MRI) and negative prognostic markers in those with depression and anxiety (Fu et al., 2020). Psychological distress has been reported to be between 28% and 74% for this population (Keir et al., 2007; Kvale et al., 2009; Goebel and Mehdorn, 2011; Goebel et al., 2011). Our analysis showed that among the overall population, mental health disorders (1.52, $P = 0.022$) and anxiety disorders (1.86, $P = 0.024$) were associated with an increased hazard. This ratio was shared in younger individuals but not in older adults and may reflect increased mortality with increased psychologic burden (Cataldo et al., 2013). Given the prevalence of depression, stress, and anxiety among patients with high grade brain tumors, a primary goal of this study was to also investigate the survival outcome associations of antidepressant and other psychiatric medication usage among GBM patients. Murine models have suggested the possibility that stress contributes to tumorigenesis and progression through neurotransmitter signaling pathways including norepinephrine (Krishnan and Nestler, 2011; Jang et al., 2016). While acute stress is adaptative, prolonged exposure negatively impacts innate and adaptive immune functions (Eskandari and Sternberg, 2002; Kohm and Sanders, 2000) while also enhancing immune suppression. We therefore hypothesized that the prescription of psychological and stress modifying agents would be associated with an improved overall survival. However, the analysis of SSRI, SNRI, atypical antidepressant, and TCAS/MAOI prescriptions showed no significant association with improved prognosis for GBM patients across both age groups. This analysis is in-line with what our group previously showed (Otto-Meyer et al., 2020) that confirms a lack of significant association with GBM patient survival after antidepressants are prescribed (Caudill et al., 2011).

In addition to our analysis of psychological comorbidities, GBM patients in this cohort had a number of systemic comorbidities that were observed more often among older patients including hypertension and cardiovascular disease. Older adults have more medical problems, consume more medications, and present often with more advanced comorbid conditions (Avorn, 1995). However, this study found no evidence of those comorbidities affecting the risk for mortality.

Compared to the normal non-oncologic population, patients with GBM have an increased risk of cardiovascular disease, deep venous thrombosis, pulmonary embolism, heart failure, coronary artery disease, and myocardial infarction (Fisher et al., 2014; Jin et al., 2021). We investigated the association between antihypertensive use, other medications, and survival. In a previous study, ACE-Is were not found to improve survival in an analysis of GBM patients (Happold et al., 2018). Our analysis confirmed this trend for younger IDHwt GBM patients but not for older adults with GBM. This age-stratified effect showing an improved hazard for older GBM patients with ACE-I prescription may be related to the ACE-I- and diuretic-mediated reduction of cerebral edema (Meinig et al., 1980; Kast et al., 2021; Esquenazi et al., 2017) without the substantial side effect profiles of steroids or other forms of therapy with a similar objective to reduce intracranial swelling. ACE-Is are cardio and renal protective with known angiotensin receptor expression by glioma cells (Happold et al., 2018; Weder, 1990). Additionally, drugs acting on the renin angiotensin aldosterone pathway that block the angiotensin II receptor (ARB) are commonly prescribed for their antihypertensive and renal protective actions. However, our analysis found no evidence of an improved hazard in overall or age-stratified cohorts.

Corticosteroids were the highest prescribed outpatient medication within our patient cohort with 83% of total patients ($n = 461$) prescribed the medication that represented 85% of younger GBM and 79% of older patients. Corticosteroids are used to reduce cerebral edema after surgery, during the course of disease, as well as during radiation (Raslan and Bhardwaj, 2007). The control of cerebral edema prevents cerebral ischemia, the compression of nearby structures, and herniation of the brain (Raslan and Bhardwaj, 2007). When we stratified for our analysis of wild type IDH glioblastoma patients, this trend was not re-demonstrated. Use of corticosteroid therapy during radiation was previously identified as an independent indicator for shorter survival (Pitter et al., 2016) and a previous meta-analysis found a reduction in overall survival for grade 4 glioma patients taking steroids during treatment (HR 1.54) (Petrelli et al., 2021). Corticosteroids impact a number of biological pathways including the hypothalamic pituitary axis (HPA) and are well known to negatively impact immune function directly as well as indirectly by enhancing the immunosuppressive functions of regulatory T cells (Tregs) (Chen et al., 2018). The GBM tumor microenvironment is enriched with immunosuppressive cells and exposure to chronic stress increases the number of Tregs (Kim et al., 2012). Additionally, and especially among patients with cancer, steroids can lead to myopathy and preferentially affect physical function (Chiarella). While our final analysis with this population did not show harm in steroid use, our findings of increased hazard in younger patients with high grade gliomas, identify this as a potential medical target that future analyses should investigate. We hypothesize that the older high grade glioma patient cohort faces less physical insult as compared to the younger patients when steroids are prescribed. This could be due in-part to a longer treatment exposure to the medication and/or a larger cumulative dose for the younger group as compared to the older group. It could also be a result of older individuals with a higher immunosuppressed baseline that is more refractory to the immunosuppressive effects of the steroid.

The limitations of our study are based on its retrospective design and reliance on the electronic health record. To mitigate bias, we followed systematic procedures for data collection and analysis. While our cohort has a larger sample size than previous investigations of this nature, (Carr et al., 2019; Stark et al., 2012) some of our subgroups for comorbidity analyses were limited in size. Additionally, the patients used in this analysis were younger than the national median and were primarily composed of white Caucasian individuals. Due to this, comorbidities, medications, and other significant attributes may be different than the general GBM patient population. While our study reviewed the common GBM tumor biomarkers, our cohort population began in the year, 2000, and some of the now well-established prognostic factors were not collected at that time. Co-morbidities were identified from the past medical history in the electronic health record and grouped into categories. Pathology was identified dichotomously and was not based on severity of co-morbidity such as stage of renal failure, ejection fraction in CHF analysis, or COPD grade. Level of severity within the older population as compared to the younger population may have varied and is an area that remains to be investigated. Prescription information was collected as outpatient medications and did not account for in-hospital administration in which patients may have had a lengthened stay. Records were based on prescriptions, dosing schedules, and refills, but did not have data identifying whether medications were physically received. Dosing was recorded, but not analyzed further. As a retrospective study, these findings are limited by variable medication adherence. Future prospective studies are necessary to validate and further explore these findings.

GBM is a highly aggressive disease where overall survival is relatively low and tends to decrease with advancing age. This study demonstrates shared and distinct prognostic factors associated with comorbidity and medication prescription that stratifies by the age of the GBM patient. It is critical to continue studying the mechanics of survival that are distinguished by subject age so that the negative age-dependent biological mechanisms can one day be therapeutically addressed. Our data suggest novel age-dependent associative changes in hazard ratios with select comorbidities and/or prescription drug classes that serve as a rationale for future mechanistic understanding that will improve the outcomes of patients with GBM.

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Declaration

All authors have read and approved of the manuscript submitted for peer review.

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Declaration of competing interest

All co-authors report no financial or otherwise conflicts of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100753.

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