RESEARCH ARTICLE

Association Between Body Mass Index and Functional Outcomes in Patients With Intracerebral Hemorrhage

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Abstract

Background and Objectives

Evidence of the so-called "obesity paradox," which refers to the protective effect and survival benefit of obesity in patients with spontaneous intracerebral hemorrhage (ICH), remains controversial. This study aims to determine the association between body mass index (BMI) and functional outcomes in patients with ICH and whether it is modified by race/ethnicity.

Methods

Included individuals were derived from the Ethnic/Racial Variations of Intracerebral Hemorrhage study, which prospectively recruited 1,000 non-Hispanic White, 1,000 non-Hispanic Black, and 1,000 Hispanic patients with spontaneous ICH. Only patients with available BMI were included. The primary outcome was 90-day mortality. Secondary outcomes were mortality at discharge, modified Rankin Scale (mRS), Barthel Index, and self-reported health status measures at 90 days. Associations between BMI and ICH outcomes were assessed using univariable and multivariable logistic, ordinal, and linear regression models, as appropriate. Sensitivity analyses after excluding frail patients and by patient race/ethnicity were performed.

Results

A total of 2,841 patients with ICH were included. The median age was 60 years (interquartile range 51–73). Most patients were overweight (n = 943; 33.2%) or obese (n = 1,032; 36.3%). After adjusting for covariates, 90-day mortality was significantly lower among overweight and obese patients than their normal weight counterparts (adjusted odds ratio [aOR] = 0.71 [0.52–0.98] and aOR = 0.70 [0.50–0.97], respectively). Compared with patients with BMI <25 kg/m^2, those with BMI ≥25 kg/m^2 had better 90-day mRS (aOR = 0.80 [CI 0.67–0.95]), EuroQoL Group 5-Dimension (EQ-5D) (aβ = 0.05 [0.01–0.08]), and EQ-5D VAS (aβ = 3.80 [0.80–6.98]) scores. These differences persisted after excluding withdrawal of care patients. There was an inverse relationship between BMI and 90-day mortality (aOR = 0.97 [0.96–0.99]). Although non-Hispanic White patients had significantly higher 90-day mortality than non-Hispanic Black and Hispanic (26.6% vs 19.5% vs 18.0%, respectively; $p < 0.001$), no significant interactions were found between BMI and race/ethnicity. No significant interactions between BMI and age or sex for 90-day mortality were found, whereas for 90-day mRS, there was a significant interaction with age ($p_{interaction} = 0.004$).

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ERICH coinvestigators are listed in the appendix at the end of the article.

Glossary

aOR = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **EQ-5D** = EuroQoL Group 5-Dimension Self-Report Questionnaire; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **HF** = heart failure; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **LOS** = length of stay; **mRS** = modified Rankin Scale; **OR** = odds ratio; **VAS** = Visual Analog Scale.

Conclusion

We demonstrated that a higher BMI is associated with decreased mortality, improved functional outcomes, and better self-reported health status at 90 days, thus supporting the paradoxical role of obesity in patients with ICH. The beneficial effect of high BMI does not seem to be modified by race/ethnicity or sex, whereas age may play a significant role in patient functional outcomes.

Introduction

The prevalence of obesity has experienced a substantial rise over the past decades, and it is currently considered a global pandemic.[1] Obesity is well-known as an independent risk factor for multiple diseases, such as diabetes mellitus, hypertension, dyslipidemia, heart failure (HF), coronary heart disease, atrial fibrillation, and stroke.[2] Nonetheless, previous studies have documented a higher incidence of hemorrhagic stroke among underweight patients, suggesting that body mass index (BMI) may have a different effect on hemorrhagic vs ischemic stroke risk.[3-5] Underweight individuals younger than 65 years harbor as high as 3 times the risk of hemorrhagic stroke compared with normal weight individuals.[6] The existence of the so-called "obesity paradox," namely the survival and overall prognosis benefit among overweight and obese patients compared with their normal weight and underweight counterparts, has been proposed in several cardiovascular diseases,[7] end-stage renal disease,[8] chronic obstructive pulmonary disease,[9] pulmonary hypertension,[10] and pulmonary embolism.[11] However, the impact of obesity on hemorrhagic stroke risk and outcomes remains unclear, and most of the existing literature has focused on the ischemic stroke subtype, thus limiting generalizability to patients with intracerebral hemorrhage (ICH).[7,12-15]

ICH accounts for 10%–15% of all strokes worldwide and is associated with severe morbidity and an estimated early-term mortality rate of 30%–40%.[16] Similar to other diseases, the clinical impact of ICH seems to be influenced by patient socioeconomic status, with a significantly higher burden among lower-income populations; furthermore, race/ethnicity also plays a significant role in outcomes and prevalence, with ICH incidence being previously reported 1.6-fold greater among Mexican American compared with White non-Hispanic population.[17,18] Despite advances in the diagnosis and treatment of ischemic stroke, we have seen minimal progress in treatment or improved outcomes following ICH. Furthermore, for the obesity paradox, data remain scarce, and its effect among patients with ICH is controversial.[19-21] In the present analysis, we hypothesized that BMI would be inversely associated with mortality and patient functional outcomes following ICH. It is well-known that stroke affects a disproportionate number of persons from minoritized racial and ethnic groups, with the highest rates documented among Black and Hispanic patients, and that race/ethnicity influence the risk of first-ever ICH.[18,22] Furthermore, obesity burden is known to affect some race/ethnic groups more than others, with non-Hispanic Black and Hispanic adults having the highest age-adjusted prevalence of obesity (49.9% and 45.6%, respectively) followed by non-Hispanic White and non-Hispanic Asian adults (41.4% and 16.1%, respectively).[23] In addition, the relationship between BMI and body fat percentage as well as overall adverse health events vary among race/ethnic groups.[24] Despite similar BMI, a higher cardiometabolic risk has been reported for Asian patients when compared with their White counterparts.[24] Thus, we hypothesized that the effect of BMI on ICH overall outcomes may differ by patient race/ethnicity.

