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Impact of Body Mass Index on Survival Outcome in Patients with Newly Diagnosed Glioblastoma: A Retrospective Single-Center Study

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Abstract

Introduction: The impact of obesity on survival outcomes in patients with glioblastoma (GBM) has not been well reported and the results for patients are currently unclear. We investigated the effect of obesity on survival outcomes in patients with newly diagnosed GBM. **Methods:** Using electronic medical records, all GBM patients that visited the Seoul St. Mary's Hospital between 2008 and 2018 were reviewed. A total of 177 patients met our eligibility criteria. The cut-off point for BMI was 23.0 kg/m^2 based on previous studies which focused on Asian populations. **Results:** A total of 177 patients met our eligibility criteria. The overall median BMI of patients was 24.5 kg/m^2 (range 15.82-39.26). About 62 patients who had a BMI less than the cut-off value were assigned to the "lower BMI" group, while 115 patients who had a BMI greater than the cut-off value were assigned to the "higher BMI" group. In Kaplan-Meier survival analysis, the median OS of the higher BMI group was longer than that of the lower BMI group (21.3 months vs 15.3 months, $P = .002$). In multivariate Cox regression analysis for OS, lower BMI was associated with inferior OS (HR 1.48 CI 1.06-2.08, $P = .002$). **Conclusion:** Our findings suggest that elevated BMI may be associated with better survival in patients with newly diagnosed GBM. Additional larger prospective studies could help validate our findings to confirm the effect of body composition and survival outcomes in GBM patients.

Keywords

body mass index, obesity, glioblastoma, cancer, survival

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Introduction

Obesity is a well-known risk factor for various cancers, including liver, gastrointestinal, breast, thyroid, renal and prostate cancers, and hematologic malignancies.[1-3] In addition, there has been a common perception that obese patients have reduced survival outcomes.[4,5] However, numerous studies have added evidence that supports a positive relationship between obesity and better survival in various cancers.[6-11] This confusing phenomenon is known as the "obesity paradox" and the potential mechanisms for this effect are currently being investigated.[12,13]

In glioblastoma (GBM), the impact of obesity on survival outcomes has not been well determined. To our knowledge, only 4 studies have investigated this association between obesity and survival outcomes in GBM or high-grade glioma patients.[14-17] Three studies reported that there were no associations between BMI and survival outcomes or that even elevated body mass index (BMI) was related to lower survival rates,[15-17] while a recent study suggested that elevated BMI is related to better survival in GBM patients.[14]

In this framework, we tried to evaluate the impact of obesity on survival outcomes in patients with newly diagnosed GBM. We used BMI as a parameter, which is a simple and internationally recognized marker for measuring the approximate adiposity in the human body.[18] We retrospectively analyzed the prognostic significance of BMI with previously

