Body Mass Index and Overall Outcome Following Subarachnoid Hemorrhage: An Obesity Paradox?

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Abstract

Background: Conventional understanding of obesity demonstrates negative consequences to overall health, while more modern studies have found that it can provide certain advantages. Current literature on the effect of body mass index (BMI) in subarachnoid hemorrhage (SAH) is similarly inconsistent.

Methods: 406 patients with SAH were retrospectively reviewed and stratified into three BMI categories: normal weight between 18.5 and 24.9 kg/m^2; overweight between 25 and 29.9 kg/m^2; and obese greater than 30 kg/m^2. Neurologic status, the presence of clinical cerebral vasospasm, and outcome as assessed by the modified Rankin scale (mRS) were obtained.

Results: Statistical differences were evident for all outcome categories. A categorical analysis of the different groups revealed that, compared to the normal weight BMI, the overweight group had an odds ratio for mortality of 0.415 ($p = 0.023$), poor mRS at 90 days of 0.432 ($p = 0.014$), and poor mRS at 180 days of 0.311 ($p = 0.001$). The obese group had a statistically significant odds ratio for poor mRS at 90 days of 2.067 ($p = 0.041$) and at 180 days of 1.947 ($p = 0.049$). These significant odds ratios persisted in a multivariable model controlling for age and Hunt & Hess grade.

Conclusions: The overweight BMI group exhibited a striking decrease for the odds of death and poor outcome compared to the normal weight BMI, whereas the obese group demonstrated the contrary. These associations persisted in a multivariable model, thus BMI can be considered an important predictor of outcome after SAH.

Introduction

Obesity has long been associated with several diseases such as stroke, diabetes, and heart disease, in which it not only increases morbidity in these pathological conditions, but also mortality.[1-4] In addition, patients who are obese are more likely to experience in hospital complications such as venous thromboembolism and infection, and have longer intensive care unit (ICU) stays.[5-8] However, recent studies have shown that an increased body mass index (BMI) may lend a protective effect in certain diseases.[9,10] This "obesity paradox" is contrary to conventional wisdom and may actually be beneficial in coronary artery disease, acute myocardial infarction, and stroke.[11-13] An understanding of how the accumulation of excess body fat influences health is still being revised. For example, one study showed that being in an overweight BMI reduced the risk of mortality compared to those who were obese.[14] It has been posited that the increased energy reserves of overweight and obese patients allow them to tolerate severe disease. The new data has encouraged research regarding the protective versus detrimental effect of obesity in various disease states. These studies will be extremely relevant given the increasing prevalence of obesity in the US and across the world.

Subarachnoid hemorrhage (SAH) is a devastating disease with an initial mortality of 50%. The effects of obesity on post-bleed outcomes in SAH have previously been studied but the relationship between the two is unclear. Some studies have found that obesity leads to a decreased overall mortality but a higher risk of delayed cerebral ischemia (DCI), which can independently increase morbidity.[15,16] One study found that obesity increased the risk of ICU related complications.[17] Still, some authors have found no differences in outcome for obese and non-obese patients who presented with SAH.[18-20] Further research is needed to determine the relationship between obesity and outcomes after SAH. In this study, we aim to analyze a

database of patients with SAH from a single urban institution to evaluate the effects of BMI on severity of SAH, complications during the hospital course, and both short and long-term outcomes.

Materials and Methods

Patients

After obtaining approval from the institutional review board, we acquired charts of patients who presented at a single academic institution with aneurysmal subarachnoid hemorrhage between 2007 and 2017. We obtained demographic information and neurologic status on admission assessed by the Hunt & Hess (H&H) grade, the modified Fisher grade, the presence of radiographic cerebral vasospasm, the presence of clinical cerebral vasospasm, and outcome as assessed by the modified Rankin scale (mRS).

The patient's BMI was calculated by the weight in kilograms divided by the height in meters squared. We grouped the patients into three categories according to World Health Organization classification: normal weight, 18.5 and 24.9 kg/m^2; overweight, between 25 and 29.9 kg/m^2; and obese, greater than 30 kg/m^2.[21] Patients were excluded from the study if they had missing data points and did not follow up at 6 months.

Outcome

Primary outcomes were measured using the mRS stratified into three time frames: hospital discharge, 90 days, and 180 days post hemorrhage. A poor mRS was defined as a score ≥ 4. The assessments were made via a standardized patient interview during an outpatient follow up visit. To assess for any possible confounding factors, we also assessed the H&H grade at

presentation, the modified Fisher score, the method of aneurysm treatment (surgical vs. endovascular), and the presence of cerebral vasospasm. A poor H&H grade was defined as being ≥ 4 and a poor modified Fisher score was defined as being ≥ 3.