Methods

Study Design

Data for this study were derived from the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study, a multicenter, prospective case-control study of patients with spontaneous ICH. The design and methodology of the ERICH protocol have been previously described in detail.[25] In brief, ERICH study was designed to recruit 1000 ICH case participants and 1,000 control participants from non-Hispanic White, non-Hispanic Black, and Hispanic populations, for a total of 3,000 case and 3,000 control participants with the aim of studying epidemiologic characteristics and genomics associated with ICH. Race/ethnicity was obtained through self-report by patient or proxy using federally mandated definitions. The data from all sites were deidentified and pooled for analysis. Patients in this study were derived from the ICH case cohort. Only patients with available BMI were included in the analysis. This study follows the guidelines set forth by

the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Standard Protocol Approvals, Registrations, and Patient Consents

ERICH participants were recruited from 19 clinical centers, that encompass 42 recruitment sites, within the United States from September 2009 to July 2016, with Institutional Review Board approval obtained at each site. Written informed consent from subject or legally authorized representative was required for all patients before study enrollment.[25]

BMI Categories

BMI was calculated as the ratio of weight in kilograms (kg) and the square of height in meters (m^2). Height was self-reported by patients, or legal proxies and weight, which in most cases corresponded to patient bed weight, were recorded at initial contact. BMI was analyzed as a continuous and categorical variable. Patients were stratified into the following BMI categories: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 kg/m^2 to <25 kg/m^2), overweight (BMI 25 kg/m^2 to <30 kg/m^2), and obese (BMI ≥30 kg/m^2). Normal weight was designated as the reference group. BMI categories were derived from the thresholds established by the Centers for Disease Control and Prevention.

Baseline Data and Variables

The baseline data comprised patient demographics and clinical presentation, ICH features, treatment approach, and overall outcomes. Patient demographics included age, sex, race/ethnicity, medical and behavioral history, medication history, preexisting modified Rankin Scale (mRS) score, ICH score, and Glasgow scale (GCS) score. Sex was treated as a binary variable (male vs female) and was obtained through self-report by patient or proxy. ICH features queried were location, initial volume, and presence of concomitant interventricular hemorrhage. Performed interventions included ICH surgical evacuation, external ventricular drain, and CSF shunt placement.

Outcomes of Interest

The primary outcome was 90-day mortality. The secondary outcomes included mRS score at 90 days, both as an ordinal and categorical variable (good outcome mRS 0–2; favorable outcome mRS 0–3); mortality rate at discharge; length of stay (LOS); EuroQol Group 5-Dimension (EQ-5D; on a scale of −0.11 to 1, with higher values indicating a better quality of life); EQ-5D Visual Analog Scale (EQ-5D VAS; on a scale of 0–100, with higher values indicating a better quality of life); and Barthel Index (on a scale of 0–100, with higher values indicating increased functional independence) at 90 days. Health-related quality of life metrics were obtained using self-report questionnaires.

Statistical Analyses

All statistical analyses were performed using Stata (v.16.1, StataCorp). Descriptive statistics (frequencies and percentages for categorical variables; medians and interquartile ranges (IQRs) for continuous variables) were used to summarize baseline demographic, clinical, imaging, and treatment characteristics, which were compared based on patient BMI (i.e., underweight vs normal weight vs overweight vs obese). Categorical variables were compared using Pearson chi-square or Fisher exact tests, as appropriate. Continuous variables were compared using Student t or Mann-Whitney U tests, as appropriate. Associations between BMI and the outcomes of interest were assessed using logistic, ordinal, and linear regression models, as appropriate, and corresponding odds ratios (ORs), β values, and 95% confidence intervals (CIs) were reported. The regression models were then adjusted for covariates with $p < 0.05$ from the univariable models. The independent variables were tested for multicollinearity using a tolerance and strict variance inflation factor cutoff of 5. Statistical significance was defined as $p < 0.05$, and all tests were 2-tailed.

Additional analyses were performed after patients were dichotomized into underweight or normal weight (BMI <25 kg/m^2) and overweight or obese (BMI ≥25 kg/m^2), with the former group used as reference. Moreover, as frail patients may be more likely to undergo withdrawal of care, we also performed a sensitivity analysis to exclude patients who were designated as comfort care during hospitalization. Since age may follow a non-normal distribution and its impact on patient outcomes may not be linear but exponential, natural log transformation was used to model age and reduce its skewness; the transformed variable was then entered to the multivariable logistic models. Finally, to investigate the interactions between patient race/ethnicity, sex, and age with BMI for mortality and mRS score at 90 days, multivariable logistic regression interaction models included respective predictors from the initial model and the interaction terms race/ethnicity (non-Hispanic White vs non-Hispanic Black vs Hispanic) × BMI, sex (male vs female) × BMI, and age × BMI.

Data Availability and Access Statement

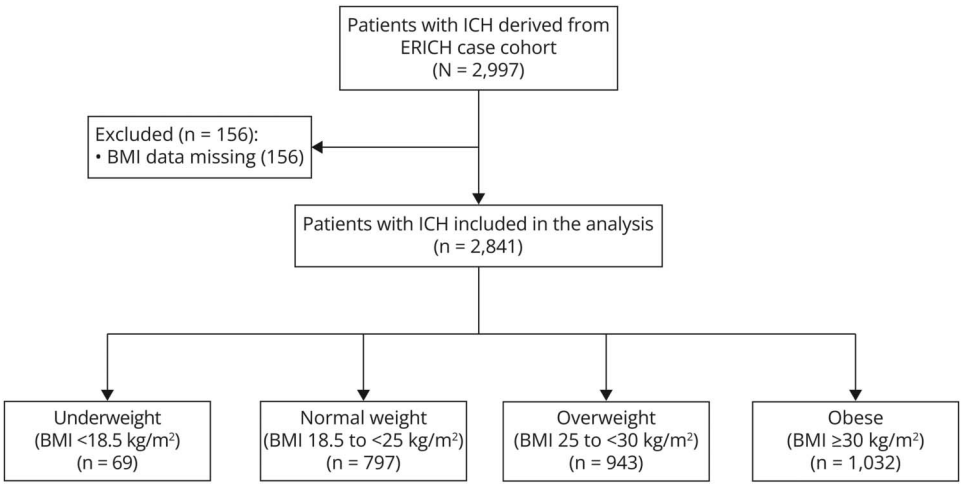
The first and senior authors had full access to all the data and take responsibility for its integrity and validity. All data relevant to the study are included in the article or uploaded as supplementary information.