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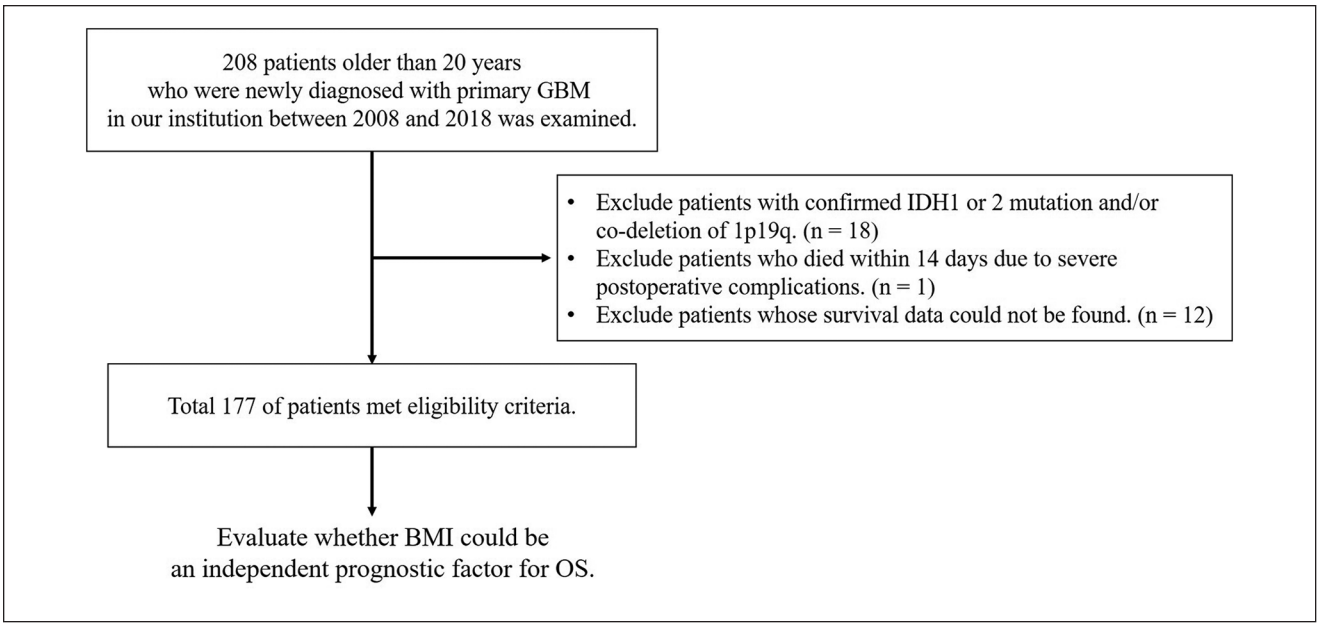

Figure 1. Study design.

well-known potential factors such as age, sex, extent of resection, and performance status.

Materials and Methods

Patient Population

The electronic medical records of 208 patients with newly diagnosed GBM treated at the Seoul St. Mary's Hospital between 01 August 2008 and 31 December 2018 were retrospectively analyzed after approval from the institutional review board of the hospital (KC19RESI0168, approval date: March 28, 2019). The eligibility criteria included: (1) newly diagnosed and primary GBM, (2) pathologically confirmed by craniotomy or stereotactic biopsy, (3) accessible baseline height and body weight, and (4) accessible survival status and/or death date. The exclusion criteria were: (1) proven Isocitrate dehydrogenase (IDH) mutation, and/or 1p19q co-deletion and (2) patients younger than 20 years. A summary of patient enrollment is illustrated in Figure 1.

Body Mass Index (BMI)

BMI was calculated using the patient's height and weight measured at the time of admission for initial surgery. The formula is BMI = weight/height × height kg/m^2. The cut-off point for BMI was 23.0 kg/m^2 based on previous studies which focused on Asian populations.[18,24] Patients who had a BMI greater than 23.0 kg/m^2 at the time of initial surgery were assigned to the "higher BMI" group, while patients with a BMI less than 23.0 kg/m^2 at the time of initial surgery were assigned to the "lower BMI" group.

Clinical Variables

Clinical variables of sex, age, extent of resection (EOR), pathological diagnosis, molecular features, dose and fraction of radiation, type of chemotherapy and number of cycles administered, radiological findings, and status of survival and/or death date were examined. The EOR was measured by comparing radiologic findings on MRI at baseline and within 48 hours after surgery. Resection of 90% of the tumor volume was defined as grossly total resection (GTR) and resection of <90% was defined as non-GTR, according to previous studies.[19,20] Isocitrate dehydrogenase 1 (IDH) mutation was evaluated by immunohistochemistry or directing sequencing. If necessary, an IDH 2 mutation was evaluated by direct sequencing. The presence of a 1p19q co-deletion was examined using fluorescence in situ hybridization (FISH). The O^6-methylguanine-DNA methyltransferase (MGMT) gene methylation status was evaluated by polymerase chain reaction. Concomitant chemoradiotherapy (CCRT) was initiated within 28 days of surgical resection[21]; the radiation dose was 5940 cGy for 33 fractions or 6000 cGy for 30 fractions and the TMZ dose was 75 mg/m^2 during CCRT, 150 mg/m^2 at first adjuvant cycle, and 200 mg/m^2 during the remaining 5 cycles of adjuvant therapy, regardless of age. Survival status and/or death dates were obtained from the Korea Central Cancer Registry database. The OS was defined as days from initial surgery to death. Patients who were confirmed to be alive on December 31, 2019, were censored. The average duration of follow-up was 19.2 months (range, 1-123 months).

