Does the obesity paradox predict functional outcome in intracerebral hemorrhage?

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OBJECTIVE Being overweight or mildly obese has been associated with a decreased risk of death or hospitalization in patients with cardiovascular disease. Similarly, overweight patients admitted to an intensive care unit (ICU) have improved survival up to 1 year after admission. These counterintuitive observations are examples of the “obesity paradox.” Does the obesity paradox exist in patients with intracerebral hemorrhage (ICH)? In this study the authors examined whether there was an association between obesity and functional outcome in patients with ICH.

METHODS The authors analyzed 202 patients admitted to the neurological ICU (NICU) who were prospectively enrolled in the Columbia University ICH Outcomes Project between September 2009 and December 2012. Patients were categorized into 2 groups: overweight (body mass index [BMI] ≥ 25 kg/m²) and not overweight (BMI < 25 kg/m²). The primary outcome was defined as survival with favorable outcome (modified Rankin Scale [mRS] score 0–3) versus death or severe disability (mRS score 4–6) at 3 months.

RESULTS The mean age of the patients in the study was 61 years. The mean BMI was 28 ± 6 kg/m². The mean Glasgow Coma Scale score was 10 ± 4 and the mean ICH score was 1.9 ± 1.3 . The overall 90-day mortality rate was 41%. Among patients with a BMI < 25 kg/m², 24% (17/70) had a good outcome, compared with 39% (52/132) among those with a BMI ≥ 25 kg/m² ($p = 0.03$). After adjusting for ICH score, sex, do-not-resuscitate code status, and history of hypertension, being overweight or obese (BMI ≥ 25 kg/m²) was associated with twice the odds of having a good outcome compared with patients with BMI < 25 kg/m² (adjusted odds ratio 2.05, 95% confidence interval 1.03–4.06, $p = 0.04$).

CONCLUSIONS In patients with ICH admitted to the NICU, being overweight or obese (BMI ≥ 25 kg/m²) was associated with favorable outcome after adjustment for established predictors. The reason for this finding requires further study.

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KEY WORDS intracerebral hemorrhage; obesity; functional recovery; intensive care unit; vascular disorders

IN spite of advances in neurocritical care, intracerebral hemorrhage (ICH) continues to be associated with high mortality and morbidity.⁹ Well-established risk factors for mortality include age > 80 years, a Glasgow Coma Scale (GCS) score < 8 , ICH volume > 30 ml, infratentorial location, intraventricular hemorrhage (IVH),

and early do-not-resuscitate (DNR) code status.^{8,9} Much less is known about factors that might confer a protective effect against poor outcome after ICH.

Obesity is now considered to be a global epidemic, and relative to normal body weight, obesity is associated with increased all-cause mortality. This may be explained

ABBREVIATIONS BMI = body mass index; CI = confidence interval; DNR = do not resuscitate; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; ICHOP = Intracerebral Hemorrhage Outcomes Project; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; NICU = neurological intensive care unit; OR = odds ratio.

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by the association of obesity with many chronic disease states, including coronary artery disease, atrial fibrillation, congestive heart failure, diabetes mellitus, and stroke.¹⁷ However, in recent meta-analyses a J-shaped or U-shaped relationship with body weight and mortality has been found, with a greater risk of death at the extremes of body weight.^{5,7}

The “obesity paradox” suggests that excess body weight may counterintuitively be protective and associated with greater survival in certain groups of people. Over the last decade, being overweight or mildly obese has been found to confer a survival benefit in patients with heart failure,¹⁶ coronary artery disease,¹⁴ and diabetes mellitus,⁵ and more recently even in patients with pneumonia.¹³

Observational studies of the obesity paradox after stroke have shown conflicting results. One retrospective study from Spain of more than 200,000 stroke patients found that obese patients had a lower in-hospital mortality risk and a lower hospital readmission rate than nonobese patients, even after adjusting for confounding factors.⁴ Another study of almost 19,000 stroke survivors found significantly better early and 10-year survival rates among overweight and obese patients than among those with normal body mass index (BMI).² By contrast, a much larger study of more than 71,000 patients hospitalized for stroke found that BMI had no impact on 30-day survival after stroke, even though BMI was inversely related to mean age at stroke onset.⁶ In another large retrospective study from the Netherlands, the authors found a lower risk of death due to recurrent stroke in the first month among patients who were overweight or obese.¹ These discrepant results may be best explained by a meta-analysis of 8 cohort studies that included 95,651 stroke patients, which found that obesity was associated with an increased risk of all-cause mortality, despite a decreased risk of stroke-specific mortality.³

Little is known about the impact of body weight on survival and recovery after ICH. In a Korean study of 1604 patients with ICH, BMI had no relationship with short-term (30-day) mortality (7.2% overall), whereas high BMI was independently associated with a reduced risk of long-term mortality, which was 27% at an average of 34 months’ follow-up.¹¹ The purpose of this study was to test the hypothesis that overweight or obese patients with ICH (BMI ≥ 25 kg/m²) are more likely to survive in the short term with favorable outcome than patients with normal BMI.