Results

Comparison of Baseline Characteristics

The ERICH study cohort database comprised 2,997 patients with spontaneous ICH diagnosis. After excluding patients with missing BMI data (n = 156), a total of 2,841 patients were included in the final analysis and further categorized based on their BMI (Figure). Most patients were obese (n = 1,032, 36.3%; median BMI = 34.3) or overweight (n = 943, 33.1%; median BMI = 27.3). The remaining 30.4% were categorized as underweight (n = 69, 2.4%; median BMI = 17.2) or normal weight (n = 797, 28%; median BMI = 22.8). The baseline demographic, clinical, and treatment data of

Figure Patient Selection and Stratification Based on BMI



BMI = body mass index; ICH = intracranial hemorrhage; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage.

patients stratified by BMI categories are presented in Table 1. The median age at presentation for the entire cohort was 60 years (IQR 51–73), with a significant difference among BMI groups ($p < 0.001$). Overweight and obese patients were predominantly male (63.5% and 57.7%, respectively) and Hispanic (38.1% and 36.7%, respectively). Compared with underweight and normal weight patients, overweight and obese had significantly higher rates of hypertension (85.1% and 87.8%, respectively; $p < 0.001$) and diabetes mellitus (30.6% and 34.4%, respectively; $p < 0.001$). Underweight and normal weight patients were significantly more likely to have a positive smoking history ($p < 0.001$) and cocaine abuse ($p < 0.001$). In addition, both had significantly higher rates of a past ICH than overweight and obese patients (7.6% and 7.1% vs 4% and 3.9%, respectively; $p = 0.005$). However, after adjusting for patient age and sex, only the overweight cohort demonstrated a significantly lower likelihood of having a past ICH (adjusted odds ratio [aOR] = 0.58 [0.38–0.90]) when compared with their normal weight counterparts. There were significant differences in the baseline mRS distribution ($p < 0.001$), initial ICH volume ($p = 0.012$), ICH score ($p = 0.001$), and presence of lobar ICH ($p < 0.001$) among the 4 BMI groups.

Comparison of Outcomes

The comparison of primary and secondary outcomes by BMI categories is presented in Table 2. Overall, the highest 90-day mortality rates were documented among underweight and normal weight patients (35.6% and 27.3%, respectively). Overweight and obese patients had a significantly lower 90-day mortality rate when compared with their normal weight counterparts (OR = 0.67 [0.52–0.85] and OR = 0.54 [0.42–0.69], respectively). These differences persisted after adjusting for baseline differences (aOR = 0.71 [0.52–0.98] for overweight; aOR = 0.70 [0.50–0.97] for obese). For the secondary outcomes, no significant differences were found between groups after adjusting for baseline differences. When analyzed as a continuous variable, after adjusting for covariates, a higher BMI was associated with lower odds of 90-day mortality (aOR = 0.97 [0.96–0.99]), but no significant association was found with the secondary outcomes (Table 3).

Secondary Analyses

The baseline demographic, clinical, and treatment data of patients stratified by 2 BMI categories are presented in eTable 1 (links.lww.com/WNL/D292). Most patients were categorized as overweight or obese (n = 1,975, 69.5%; median BMI = 30.2), whereas the remaining 30.5% (n = 866) were considered underweight or normal weight (median BMI = 22.5). The comparison of primary and secondary outcomes of patients with BMI <25 kg/m^2 vs those with BMI ≥25 kg/m^2 is presented in Table 3. The underweight or normal weight group had a significantly higher 90-day mortality rate compared with the overweight or obese group (27.9% vs 18.4% OR = 0.58 [0.47–0.71]). This difference remained significant after adjusting for baseline differences (aOR = 0.67 [0.52–0.86]). Furthermore, after adjusting for baseline differences, patients with BMI ≥ 25 kg/m^2 had better mRS (aOR = 0.80 [0.67–0.95]), EQ-5D (aβ = 0.05 [0.01–0.08]), and EQ-5D VAS (aβ = 3.80 [0.80–6.98]) scores at 90 days. No significant differences were found for the remaining secondary outcomes (Table 4).

Sensitivity analyses for the outcomes of interest after excluding those in whom care was withdrawn (n = 289) are presented in eTables 2 and 3 (links.lww.com/WNL/D292). Underweight patients had a higher 90-day mortality rate (OR = 2.01 [1.04–3.87]), whereas overweight and obese patients had better survival rates (OR = 0.65 [0.46–0.90] and OR = 0.50 [0.36–0.70], respectively). However, this difference only remained significant for obese patients after adjusting for baseline characteristics (aOR = 0.58 [0.37–0.89]). For

Table 1 Baseline Demographic, Clinical, and Treatment Characteristics of Patients With ICH by BMI Categories