Table 1. Patient Characteristics.

Variables	Higher BMI (N = 115)	Lower BMI (N = 62)	Total (N = 177)	*P* value
Sex, n (%)				.105
Female	47 (40.9)	34 (54.8)	81 (45.8)	
Male	68 (59.1)	28 (45.2)	96 (54.2)	
Age at diagnosis, years				
Mean (range)	60.3 (20-84)	62.3 (20-85)	61.0 (20-85)	.355
Age ≥65, n (%)	64 (55.7)	30 (48.4)	94 (53.1)	.444
Extent of resection, n (%)				.028
GTR	80 (69.6)	32 (51.6)	112 (63.3)	
Non-GTR	35 (30.4)	30 (48.4)	65 (36.7)	
MGMT methylation, n (%)				.284
Yes	41 (35.7)	29 (46.8)	70 (39.5)	
No	52 (45.2)	21 (33.9)	73 (41.2)	
Unknown	22 (19.1)	12 (19.4)	34 (19.2)	
ECOG grade, n (%)				.173
0 or 1	62 (53.9)	26 (41.9)	88 (49.7)	
≥2	53 (46.1)	36 (58.1)	89 (50.3)	
Mean BMI, kg/m^2 (range)	26.4 (23.0-39.3)	20.9 (15.8-22.9)	24.5 (15.8-39.3)	<.001
Mean weight, kg (range)	70.0 (48.0-104.0)	55.2 (38.0-70.0)	64.8 (38.0-104)	<.001
Mean height, cm (range)	163 (138-185)	162 (135-178)	162 (135-185)	<.001
Diabetes mellitus (%)	11 (9.6)	7 (11.3)	18 (10.2)	.919
Hypertension (%)	48 (41.7)	26 (41.9)	74 (41.8)	>.999
Dyslipidemia (%)	19 (16.5)	10 (16.1)	29 (16.4)	>.999

Statistical Analysis

All clinical variables were considered with descriptive statistics. The differences between groups were compared using the chi-square test or Fisher's exact test. The normality test was performed for continuous variables. Kaplan-Meier survival analysis and the log-rank test were used to estimate the median OS. Univariate and multivariate analyses were conducted using a Cox proportional regression model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Multivariate analysis was performed on the variables with P values < .2, and P values < .05 were considered to indicate statistical significance. All statistical analysis was estimated using R Statistical Software (Version 3.2.3).

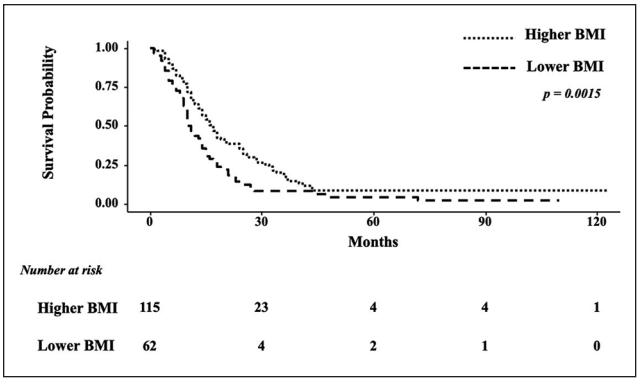

Figure 2. Kaplan-Meier survival curve for overall survival comparing the lower BMI group with the higher BMI group.