Statistical Analysis

All statistical analyses were performed using SPSS version 24 (IBM Corporation, Armonk, NY) for Macintosh, with a *P* value of ≤ 0.05 as our threshold for statistical significance. Kruskal-Wallis *H* tests, analysis of variances, and Pearson chi-square tests were used to assess differences in patient demographics and outcomes. On univariate analysis the associations between BMI and age, H&H grade, anterior or posterior aneurysm location, aneurysm size, DCI, and rebleed rate with mortality and mRS at 90 and 180 days were done with a bivariate correlation using the Spearman's test with BMI as a continuous variable and the Kruskal-Wallis *H* test with BMI as a categorical variable. Multivariate analysis of BMI as categorical values was done using a logistic regression model with calculated odds ratios (OR) and a 95% confidence intervals (CI).

Results

Demographics

406 patients diagnosed with SAH were identified using the above-mentioned criteria. Patient demographic and admission data were divided among the three BMI classifications and is listed in **Table 1**. 122 patients (30%) were classified in the normal weight category, 154 (38%) in the overweight category, and 130 (32%) in the obese category. There was a significant difference for the median (interquartile range) BMI amongst the three categories: normal weight, 23.1

(21.5-24.3); overweight, 26.9 (25.8-28.5); and obese, 34.2 (31.4-37.8) (p = .001). There were no significant differences for age, sex, nicotine users, median H&H grade, modified Fisher grade, aneurysm location, aneurysm size, intraventricular hemorrhage, radiographic vasospasm, treatment modalities, or hospital course.

Outcomes

Patient outcomes are listed in **Table 2**. Among the three groups, there were significant differences for mortality at discharge (32.8%, 16.8%, and 29.3, respectively: p = .048), poor mRS at discharge (49.2%, 29.5%, 66.7%, respectively: p = .001), poor mRS at 90 days (49.2%, 23.2%, 65.3%, respectively: p = .001), and poor mRS at 180 days (45.9%, 17.9%, 59.7%, respectively: p = .001).

Subgroup Analyses

The evaluation of both BMI as a continuous and categorical variable along with patient demographic information and admission data related to the initial SAH severity compared to outcomes on univariate analysis is listed in **Table 3** and **Table 4**. Age, a poor H&H grade, a poor modified Fisher score, and DCI were significantly correlated to mortality at discharge and poor mRS at 90 and 180 days. An anterior circulation aneurysm location, aneurysm size, and rebleed rate were not correlated.

As a continuous variable, BMI was not significantly associated with mortality at discharge (OR: 1.002, 95% CI: 0.954-1.053, p = .932), but a significant association existed for a poor mRS at both 90 days (OR: 1.050, 95% CI: 1.004-1.098, p = .031) and 180 days (OR: 1.048, 95% CI: 1.003-1.096, p = .037). As categorical variables compared to the normal weight group,

an overweight BMI was significantly associated with a lower mortality (OR: 0.415, 95% CI: 0.195-0.886, p = .023), and less of a risk for a poor mRS at 90 days (OR: 0.432, 95% CI: 0.221-0.842, p = .014), and at 180 days (OR: 0.311, 95% CI: 0.156-0.622, p = .001). The obese BMI when compared to the normal weight category was not significantly associated for mortality but was for poor mRS at 90 days (OR: 2.067, 95% CI: 1.032-4.139, p = .041) and poor mRS at 180 days (OR: 1.947, 95% CI: 1.105-3.888, p = .049).

Multivariate analysis with BMI as categorical variables along with the significant univariate associations is listed in **Table 5**. Age and a poor H&H grade remained significantly associated to mortality, and poor mRS at 90 and 180 days, whereas a poor modified Fisher score and DCI was not significant. Compared to the normal weight BMI in the multivariable model including age and H&H grade, the overweight BMI was significantly associated with a better mortality (OR: 0.309, 95% CI: 0.102-0.937, p = .038), less of a risk for a poor mRS at 90 days (OR: 0.243, 95% CI: 0.085-0.692, p = .008), and poor mRS at 180 days (OR: 0.122, 95% CI: 0.039-0.383, p = .001). The obese BMI when compared to the normal weight category in the multivariable model was significantly associated with poor mRS at 90 days (OR: 5.064, 95% CI: 1.753-14.627, p = .003) and poor mRS at 180 days (OR: 2.918, 95% CI: 1.036-8.220, p = .043).