Characteristic	Underweight n = 69	Normal weight n = 797	Overweight n = 943	Obese n = 1,032	*p* Value
Age in years, median (IQR)	74 (59–84)	65 (55–79)	61 (52–73)	57 (49–66)	<0.001
Sex					<0.001
Male	31/69 (44.9)	444/797 (55.7)	599/943 (63.5)	596/1,032 (57.7)	
Female	38/69 (55.1)	353/797 (44.3)	344/943 (36.5)	436/1,032 (42.3)	
Race/ethnicity					<0.001
White	21/69 (30.4)	315/797 (39.5)	315/943 (33.4)	284/1,032 (27.5)	
Black	29/69 (42.0)	275/797 (34.5)	268/943 (28.4)	369/1,032 (35.7)	
Hispanic	19/69 (27.5)	207/797 (25.9)	360/943 (38.1)	379/1,032 (36.7)	
Behavioral history					
Ever smoked	45/68 (66.2)	420/792 (53.0)	461/938 (49.1)	441/1,027 (42.9)	<0.001
No. cigarettes per day, median (IQR)	10 (5–20)	10 (5–20)	10 (5–20)	10 (4–20)	0.780
Alcohol use	22/61 (36.1)	329/747 (44.0)	360/884 (40.7)	376/958 (39.2)	0.194
Cocaine use	6/63 (9.5)	78/742 (10.5)	57/866 (6.9)	45/935 (4.8)	<0.001
Marijuana use	4/61 (6.6)	44/727 (6.0)	37/857 (4.3)	36/929 (3.8)	0.163
Medical history					
Hypertension	57/69 (82.6)	634/793 (79.9)	798/938 (85.1)	905/1,031 (87.8)	<0.001
Diabetes mellitus	13/69 (18.8)	161/796 (20.2)	289/943 (30.6)	355/1,031 (34.4)	<0.001
Dyslipidemia	33/68 (48.5)	321/785 (40.9)	466/926 (50.3)	452/1,016 (44.5)	0.001
Atrial fibrillation	10/68 (14.7)	109/795 (13.7)	140/943 (14.8)	144/1,032 (14.0)	0.909
MI	7/68 (10.3)	62/793 (7.8)	90/943 (9.5)	86/1,031 (8.3)	0.571
CAD	12/68 (17.7)	128/793 (16.1)	180/941 (19.1)	157/1,028 (15.3)	0.131
Ischemic stroke/TIA	13/66 (19.7)	131/788 (16.6)	141/929 (15.1)	143/1,020 (14.0)	0.340
ICH	5/66 (7.6)	56/788 (7.1)	37/927 (4)	40/1,021 (3.9)	0.005
SAH	1/64 (1.6)	4/786 (0.5)	5/928 (0.5)	5/1,021 (0.5)	0.725
PVD	2/66 (3.0)	18/779 (2.3)	33/913 (3.6)	17/994 (1.7)	0.065
Medication history					
Antihypertensive	37/42 (88.1)	444/552 (80.4)	568/707 (80.3)	658/822 (80)	0.649
Anticoagulant	10/69 (14.5)	81/783 (10.3)	111/930 (11.9)	93/1,019 (9.1)	0.154
Warfarin	6/10 (60.0)	57/81 (70.4)	76/111 (68.5)	75/93 (80.6)	
UFH/LMWH	0/10 (0)	4/81 (4.9)	5/111 (4.5)	3/93 (3.2)	
DOACs	0/10 (0)	4/81 (4.9)	6/111 (5.4)	6/93 (6.5)	
Unspecified	4/10 (40.0)	16/81 (19.8)	24/111 (21.6)	9/93 (9.7)	
Antiplatelet	32/69 (46.4)	336/786 (42.7)	446/935 (47.7)	429/1,024 (41.9)	0.054
Cholesterol reducing	15/69 (21.7)	189/797 (23.7)	256/943 (27.1)	236/1,032 (22.8)	0.132
GCS, median (IQR)	14 (11–15)	15 (11–15)	15 (11–15)	15 (11–15)	0.914
Baseline mRS score					<0.001
0	35/68 (51.4)	510/795 (64.1)	672/939 (71.6)	778/1,028 (75.7)	
1	12/68 (17.6)	112/795 (14.1)	119/939 (12.7)	86/1,028 (8.4)	

Continued

Table 1 Baseline Demographic, Clinical, and Treatment Characteristics of Patients With ICH by BMI Categories *(continued)*

Characteristic	Underweight n = 69	Normal weight n = 797	Overweight n = 943	Obese n = 1,032	*p* Value
2	8/68 (11.7)	90/795 (11.3)	81/939 (8.6)	94/1,028 (9.1)	
3	5/68 (7.3)	49/795 (6.2)	37/939 (3.9)	42/1,028 (4.1)	
4	7/68 (10.3)	26/795 (3.3)	26/939 (2.7)	22/1,028 (2.1)	
5	1/68 (1.5)	8/795 (1.0)	4/939 (0.4)	6/1,028 (0.6)	
Initial ICH volume, median (IQR)	12.6 (4.4–30.7)	10.8 (4.1–27.3)	11.5 (4.1–29.4)	10.0 (3.4–23.8)	0.012
Lobar ICH	24/69 (34.8)	292/797 (36.6)	277/943 (29.4)	259/1,032 (25.1)	<0.001
Presence of IVH	27/69 (39.1)	365/797 (45.8)	425/943 (45.1)	429/1,032 (41.6)	0.204
ICH score, median (IQR)	1.5 (1–2)	1 (0–2)	1 (0–2)	1 (0–2)	0.001
Intervention					
Surgical evacuation	6/69 (8.7)	80/797 (10)	89/942 (9.4)	106/1,031 (10.3)	0.916
EVD placement	11/69 (15.9)	146/797 (18.3)	192/943 (20.4)	214/1,032 (20.7)	0.475
CSF shunt placement	1/69 (1.5)	28/797 (3.5)	55/942 (5.8)	48/1,032 (4.6)	0.074

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; DOACs = direct oral anticoagulants; EVD = external ventricular drain; GCS = Glasgow Coma Scale; ICH = intracranial hemorrhage; IQR = interquartile range; IVH = interventricular hemorrhage; LMWH = low-molecular-weight heparin; MI = myocardial infraction; mRS = modified Rankin Scale; No. = number; PVD = peripheral vascular disease; SAH = subarachnoid hemorrhage; TIA = transient ischemic attack; UFH = unfractionated heparin.
Data given as number of patients (%) unless otherwise indicated.

comparisons between 2 BMI groups, even after excluding frail patients and adjusting for baseline characteristics, patients with BMI ≥25 kg/m^2 demonstrated a significantly lower 90-day mortality rate (aOR = 0.67 [0.52–0.86]), better mRS scores (aOR = 0.80 [0.67–0.95]), and health-related quality of life metrics at 90 days (aβ = 0.05 [0.01–0.08] for EQ-5D and aβ = 3.89 [0.80–6.98] for EQ-5D VAS) compared with those with a BMI <25 kg/m^2.

Analyses by Patients Race/Ethnicity, Sex, and Age

A comparison between baseline characteristics among non-Hispanic White, non-Hispanic Black, and Hispanic patients based on BMI categories (i.e., underweight vs normal weight vs overweight vs obese) is presented in eTables 4, 5, and 6 (links.lww.com/WNL/D292), respectively.

Overall, there was a significantly higher 90-day mortality rate for non-Hispanic White patients when compared with non-Hispanic Black and Hispanic patients (26.6% vs 19.5% vs 18.0%, respectively; $p < 0.001$). However, there were no significant interactions between BMI × race/ethnicity for the primary outcome (obese and overweight vs normal and underweight non-Hispanic Black; $p_{interaction} = 0.303$; obese and overweight vs normal and underweight Hispanic; $p_{interaction} = 0.897$) and mRS at 90 days (obese and overweight vs normal and underweight non-Hispanic Black; $p_{interaction} = 0.679$; and obese and overweight vs normal and underweight Hispanic; $p_{interaction} = 0.545$). Analyses evaluating primary and secondary outcomes by race/ethnicity based on BMI categories are presented in eTables 7–9 (links.lww.com/WNL/D292). After adjusting for baseline characteristics, a lower mortality rate was observed only among obese non-Hispanic Black patients (aOR = 0.55 [0.31–0.95]), whereas no significant differences were found for non-Hispanic White and Hispanic patients.