Methods

Study Population

Between February 2009 and September 2012, all patients with spontaneous ICH admitted to the Columbia University Medical Center Neurological Intensive Care Unit (NICU) were offered enrollment in the Intracerebral Hemorrhage Outcomes Project (ICHOP). Patients with secondary causes of ICH, such as vascular structural lesions, were not included. As part of the protocol at Columbia University, all patients with ICH are admitted for observation to the NICU and undergo 1 or 2 stability scans before being transferred to the step-down unit or stroke unit. The ICHOP is able to potentially include all consec-

utive patients with ICH at Columbia University Medical Center. The study was approved by the IRB, and written informed consent was obtained from the patient or an appropriate surrogate representative when the patient lacked capacity to consent. Patients younger than 18 years; patients with ICH due to malignancy, trauma, or hemorrhagic conversion of acute ischemic stroke; and patients with incomplete outcomes or BMI data were excluded from the study analysis. Patients received standard care for ICH in accordance with American Heart Association guidelines.⁹

Data Collection

Standard demographic, radiographic, and clinical data (including admission GCS scores) were prospectively collected by members of the study team, and the clinical course of each patient was reviewed in weekly meetings. Admission BMI was calculated using admission weight and height measured at the time of the initial emergency department or in-hospital evaluation. Based on prior studies, the obesity paradox was found to exist for patients with BMI ≥ 25 kg/m² but < 30 kg/m². For the purposes of the present analysis patients were classified as normal or underweight (BMI < 25 kg/m²) versus overweight or obese (BMI ≥ 25 kg/m²). Hence, we chose to dichotomize our BMI data at 25 kg/m². Admission CT scan was evaluated for hematoma volume, location, and the presence of IVH. Outcome at 90 days was determined by structured telephone or in-person interview. Favorable outcome was defined as a modified Rankin Scale (mRS) score of 0–3, indicating survival with no, minimal, or moderate disability, as opposed to poor outcome (mRS score 4–6), indicative of severe disability (bedbound or unable to walk without assistance) or death. Our study was a prospective, observational cohort study, and choosing to dichotomize the mRS score at 3 gave us a better chance of understanding whether an obesity paradox existed in patients with ICH.

Statistical Analysis

Univariate analyses of pertinent clinical variables comparing the 2 BMI groups and outcome were conducted using chi-square tests for categorical data, the Fisher’s exact t-test for normally distributed continuous variables, and the Mann-Whitney U-test for nonnormally distributed variables. A binary logistic regression model evaluating the relationship between BMI group and outcome was created using the ICH score (capturing age, coma level, ICH volume and location, and IVH),⁸ DNR status, and 2 variables that differed in frequency between the 2 BMI groups (sex and preexisting hypertension) as covariates. All analyses were performed using IBM SPSS software (version 22, IBM Corp.).

Results

A total of 286 patients with spontaneous ICH were enrolled in ICHOP during the study period. Of these patients, 202 (71%) had BMI and 3-month outcome information. Overall, 35% ($n = 70$) were classified as normal or underweight (< 25 kg/m²), as opposed to 65.3% ($n = 132$) who were overweight or obese (≥ 25 kg/m²). The high BMI group was more likely to be male and to be hyperten-

sive; there were no other significant differences in terms of baseline demographic or clinical variables (Table 1). In the ICU, 47% of the patients underwent mechanical ventilation, 29% had an external ventricular drain placed, and 14% underwent craniotomy.

Overall mortality at 3 months was 41% (82/202). Shift analysis showed an increase in the proportion of good outcomes and a reduction in mortality and poor outcome across the entire spectrum of mRS scores (Fig. 1). BMI ≥ 25 kg/m² was the only variable in the univariable analysis to be significantly associated with favorable outcome (Table 2). This association was confirmed in the multivariable analysis controlling for ICH score, sex, DNR status, and hypertension (adjusted odds ratio [OR] 2.05, 95% confidence interval [CI] 1.03–4.06, $p = 0.04$).

Discussion

In this study we found that overweight or obese patients with ICH were more likely to survive with favorable outcome at 3 months than those with normal BMI, confirming the presence of an obesity paradox in this critically ill population. Better understanding of the mechanisms that underlie this phenomenon may have implications for future treatment and rehabilitation strategies.