Discussion

Our conventional understanding of the systemic effects of obesity would lead us to believe that BMI directly influences worsened mortality and morbidity, which could be applicable to patients with SAH. A study from 2005 found that there was a 1.15 (95% CI: 1.02–1.29) increase in the risk of radiographic cerebral infarction for every 1 kg/m^2 increase in BMI.[16]

In a recent study, Elliott et al. found that morbid obesity (BMI greater than 40 kg/m^2) was associated with an increased length of stay, hospital costs, and acute respiratory failure.[22]

Lately, the notion of an "obesity paradox" has begun to redefine our knowledge of the effects of obesity. For patients with first time acute stroke, one study found that in a cohort of 2785 obese and overweight patients, short and long-term survival was better at one week, one month, and 10 years.[13] However for patients with SAH, a study found that patients with a lower BMI also had a lower mRS.[20] Hughes et al. found evidence of the obesity paradox in 281 patients for mortality but not for functional outcome in both univariate and multivariate analyses.[15] Interestingly, in Elliott et al.'s aforementioned study that found a detrimental association between morbid obesity and ICU length of stay, hospital costs, and acute respiratory failure, the group's multivariate analysis demonstrated that obesity had a converse impact on mortality with an OR of 0.83 (95% CI: 0.74-0.92).[22]

Still, many studies have reported no association between obesity and outcome.[18,19,23] In an analysis of 741 patients with SAH, one study found that the median BMI was higher in patients with a more severe Glasgow Outcome Scale value; however, this did not persist in a multivariate analysis.[18] Kagerbauer et al.'s study found no association between BMI and poor neurological outcome in aneurysmal SAH.[19] Finally, an analysis of 2695 patients in the tirilazad trial database across many different countries did not find a significant association between patient weight and poor outcome on univariate anaylsis.[23]

Based on the current literature, a general consensus does not exist on the effect of BMI on SAH. A seemingly equal share of studies exist that show how obesity can be detrimental, protective, or have no effect on morbidity and mortality after SAH. This is further complicated by the distinction between survival and functional outcome, with the trend slanting towards BMI

having a greater influence on the latter. While most studies do not examine mortality as a primary endpoint, and rather examine functional outcome at 6 months, this could also be due to the inherent physiology of obesity. Proponents of the obesity paradox have suggested that the readily available nutritional and caloric energy stockpiles can lend to the protective effect of obesity after a severe insult to the body, such as in SAH.[15,24] Conversely, others have postulated that the prolonged multifactorial damage caused by obesity severely decreases the ability to mount an adequate response to acute injury, and that an obesity paradox is due to confounding variables.[10,15] This disparity is furthered by the multitude of conflicting reports in the literature.

Our data of 406 patients after SAH supports the idea of an obesity paradox to an interesting extent. Framing BMI as a continuous variable in our univariate analysis shows a significant association with a poor mRS at 90 and 180 days, whereas there is no association to mortality. Nevertheless, the risk for a poor mRS at these time points (OR: 1.050 and 1.048) is relatively negligible. Stratifying BMI using the conventional World Health Organization classification system reveals that when compared to the normal weight BMI, both the overweight and obese groups have inverse associations with mortality and functional outcome. Patients with an overweight BMI were 58.5% less likely to have died, 56.8% less likely to have had a poor mRS at 90 days, and 68.9% less likely to have had a poor mRS at 180 days when compared to those with a normal weight. For the obese group, the risk for a poor functional outcome at 90 and 180 days were approximately twofold (OR: 2.067 and 1.947) higher than the normal weight BMI.

The distinction between using BMI as a categorical variable compared to just a continuous one reveals an important trend in our univariate results. At face value, BMI as continuous variable masks the association between mortality and functional outcome of the

overweight group compared to a normal weight group. This profoundly impacts our study because it could help support the notion of an obesity paradox that would not be readily apparent. BMI as a categorical variable also neatly packages the concept in to one that is well known and commonly used.

A multivariable model including age and H&H grade was used to further determine the effect BMI has on mortality and morbidity. These two factors, along with a poor modified Fischer score and DCI, were significantly associated with mortality and poor mRS in our univariate analysis, but the modified Fisher score and DCI dropped out in the analysis. The overweight group had a 69.1% less risk of mortality, a 75.7% less risk for poor outcome at 90 days, and an 87.8% less risk for poor outcome at 180 days compared to the normal weight group. Conversely, the obese group was 406.4% more likely to have a poor outcome at 90 days and 191.8% more likely to have a poor outcome at 180 days compared to the normal weight BMI. Mortality was not significantly different between the obese and normal weight group for this model.