Sex (male vs female) did not have a significant interaction with BMI for the primary outcome ($p_{interaction} = 0.772$) and mRS at 90 days ($p_{interaction} = 0.843$). Furthermore, after natural log transformation of age under the assumption of its nonlinear relationship with outcome, obese patients demonstrated significantly better 90-day mRS scores compared with their normal weight counterparts (aOR = 0.80 [0.65–0.98]) and a significant inverse relationship between BMI and mRS at 90 days was also documented (aOR = 0.98 [0.97–0.99]). In the case of 2 BMI groups, a significantly higher likelihood of achieving an mRS of 0–2 at 90 days (aOR = 1.25 [1.00–1.55]) and better Barthel Index (aβ = 4.31 [0.57–8.06]) was demonstrated among patients with BMI ≥25 kg/m^2. Although no significant interaction was found between BMI and age for the primary outcome ($p_{interaction} = 0.971$ and $p_{interaction} = 0.687$ before and after natural log transformation of age, respectively), there was a significant interaction for mRS at 90 days in the multivariable models, where older age was associated with a stronger positive effect on poor outcomes (i.e., higher odds of having a worse 90-day mRS score) among patients with BMI <25 kg/m^2 compared with those with a BMI ≥25 kg/m^2 ($p_{interaction} = 0.004$ and $p_{interaction} = 0.001$ before and after natural log transformation of age, respectively).

Table 2 Comparisons of Primary and Secondary Outcomes of Patients With ICH by 4 BMI Categories

Outcome		Unadjusted value	*p* Value	Adjusted value[d]	*p* Value
Primary outcome					
Mortality at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
Normal weight	185/677 (27.3)	Ref.	Ref.	Ref.	Ref.
Underweight	21/59 (35.6)	1.46 [0.84 to 2.57]	0.177	1.65 [0.82 to 3.28]	0.153
Overweight	161/796 (20.2)	0.67 [0.52 to 0.85]	0.001	0.71 [0.52 to 0.98]	0.038
Obese	151/893 (16.9)	0.54 [0.42 to 0.69]	<0.001	0.70 [0.50 to 0.97]	0.035
Secondary outcomes					
mRS 0–2 at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
Normal weight	224/677 (33.1)	Ref.	Ref.	Ref.	Ref.
Underweight	11/59 (18.6)	0.46 [0.23 to 0.90]	0.025	0.57 [0.25 to 1.31]	0.190
Overweight	292/797 (36.6)	1.16 [0.94 to 1.45]	0.155	1.16 [0.88 to 1.53]	0.281
Obese	357/893 (39.9)	1.34 [1.09 to 1.65]	0.005	1.14 [0.86 to 1.50]	0.343
mRS 0–3 at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
Normal weight	319/677 (47.1)	Ref.	Ref.	Ref.	Ref.
Underweight	21/59 (35.5)	0.62 [0.35 to 1.07]	0.091	0.69 [0.33 to 1.42]	0.320
Overweight	409/797 (51.3)	1.18 [0.96 to 1.45]	0.108	1.14 [0.87 to 1.49]	0.332
Obese	401/893 (55.1)	1.37 [1.12 to 1.68]	0.002	1.12 [0.85 to 1.47]	0.405
mRS at 90 d	Median (IQR)	OR [95% CI]		OR [95% CI]	
Normal weight	4 (2 to 6)	Ref.	Ref.	Ref.	Ref.
Underweight	5 (3 to 6)	1.75 [1.08 to 2.82]	0.022	1.31 [0.75 to 2.26]	0.333
Overweight	3 (2 to 5)	0.80 [0.67 to 0.96]	0.022	0.84 [0.68 to 1.03]	0.098
Obese	3 (2 to 4)	0.68 [0.57 to 0.81]	<0.001	0.83 [0.67 to 1.02]	0.078
Mortality at discharge	N (%)	OR [95% CI]		OR [95% CI]	
Normal weight	93/797 (11.7)	Ref.	Ref.	Ref.	Ref.
Underweight	8/69 (11.6)	0.99 [0.46 to 2.14]	0.985	1.04 [0.41 to 2.59]	0.928
Overweight	94/943 (9.9)	0.83 [0.61 to 1.13]	0.254	0.94 [0.63 to 1.39]	0.761
Obese	104/1,032 (10.1)	0.84 [0.63 to 1.14]	0.277	1.13 [0.75 to 1.69]	0.541
EQ-5D score at 90 d[a]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
Normal weight	0.572 (0 to 0.827)	Ref.	Ref.	Ref.	Ref.
Underweight	0.271 (0 to 0.821)	−0.06 [−0.17 to 0.03]	0.199	−0.04 [−0.13 to 0.04]	0.323
Overweight	0.688 (0.077 to 0.843)	0.06 [0.02 to 0.10]	0.002	0.03 [−0.00 to 0.07]	0.085
Obese	0.688 (0.165 to 0.827)	0.07 [0.03 to 0.11]	<0.001	0.02 [−0.01 to 0.06]	0.209
EQ-5D VAS score at 90 d[b]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
Normal weight	50 (0 to 75)	Ref.	Ref.	Ref.	Ref.
Underweight	40 (0 to 75)	−6.74 [−15.6 to 2.18]	0.139	−5.09 [−13.47 to 3.28]	0.233
Overweight	60 (20 to 80)	4.42 [0.98 to 7.85]	0.012	2.74 [−0.51 to 6.00]	0.099
Obese	60 (30 to 80)	6.43 [3.08 to 9.79]	<0.001	1.73 [−1.56 to 5.04]	0.302

Continued

Table 2 Comparisons of Primary and Secondary Outcomes of Patients With ICH by 4 BMI Categories *(continued)*