Results

Patient Characteristics

A total of 177 patients met our eligibility criteria. The overall median BMI of patients was 24.5 kg/m^2 (range 15.82-39.26 kg/m^2). About 62 patients who had a BMI less than the cut-off value were assigned to the "lower BMI" group, while 115 patients who had a BMI greater than the cut-off value were assigned to the "higher BMI" group. There were no differences in regard to baseline characteristics including sex, age, height, EOR, performance score, molecular features and metabolic disease including diabetes mellitus, hypertension, and dyslipidemia between the 2 groups, while the weight of the lower BMI group was lower than that of the higher BMI group. The detailed baseline characteristics of these groups are described in Table 1.

BMI and Overall Survival

We used a Kaplan-Meier survival analysis to evaluate whether BMI was associated with OS. The Kaplan–Meier survival curves of OS for the low BMI and high BMI groups are illustrated in Figure 2. The median OS of the higher BMI group was longer than that of the lower BMI group (21.3 months vs 15.3 months, P = .002).

Table 2. Univariate and Multivariate Cox Regression Analysis for Overall Survival.

	Univariate analysis		Multivariate analysis	
Variables	Hazard ratio (95%CI[a])	*P* value	Hazard ratio (95%CI[a])	*P* value
Sex (male vs female)	0.853 (0.619, 1.176)	.3315		
Age ≥ 65 (vs <65)	1.628 (1.176, 2.253)	.0033	1.307 (0.934, 1.831)	.1189
non-GTR (vs GTR)	2.676 (1.920, 3.729)	<.001	1.803 (1.258, 2.582)	.0013
ECOG grade ≥ 2 (vs ECOG grade 0 or 1)	3.181 (2.253, 4.490)	<.001	2.387 (1.631, 3.496)	<.001
BMI ≥ 23 (vs <23)	1.701 (1.221, 2.369)	.0017	1.483 (1.058, 2.078)	.0221

[a]Confidence interval is 95%.

BMI and Prognostic Factors

In univariate and multivariate analyses for OS, lower BMI (less than 23.0 kg/m^2) was associated with inferior OS (HR 1.48 CI 1.06-2.08, $P = .002$). Non-GTR (HR 1.80 CI 1.26-2.58, $P = .001$) and an ECOG of 2 or 3 (HR 2.39 CI 1.63-3.50, $P < .001$) were also associated with inferior OS, while sex and age ≥ 65 years were not associated with OS in this study. The detailed results of the univariate and multivariate Cox analyses for OS are described in Table 2.

Discussion

Obesity is one of the most important medical and social issues, and it is being rigorously evaluated for the potential associations with not only the risk of cancer but also survival outcomes in numerous cancers. While obesity has been proven to be a strong risk factor for developing cancers, the associations between obesity and survival outcomes in cancers is currently unclear. While there is a common conception that obesity is associated with inferior survival outcomes in cancer patients, numerous studies have provided evidence to support positive associations between obesity and survival.[6-11]

There are some possible explanations for this unexpected result. Almost studies have used BMI as a parameter to represent obesity, however, elevated BMI could also be associated with greater muscle mass.[12,13] This inadequate measure of excess adiposity could lead to this confusing result. On the other hand, an elevated BMI at the time of diagnosis could be related to less aggressive forms of cancer.[22] Moreover, additional nutrient reserves in excess adipose tissue can help patients resist the toxicities that can result from chemotherapy and/or radiotherapy, which eventually reduce mortality rates.[22] In addition, recent studies have found stronger immune and inflammatory responses in obese patients, which may be associated with the protective effect of obesity on survival in cancer patients.[23]

In GBM patients, only a limited number of studies have evaluated the associations between BMI and survival and the results have been controversial. Jones et al. first evaluated these associations between BMI and OS but did not find any associations.[15] In contrast, 2 studies that included 171 and 853 patients with high grade glioma both showed that elevated BMI is associated with inferior OS.[16,17] However, a recent study that included 392 GBM patients showed that patients with elevated BMI have better survival.[14]