These results demonstrate that being overweight could lend a protective effect after SAH, but tipping the scale to a higher BMI in the obese category could be detrimental. Our results seem to support the two major tenets of the obesity paradox; a surplus of calories and essential micronutrients can potentially cushion the devastating consequences after SAH, yet a critical point is reached where the physiologic detriment associated with obesity negates these benefits. One theory is that since the amount of visceral adiposity decreases with age, older patients possess an obesity that is inherently less risky.[25] Since age is an independent morbidity risk factor for SAH, this etiology may be especially relevant. Additionally, the obesity paradox may reflect an inability of BMI to distinguish between lean body mass and fat mass. Therefore, other

measures of body habitus such as waist circumference may be more relevant in SAH. Previously, obese patients have been shown to have greater vascular function, including flow-mediated dilation, due to better mobilization of endothelial progenitor cells.[26] Finally, obesity has been associated with increased levels of circulating coagulation factors such as factor VII, factor VIII, and fibrinogen, which may allow for more rapid coagulation during the ictal SAH hemorrhagic event.[27] Our results also reinforce the importance of a strict and rigorous post-SAH nutrition rehabilitation plan.

Along with the usual limitations of any retrospective study, one weakness of this study was the lack of inclusion of comorbid conditions. This would skew more towards the obese category but would not rationalize the results seen for the overweight BMI. Also, while the BMI categorization provides an easily quantifiable way to stratify patients in terms of risks for mortality and morbidities, it has been criticized for not fully for assessing nutritional or caloric status, which could be done by other means.

Conclusions

This study was used to clarify the influence BMI has on SAH outcomes. The overweight group exhibited a striking decrease for the odds of death and poor outcome compared to the normal weight category. In contrast, the obese group had an increased risk of death and poor outcome. These associations persisted in a multivariable model including age and H&H grade, thus BMI is an independent predictor of outcome after SAH.

Declarations of Interest: None.

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Table 1. Patient demographic and admission data relating to subarachnoid hemorrhage by body mass index categories

Category	Parameter	Total	BMI Categories: Normal 18.5 - 24.9 kg/m^2	Overweight 25 - 29.9 kg/m^2	Obese ≥ 30 kg/m^2	p
Demographics	Median BMI (kg/m^2) (IQR)	27.2 (24.9-31.3)	23.1 (21.5-24.3)	26.9 (25.8-28.5)	34.2 (31.4-37.8)	.001*
	Mean Age (years) ± SD	52.77 ± 14.3	55.33 ± 15.9	52.29 ± 12.5	51.29 ± 14.8	.24
	Female %	70.1	72.1	70.5	68	.867
	Nicotine Users %	42.7	45.5	44.3	38.2	.054
Admission and Radiographic Characteristics	Median Hunt & Hess Grade (IQR)	3 (2-4)	3 (2-4)	3 (1-4)	3 (2-4)	.71
	Modified Fisher Grade ≥ 3 %	79.9	86.3	76.2	79.7	.366
	Anterior Aneurysm Location %	58.1	58.2	61.2	56.6	.076
	Aneurysm Size (mm) ± SD	6.77 ± 3.1	6.42 ± 3.4	6.93 ± 2.9	7.01 ± 3.2	.619
	Intraventricular Hemorrhage %	77.9	80.3	72.6	82.7	.255
	Radiographic Vasospasm %	42.5	41.2	44.4	43.5	.354
Treatment	Coil %	61.2	61.7	62.3	60.3	.409
	EVD %	68.4	69.5	67.7	67	.349
	VP Shunt %	17.2	14	19.1	16.5	.204
Hospital Course	Rebleed %	6.5	8.2	5.3	6.7	.766
	DCI %	60.6	60.7	56.8	65.3	.531
	Seizure %	5.7	4.9	7.4	4.2	.633
	Median Hospital Length of Stay (IQR)	13 (10-20)	12 (8-20)	13 (10-18)	14 (11-20)	.694

BMI: body mass index; IQR: interquartile range; SD: standard deviation; EVD: external ventricular drain; VP: ventriculoperitoneal; DCI: delayed cerebral ischemia; * = significant $p < 0.05$

Table 2. Outcomes relating to subarachnoid hemorrhage by body mass index categories