Outcome		Unadjusted value	*p* Value	Adjusted value[d]	*p* Value
Barthel Index at 90 d[c]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
Normal weight	60 (0 to 100)	Ref.	Ref.	Ref.	Ref.
Underweight	10 (0 to 90)	−12.15 [−23.25 to −1.06]	0.032	−7.00 [−16.91 to 2.89]	0.165
Overweight	65 (5 to 100)	3.35 [−0.92 to 7.62]	0.124	1.08 [−2.78 to 4.95]	0.582
Obese	80 (15 to 100)	8.17 [4.00 to 12.34]	<0.001	1.73 [−2.16 to 5.64]	0.383
LOS, d	Mean ± SD	Beta [95% CI]		Beta [95% CI]	
Normal weight	12.1 ± 11.8	Ref.	Ref.	Ref.	Ref.
Underweight	12.7 ± 10.8	0.61 [−3.21 to 4.45]	0.753	1.13 [−2.84 to 5.10]	0.576
Overweight	13.9 ± 19.9	1.90 [0.43 to 3.38]	0.011	0.97 [−0.57 to 2.53]	0.216
Obese	13.1 ± 13.8	1.09 [−0.35 to 2.53]	0.138	−0.34 [−1.91 to 1.23]	0.671

Abbreviations: BMI = body mass index; CI = confidence interval; EQ-5D = EuroQoL Group 5-Dimension Self-Report Questionnaire; ICH = intracerebral hemorrhage; LOS = length of stay; mRS = modified Rankin Scale; OR = odds ratio; VAS = Visual Analog Scale.
[a] The EuroQoL Group 5-Dimension (EQ-5D) Self-Report Questionnaire is a standardized instrument for the measurement of generic health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from −0.11 to 1.00, with higher scores indicating better health and death indicated by score of 0.
[b] EQ-5D Visual Analog Scale (EQ-5D VAS) is the second part of the EQ-5D Questionnaire, where the patient is asked to mark his/her health status on a 20-centimeter vertical scale with end points of 0 (i.e., "the worst health you can imagine") and 100 (i.e., "the best health you can imagine").
[c] The Barthel Index is an ordinal 10-item scale for measuring performance of activities of daily living. Score ranges from 0 to 100, with 0 indicating severe disability and 100 indicating no disability.
[d] Values were adjusted for age, sex, race/ethnicity, smoke history, cocaine use, history of hypertension, history of diabetes, history of ICH, history of hyperlipidemia, baseline mRS, initial ICH volume, and presence of lobar ICH.

Discussion

Our analysis of the data from the large multicenter ERICH study on ICH has yielded several significant findings regarding the obesity paradox. First, we found that overweight and obese patients had around 30% lower odds of mortality at 90 days compared with their normal weight counterparts, even after adjusting for other measured risk factors of post-ICH mortality. Second, a significant inverse correlation between BMI and mortality at 90 days was identified after adjusting for patient baseline characteristics. Third, the effect of BMI on ICH 90-day mortality risk does not seem to be modified by patient race/ethnicity, sex, or age.

The influence of BMI on patient absolute risk of hemorrhagic stroke and overall outcomes remains under investigation. The paradoxical survival benefit associated with increased BMI was first established among patients with HF and thereafter documented in a number of other conditions.[7-11,26,27] Previous studies evaluating the obesity paradox among stroke patients have yielded controversial results.[19-21,28-35] For absolute risk, although underweight and normal weight patients had significantly higher rates of a past ICH compared with overweight and obese groups, after adjusting for age and sex, a significant correlation persisted only among overweight patients (aOR = 0.58 [0.38–0.90]. Furthermore, in this study, overweight and obese patients had a significantly lower mortality rates at 90 days compared with their normal weight counterparts. In addition, patients with a BMI ≥25 kg/m^2 also had better mRS, EQ-5D, and EQ-5D VAS scores at 90 days than those with BMI <25 kg/m^2. Similarly, Dangayach et al.[20] demonstrated that overweight and obese patients with ICH had lower mortality and severe disability (defined as mRS of 5–6) rates at 90 days compared with those with a normal BMI. Sun et al.[29] also showed a decreased mortality and better functional outcomes at the 12-month follow-up associated with being obese at the time of ICH onset. Other studies have also suggested that obesity and morbid obesity seem to be protective against mortality in ICH.[21,33] This finding was later corroborated by Hoffman et al., who documented lower odds of in-hospital mortality among obese (OR = 0.62; $p < 0.001$) and morbidly obese patients (OR = 0.76; $p < 0.001$).[19]

On the contrary, a number of other studies did not support the existence of an obesity paradox in patients with ICH. They reported a higher likelihood of poor disposition outcomes among obese patients (OR = 6.85; $p = 0.001$) than those with a normal weight, particularly in the non-White population.[34,36] Cao et al.[35] investigated this relationship among patients with ICH enrolled in the China Stroke Center Alliance study and demonstrated that underweight patients had higher odds (OR = 2.05 [1.19–3.55]) of in-hospital mortality than those with normal weight, but no significant association was observed for overweight or obese patients. In addition, they found that obesity increased the odds of hematoma expansion (OR = 1.32 [1.16–1.50]) and that there was an increased risk of in-hospital complications among underweight and obese patients.[35]

Table 3 Comparisons of Primary and Secondary Outcomes of Patients With ICH Based on BMI as a Continuous Variable

Outcome	Effect variable	Unadjusted value	*p* Value	Adjusted value[d]	*p* Value
Primary outcome					
Mortality at 90 d	OR	0.96 [0.95 to 0.98]	<0.001	0.97 [0.96 to 0.99]	0.016
Secondary outcomes					
mRS 0–2 at 90 d	OR	1.01 [1.00 to 1.02]	0.003	1.01 [0.99 to 1.02]	0.145
mRS 0–3 at 90 d	OR	1.01 [1.00 to 1.02]	0.018	1.00 [0.99 to 1.01]	0.541
mRS at 90 d	OR	0.98 [0.97 to 0.99]	<0.001	0.98 [0.97 to 1.00]	0.067
Mortality at discharge	OR	0.98 [0.97 to 1.00]	0.161	0.99 [0.97 to 1.01]	0.422
EQ-5D score at 90 d[a]	Beta	0.00 [0.00 to 0.00]	0.002	0.00 [−0.00 to 0.00]	0.165
EQ-5D VAS score at 90 d[b]	Beta	0.30 [0.12 to 0.49]	0.001	0.14 [−0.04 to 0.34]	0.137
Barthel Index at 90 d[c]	Beta	0.39 [0.17 to 0.62]	0.001	0.14 [−0.09 to 0.37]	0.236
LOS, d	Beta	0.06 [−0.01 to 0.14]	0.105	−0.00 [−0.08 to 0.07]	0.962