Compared with the aforementioned ABBA-ICH (Acute Brain Bleeding Analysis–ICH) cohort of ICH patients from Korea, which found evidence of an obesity paradox only with regard to long-term mortality,¹¹ we found a lower proportion of death and severe disability (mRS score of 5 or 6) at 3 months among patients with high BMIs. Thirty-day mortality in the ABBA-ICH cohort was just 7%, compared with 40% at 90 days in our study, which focused only on patients admitted to the NICU. In most US cohorts mortality from ICH has been reported to be about 30% (95% CI 20%–38%).¹⁵

In studies of patients with congestive heart failure, the effect of the obesity paradox seems to be modified by the fact that younger patients who are obese or overweight developed heart failure earlier than patients with normal body weight. It has thus been hypothesized that the existence of an obesity paradox can be partially explained by the younger age of congestive heart failure onset in high BMI patients.¹⁶ The 2 groups in our study did not differ with respect to their age, and the effect of the obesity paradox was not modified by age in our cohort. A J-shaped or U-shaped relationship exists between BMI and mortality for patients with heart failure and diabetes mellitus. Given the small number of patients at the extremes of BMI in our study, we could not explore this relationship.

An important finding of our study is the association of high BMI not only with reduced mortality, but also with a lower risk of severe disability (Fig. 1). The precise reason that excess adipose tissue may protect against death or severe disability after ICH is unclear. The most commonly cited hypothesis is that fat acts as a metabolic reservoir or buffer to protect individuals in fragile metabolic states.^{11,12} In a Chinese study of overweight stroke survivors, high BMI was independently associated with favorable 3-month functional recovery.¹⁸ Jönsson and colleagues have hypothesized that excess adipose may protect against nutritional

TABLE 1. Baseline characteristics according to BMI

Characteristic	Entire Cohort	BMI		p Value
		<25 kg/m ²	≥ 25 kg/m ²	
No. of patients	202	70	132	
Demographics				
Mean age in yrs $\pm$ SD	61 $\pm$ 18	60 $\pm$ 22	61 $\pm$ 16	0.16
Males	116 (57)	30 (43)	86 (65)	0.002
Mean BMI in kg/m ² $\pm$ SD	28 $\pm$ 6	22 $\pm$ 2.2	31 $\pm$ 5	0.00
Past medical history				
Hypertension	138 (68)	40 (57)	98 (74)	0.06
Diabetes mellitus Type 2	25 (12)	11 (16)	34 (26)	0.87
Kidney disease*	25 (12)	12 (17)	13 (10)	0.15
Congestive heart failure	10 (5)	4 (6)	6 (5)	0.74
Admission characteristics				
DNR code status	50 (25)	18 (26)	32 (24)	0.82
Mean APACHE-2 physiological sum score $\pm$ SD†	15 $\pm$ 8.4	14 $\pm$ 8	15 $\pm$ 8	0.67
Premorbid mRS score				0.50
0–1 (no disability)	143 (71)	44 (65)	99 (79)	
2–3 (mild disability)	30 (15)	14 (20)	16 (13)	
4–5 (moderate disability)	20 (10)	10 (15)	10 (8)	
Mean GCS score $\pm$ SD	10 $\pm$ 4	12 $\pm$ 3	10 $\pm$ 4	0.99
Mean ICH score $\pm$ SD‡	1.9 $\pm$ 1.3	1.8 $\pm$ 1.3	1.9 $\pm$ 1.3	0.84
ICH location				0.24
Lobar	61 (30)	25 (37)	36 (27)	
Deep	134 (66)	42 (63)	92 (70)	
Hospital complications & procedures				
Surgical evacuation	28 (14)	11 (16)	17 (13)	0.59
External ventricular drain	59 (29)	23 (33)	36 (27)	0.42
Fever	107 (53)	36 (51)	71 (54)	0.82
Mechanical ventilation	94 (47)	34 (49)	60 (45)	0.60
Pneumonia	56 (28)	18 (26)	38 (29)	0.68
90-day outcome				
mRS score 0–3 (no disability)	69 (34)	17 (24)	52 (39)	0.03
mRS score 4–6 (moderate-severe disability or death)	133 (66)	53 (76)	80 (61)	0.04
Mortality	82 (41)	32 (46)	49 (37)	0.3

APACHE = Acute Physiology and Chronic Health Evaluation.

Data given as number of patients (%) unless otherwise indicated. Boldface type indicates statistical significance; p values are 2-sided.

* Defined as creatinine level ≥ 2.0 mg/dl.