		BMI Categories			
	Total	Normal 18.5 - 24.9 kg/m^2	Overweight 25 - 29.9 kg/m^2	Obese ≥ 30 kg/m^2	p
Mortality at Discharge %	25.1	32.8	16.8	29.3	.048*
Poor mRS (≥ 4) at Discharge %	46.8	49.2	29.5	66.7	.001*
Poor mRS (≥ 4) at 90 days %	43.7	49.2	23.2	65.3	.001*
Poor mRS (≥ 4) at 180 days %	38.5	45.9	17.9	58.7	.001*

BMI: body mass index; mRS: modified Rankin scale; * = significant $p < 0.05$

Table 3. Patient demographic information and admission data related to subarachnoid hemorrhage compared to outcomes on univariate analysis

	Mortality		Poor mRS (≥4) at 90 days		Poor mRS (≥4) at 180 days	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.081 (1.054-1.109)	.001*	1.056 (1.034-1.078)	.001*	1.061 (1.038-1.084)	.001*
Hunt & Hess Grade (≥ 4)	10.944 (5.554-21.565)	.001*	8.473 (4.318-16.628)	.001*	8.134 (4.254-15.550)	.001*
Modified Fisher Grade (≥ 3)	20.901 (2.802-55.92)	.003*	3.368 (1.553-7.303)	.002*	3.708 (1.618-8.498)	.002*
Anterior Aneurysm Location	1.001 (0.50-1.20)	.88	1.003 (0.54-2.99)	.51	1.02 (0.546-2.22)	.729
Aneurysm Size	1.050 (0.333-1.04)	.732	1.054 (0.39-1.099)	.766	1.063 (0.44-1.055)	.865
DCI	2.000 (1.075-3.720)	.029*	2.242 (1.325-3.792)	.003*	2.469 (1.447-4.211)	.001*
Rebleed	1.310 (0.437-3.926)	.63	1.063 (0.386-2.929)	.906	1.202 (0.436-3.313)	.722

mRS: modified Rankin scale; OR: odds ratio; CI: confidence interval; DCI: delayed cerebral ischemia; * = significant $p < 0.05$

Table 4. BMI as continuous and categorical variables related to subarachnoid hemorrhage compared to outcomes on univariate analysis

	Mortality		Poor mRS (≥4) at 90 days		Poor mRS (≥4) at 180 days	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
BMI Continuous	1.002 (0.954-1.053)	.932	1.050 (1.004-1.098)	.031*	1.048 (1.003-1.096)	.037*
BMI Categorical						
Overweight	0.415 (0.195-0.886)	.023*	0.432 (0.221-0.842)	.014*	0.311 (0.156-0.622)	.001*
Obese	0.851 (0.410-1.766)	.665	2.067 (1.032-4.139)	.041*	1.947 (1.105-3.888)	.049*

mRS: modified Rankin scale; OR: odds ratio; CI: confidence interval; BMI: body mass index; * = significant $p < 0.05$

Table 5. Multivariate analysis with BMI as categorical variables along with the significant univariate associations

	Mortality		Poor mRS (≥4) at 90 days		Poor mRS (≥4) at 180 days	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.084 (1.049-1.120)	.001*	1.100 (1.061-1.141)	.001*	1.099 (1.060-1.140)	.001*
Hunt & Hess Grade (≥ 4)	15.802 (5.806-43.010)	.001*	18.888 (6.479-55.059)	.001*	19.600 (6.526-58.862)	.001*
Modified Fisher Grade (≥ 3)	3.661 (0.438-30.600)	.113	0.777 (0.272-2.214)	.636	0.700 (0.229-2.139)	.532
DCI	2.195 (0.830-5.800)	.113	2.097 (0.906-4.857)	.084	2.569 (0.910-6.206)	.066
BMI Categorical						
Overweight	0.309 (0.102-0.937)	.038*	0.243 (0.085-0.692)	.008*	0.122 (0.039-0.383)	.001*
Obese	-	-	5.064 (1.753-14.627)	.003*	2.918 (1.036-8.220)	.043*

mRS: modified Rankin scale; OR: odds ratio; CI: confidence interval; DCI: delayed cerebral ischemia; BMI: body mass index; * = significant $p < 0.05$

Abbreviation List

BMI: Body Mass Index

CI: Confidence Interval

CT: Computed Tomography

DCI: Delayed Cerebral Ischemia

EVD: External Ventricular Drain

H&H: Hunt & Hess

ICU: Intensive Care Unit

IQR: Interquartile Range

mRS: Modified Rankin scale

OR: Odds ratio

SAH: Subarachnoid Hemorrhage

SD: Standard Deviation

VP: Ventriculoperitoneal