Abbreviations: BMI = body mass index; CI = confidence interval; EQ-5D = EuroQoL Group 5-Dimension Self-Report Questionnaire; ICH = intracerebral hemorrhage; LOS = length of stay; mRS = modified Rankin Scale; OR = odds ratio; VAS = Visual Analog Scale.
[a] The EuroQoL Group 5-Dimension (EQ-5D) Self-Report Questionnaire is a standardized instrument for the measurement of generic health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from −0.11 to 1.00, with higher scores indicating better health and death indicated by score of 0.
[b] EQ-5D Visual Analog Scale (EQ-5D VAS) is the second part of the EQ-5D Questionnaire, where the patient is asked to mark his/her health status on a 20-centimeter vertical scale with end points of 0 (i.e., "the worst health you can imagine") and 100 (i.e., "the best health you can imagine").
[c] The Barthel Index is an ordinal 10-item scale for measuring performance of activities of daily living. Score ranges from 0 to 100, with 0 indicating severe disability and 100 indicating no disability.
[d] Values were adjusted for age, sex, race/ethnicity, smoke history, cocaine use, marijuana use, history of hypertension, history of diabetes, history of ICH, history of hyperlipidemia, baseline mRS, presence of lobar ICH, and CSF shunt placement.

The mechanism behind the obesity paradox is not entirely clear and is believed to involve several factors, such as an increased sympathetic nervous system activity, mitochondrial function augmentation, and higher serum lipoproteins levels.[37,38] Another explanation is that the presence of a greater metabolic reserve among overweight and obese patients partially overcomes the increased energy expenditure that occurs during catastrophic events and its resultant chronically debilitated states.[37] Moreover, previous studies have suggested that being overweight in the aged population does not pose an additional risk of death, concluding that frailty may be a mediating mechanism of the obesity paradox.[39] Following this notion, we could expect that the obesity paradox functions over a long period of time after the occurrence of a critical illness (such as ICH) and, thus, could partially explain the differences regarding the specific timing of the survival benefit seen among overweight and obese patients. For example, although multiple studies have shown lower in-hospital mortality and early readmittance risk among obese patients,[19,21,30] Kim et al.[32] showed that obesity was associated with a lower risk of long-term mortality but had no significant effect on 30-day mortality risk after ICH. In addition, Vemmos et al.[31] found that after adjusting for confounding variables, overweight (HR = 0.82 [0.71–0.94]) and obese patients (HR = 0.71 [0.59–0.86]) had a significantly lower risk of 10-year mortality following first-ever acute stroke compared with normal weight patients. In this study, although a higher BMI was correlated with lower mortality rates at 90 days, no significant differences in mortality at discharge were documented. As survival benefit is only apparent after the acute phase of the disease, it may be hypothesized that mechanisms underlying the obesity paradox are more important in the recovery (i.e., follow-up) phase vs the acute (i.e., in-hospital) phase after ICH.

This study has the advantage of assessing patient outcomes at the 90-day follow-up, whereas most of available data tend to be limited to in-hospital and at discharge outcomes. In addition, it accounts for multiple baseline characteristics, which allow adjusting for potential confounders. It should be noted that despite the significantly higher prevalence of hypertension among overweight and obese patients, treatment rates, although not statistically significant, were higher among underweight patients. This finding could suggest a higher frequency of undiagnosed hypertension among the overweight and obese groups, which could influence their response to acute stressors and partially explain the obesity paradox, as patients with long-standing hypertension, in this case those with lower BMI, might have a lower tolerance and therefore worse overall outcomes.

Furthermore, the significant age difference in our cohort should be noted, as increased age is considered a risk factor for ICH in the general population.[40] In this article, obese patients were significantly younger than their nonobese counterparts, whereas underweight patients represented the oldest

Table 4 Comparisons of Primary and Secondary Outcomes of Interest Between Underweight and Normal Weight vs Overweight and Obese Patients With ICH

Outcome		Unadjusted value	*p* Value	Adjusted value[d]	*p* Value
Primary outcome					
Mortality at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
BMI <25 kg/m^2	206/736 (27.9)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	312/1,689 (18.4)	0.58 [0.47 to 0.71]	<0.001	0.67 [0.52 to 0.86]	0.002
Secondary outcomes					
mRS 0–2 at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
BMI <25 kg/m^2	235/736 (31.9)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	649/1,690 (38.4)	1.32 [1.10 to 1.59]	0.002	1.21 [0.97 to 1.51]	0.079
mRS 0–3 at 90 d	N (%)	OR [95% CI]		OR [95% CI]	
BMI <25 kg/m^2	340/736 (46.2)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	901/1,690 (53.1)	1.33 [1.11 to 1.58]	0.001	1.17 [0.95 to 1.44]	0.131
mRS at 90 d	Median (IQR)	OR [95% CI]		OR [95% CI]	
BMI <25 kg/m^2	4 (2 to 6)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	3 (2 to 5)	0.70 [0.60 to 0.82]	<0.001	0.80 [0.67 to 0.95]	0.014
Mortality at discharge	N (%)	OR [95% CI]		OR [95% CI]	
BMI <25 kg/m^2	101/866 (11.6)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	198/1975 (10.0)	0.84 [0.65 to 1.08]	0.191	0.87 [0.64 to 1.17]	0.372
EQ-5D score at 90 d[a]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
BMI <25 kg/m^2	0.52 (0 to 0.82)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	0.68 (0.11 to 0.83)	0.07 [0.04 to 0.11]	<0.001	0.05 [0.01 to 0.08]	0.006
EQ-5D VAS score at 90 d[b]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
BMI <25 kg/m^2	50 (0 to 75)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	60 (30 to 80)	6.01 [3.11 to 8.92]	<0.001	3.80 [0.80 to 6.98)	0.013
Barthel Index at 90 d[c]	Median (IQR)	Beta [95% CI]		Beta [95% CI]	
BMI <25 kg/m^2	60 (0 to 100)	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	75 (10 to 100)	6.87 [3.25 to 10.49]	<0.001	3.56 [−0.18 to 7.30]	0.062
LOS, d	Mean ± SD	Beta [95% CI]		Beta [95% CI]	
BMI <25 kg/m^2	12.1 ± 11.7	Ref.	Ref.	Ref.	Ref.
BMI ≥25 kg/m^2	13.5 ± 17.0	1.43 [0.18 to 2.67]	0.024	0.09 [−1.21 to 1.40]	0.891