† Scale: 0 = no physiological derangement; 44 = maximal physiological derangement.

‡ Range: 0 (0% mortality) to 5 (100% mortality). The predicted mortality rate for an ICH score of 2 is 26%.

FIG. 1. Distribution of 90-day mRS outcomes according to BMI. The primary outcome measure was assessed using the mRS, a functional outcome scale. The 7 outcome categories are 0 (no symptoms), 1 (no significant disability despite symptoms and able to perform all usual duties and activities), 2 (slight disability; unable to perform all previous activities but able to look after own affairs without assistance), 3 (moderate disability; requires some help, but able to walk without assistance), 4 (moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance), 5 (severe disability; bedridden, incontinent, and requires constant nursing and attention), and 6 (death). Figure is available in color online only.

compromise and weight loss after stroke resulting from dysphagia and underfeeding, decreased appetite and a hypercatabolic state due to cytokine elevation, and poststroke depression.¹⁰ Indeed, there is evidence that hemorrhagic stroke survivors are more prone to long-term weight loss than those with ischemic stroke.¹⁰

A surprising finding in our cohort was that the ICH score did not predict outcome at 3 months. Although the ICH score was originally developed for prediction of 30-day mortality, it has been shown to be a good predictor of short- and long-term outcomes. Our finding of a lack of association of ICH score with 3-month outcomes may be due to the similarity in distribution of ICH scores of ≥ 2 in both groups. Likewise, our BMI groups also did not differ in the proportions of patients with ICH scores ≥ 2 .

Our study suffers from a number of limitations. The validity of our findings should be tempered by the relatively small size of our cohort, and generalizability should be tempered by the fact that this was a single-center study that only included ICH patients admitted to an ICU. Our analysis was also limited to the 71% of patients during the study period who had 90-day outcome data, which may have introduced selection bias. BMI might not be the best

measure of adiposity; we did not use more direct measures of central adiposity, such as waist circumference or triceps skinfold thickness. Another limitation of our study is that we did not include baseline measures of frailty or cardiorespiratory fitness. Recent studies have shown that the interaction between cardiorespiratory fitness and BMI might be more important than BMI alone in understanding whether an obesity paradox exists in a particular disease process.¹² We did not record measurements of weight at the time of follow-up in our cohort. Unintentional weight loss at 3 months might be a more important determinant of outcome than BMI at admission.¹⁰ Perhaps the relationship between adiposity and inflammation, and adiposity and cardiovascular fitness, needs to be explored in future studies, not only in patients with ICH but also in other patient populations. Understanding the mechanism of the obesity paradox could help identify new therapeutic targets for ICH.

Conclusions

These data suggest that being overweight at the time of ICH onset confers a protective benefit that results in a

TABLE 2. Univariable and multivariable predictors of favorable outcome at 90 days

Variable	Univariable Analysis			Multivariable Analysis		
	mRS Score 0–3 (n = 69)	mRS Score 4–6 (n = 133)	p Value	Adjusted OR	95% CI	p Value
Median ICH score (IQR)	2 (1–3)	2 (1–3)	0.47	0.84	0.64–1.11	0.23
Male sex (%)	42 (61)	74 (56)	0.55	0.87	0.46–1.63	0.68
Code status: DNR (%)	16 (23)	34 (26)	0.70	1.15	0.50–2.62	0.73
Hypertension (%)	48 (70)	90 (68)	0.78	0.93	0.47–1.83	0.83
BMI ≥ 25 kg/m ² (%)	52 (75)	80 (60)	0.04	2.05	1.03–4.06	0.04

IQR = interquartile range.

In the multivariable model, ORs < 1.00 indicate an association with poor outcome, whereas values > 1.00 indicate an association with favorable outcome, defined as survival with no or mild to moderate disability (mRS Score 0–3). Boldface type indicates statistical significance.

lower risk of death or severe disability at 3 months. If confirmed, better understanding of the mechanisms by which excess adipose tissue is advantageous may lead to the development of novel treatment strategies that can reproduce this effect.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Mayer, Dangayach, Grewal. Acquisition of data: Dangayach, Bruce, Chhatlani, Connolly, Falo. Analysis and interpretation of data: Mayer, Dangayach, De Marchis, Sefcik. Drafting the article: Mayer, Dangayach, Grewal. Critically revising the article: Dangayach, De Marchis, Connolly, Claassen. Reviewed submitted version of manuscript: Mayer, Dangayach, Agarwal, Schmidt. Statistical analysis: Dangayach. Administrative/technical/material support: Connolly, Falo. Study supervision: Claassen.

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