In this context, we tried to evaluate whether elevated BMI can affect survival outcomes in patients with newly diagnosed GBM. We used BMI as a surrogate marker for representing obesity and set a cut-off point for BMI as 23.0 kg/m^2, based on previous studies on Asian populations.[18,24] There has been debate about a universal cut-off point of BMI for measuring obesity. Because the percentage of body fat and fat distribution can be different across populations, BMI classification, which was derived from studies on Caucasian populations, can lead to underestimating the obesity risk in Asian populations. Numerous studies have showed that east Asian populations had an increased risk of developing type 2 diabetes and have cardiovascular risks even below the cut-off point of 25.0 kg/m^2.[18,24] For this reason, the alternative cut-off point of 23.0 kg/m^2 was used in this study, instead of a classic cut-off point of BMI as 25 kg/m^2, based on previous studies which focused on Asian populations.[18,24]

In this study, we classified the patients who had a BMI greater than 23.0 kg/m^2 as the "higher BMI" group and patients who had a BMI lower than 23.0 kg/m^2 as the "lower BMI" group. Our study showed that the median OS of the higher BMI group was longer than that of the lower BMI group (21.3 months vs 15.3 months, $P = .002$). In multivariate Cox regression analysis, lower BMI was also associated with inferior OS (HR 1.48 CI 1.06-2.08, $P = .002$). Our findings are consistent with a recent study that showed that elevated BMI was associated with better survival in GBM patients.[14] Previous studies that have reported that elevated BMI was related to worse OS, had some limitations; heterogeneous pathology, or using self-reported body weight and height, and missing information

on performance status and surgery.[15-17] In contrast, we measured the height and body weight at the time of initial surgery in our hospital. In multivariate analysis, we considered previously well-known prognostic factors such as age, EOR, and performance status and the results are consistent with previous reports. In addition, we tried to include homogenous pathological groups and included newly diagnosed GBM patients with no evidence of IDH1 or 2 mutations or 1p19q co-deletion. Altogether, the results of this study suggest that elevated BMI (more than 23.0 kg/m^2) is associated with better survival in Asian patients with newly diagnosed GBM. However, concluding that obesity is good for prognosis of GBM patients from our findings is not appropriate. To validate our findings and establish the appropriate body weight for GBM patients, additional prospective and larger-scale studies are needed. Especially, further studies investigating the associations between weight change and GBM aggressiveness are needed to clarify the possibility of bias in lower BMI patients. To understand the pathophysiological mechanisms of this association, further preclinical studies including animal models of obesity should also be considered.

Our study had several limitations. First, due to the retrospective and non-randomized study design, the possibility of selection bias may exist. Second, molecular markers, such as IDH1 or 2 mutations, 1p19q co-deletion, and MGMT gene methylation status, are one of the strongest prognostic factors however, these factors were not fully identified or investigated in this study. Third, BMI may not be correlated with body fat accumulation in patients. In this study, there are no differences in regard to underlying disease related obesity including diabetes, hypertension, and dyslipidemia between 2 groups. To clarify this phenomenon of obesity paradox in GBM patients, other anthropometric parameters to reflect obesity better than BMI such as waist circumference should be included.[25] Fourth, although we considered many factors that potentially influenced the overall survival of GBM patients, several factors such as the starting time of CCRT after surgical resection were not included in multivariate analysis.

Conclusion

In conclusion, elevated BMI at the time of surgery may be associated with survival outcomes in GBM patients. Further clinical and preclinical studies may help to explain this potential association between body composition and survival outcomes in brain cancer patients.

Author Contributions

Conceptualization: SA; methodology and data curation: J-SP and SA; writing—original draft: J-SC and SA; writing—review and editing: J-SP, S-SJ, and Y-KH; funding acquisition: SA.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study has been approved by the Institutional Review Board of Seoul St. Mary's Hospital.

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