Abbreviations: BMI = body mass index; CI = confidence interval; EQ-5D = EuroQoL Group 5-Dimension Self-Report Questionnaire; ICH = intracerebral hemorrhage; LOS = length of stay; mRS = modified Rankin Scale; OR = odds ratio; VAS = Visual Analog Scale.
[a] The EuroQoL Group 5-Dimension (EQ-5D) Self-Report Questionnaire is a standardized instrument for the measurement of generic health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from −0.11 to 1.00, with higher scores indicating better health and death indicated by score of 0.
[b] EQ-5D Visual Analog Scale (EQ-5D VAS) is the second part of the EQ-5D Questionnaire, where the patient is asked to mark his/her health status on a 20-centimeter vertical scale with end points of 0 (i.e., "the worst health you can imagine") and 100 (i.e., "the best health you can imagine").
[c] The Barthel Index is an ordinal 10-item scale for measuring performance of activities of daily living. Score ranges from 0 to 100, with 0 indicating severe disability and 100 indicating no disability.
[d] Values were adjusted for age, sex, race/ethnicity, smoke history, cocaine use, marijuana use, history of hypertension, history of diabetes, history of ICH, history of hyperlipidemia, baseline mRS, presence of lobar ICH, and CSF shunt placement.

population ($p < 0.001$). This difference could be explained by their significantly increased prevalence of comorbidities, such as hypertension, diabetes, and hyperlipidemia, all of which are well-known stroke risk factors, which ultimately lead to the occurrence of ICH at a younger age. However, even after adjusting for age as a linear and nonlinear variable, the obesity

paradox remained present. After adjusting for natural log-transformed age, a significant inverse relationship between BMI and mRS score at 90 days and better Barthel Index score among patients with BMI ≥25 kg/m^2 were documented. These differences suggest that the influence of age on the obesity paradox may not be linear but exponential. Moreover, even after excluding patients in whom care was withdrawn, to avoid potential bias derived from age-related frailty, overweight and obese patients were 67% more likely to survive at 90 days after ICH compared with their normal weight and underweight counterparts. Although there was no significant interaction between age and BMI for the primary outcome of interest, a significant interaction was found for mRS at 90 days, where increasing age was associated with a stronger positive effect on the likelihood of poor outcome (i.e., higher 90-day mRS score) among underweight and normal weight patients compared with their overweight and obese counterparts ($p_{interaction}$ = 0.004 and $p_{interaction}$ = 0.001 before and after natural log transformation of age, respectively).

Another strength of our study involves the assessment of the role that race/ethnicity plays in the obesity paradox, which tends to be overlooked in most studies. The well-known significant differences in BMI and body fat percentage as well as ICH mortality rates based on race/ethnicity highlight the importance of studying its overall effect on patient outcomes. For instance, the mortality rate among Asian populations following an ICH has been reported as 2.3%–9.3%, whereas for Western populations, it ranges from 30% to 40%.[41-43] Because racial and ethnic disparities in all-cause mortality exist in the United States, it is imperative to explore not only the concept of the obesity paradox but also to assess the influence of racial diversity among patients with acute ICH. In our cohort, although the mortality rates at 90 days were significantly higher among non-Hispanic White when compared with non-Hispanic Black and Hispanic patients (26.6% vs 19.5% vs 18.0%, respectively), no significant interaction between BMI and patient race/ethnicity was documented for the outcomes of mortality and mRS score at 90 days. Thus, evaluating other factors that could explain the mortality rate differences between these groups should be pursued.

Sex has been previously associated with significant differences in stroke incidence, presentation, and overall outcomes, thus we evaluated whether it has an effect of the obesity paradox.[44] Although female patients have a higher incidence of aneurysm and subarachnoid hemorrhage, their male counterparts have higher rates of hemorrhagic stroke; however, female patients face disproportionately higher stroke-related mortality and morbidity.[44] In addition, significant race/ethnic disparities on the risk of stroke have been reported among this group; for example, data from the Women's Health Initiative demonstrated that Black female patients had a 47% higher risk of stroke compared with their White counterparts, with racial disparities being greatest among those aged 50 to 60 years.[45] In this study, the survival benefit and improved functional outcomes among patients with overweight and obese ICH did not seem to be influenced by their sex.

We would like to emphasize that although a survival benefit was documented among overweight and obese patients following an acute ICH, the obesity paradox should not be interpreted as a rejection of the well-known benefits associated with maintaining a healthy weight and the utility of purposeful weight reduction.[1,46,47] Alternatively, it should be regarded as a phenomenon that warrants further investigation to better understand the mechanisms by which excess adipose tissue might be advantageous among patients with ICH. By doing so, we can explore and develop novel therapies that can reproduce this effect and ultimately lead to an improvement in patient overall outcomes. The expanding obesity epidemic in the United States, which is reflected by the significant proportion that overweight and obese patients represented in this study (69.5%, n = 1,975), urges clinicians to better understand the obesity paradox, which might influence the concept of an "optimal BMI" as more data continue to emerge.[1,48] Furthermore, an important focus should also be placed on underweight patients, especially with the faster pace at which the population is aging.[49,50] Although not statistically significant, it is worth mentioning that the highest mortality rates and worse mRS scores were recorded among underweight patients.

There are some potential limitations in this study that deserve comment. For instance, the use of BMI might not be the best measure of adiposity as it cannot distinguish between lean body and fat mass; thus, it may be useful to assess other measurements, such as waist circumference or waist-hip ratio. In most cases, patients with ICH are critically ill and placed in absolute bed rest which precludes detailed and accurate anthropometric measurements. Moreover, we did not include the measures of frailty or cardiorespiratory fitness, which have been shown to play an important role in the obesity paradox.[38] In addition, this study might be subject to survival bias and reverse causation, which are the main limitations of most studies evaluating the obesity paradox. Despite the limitations, this study remains significant because it provides an analysis of the association between BMI and functional outcomes after ICH on a large multicenter cohort, which provides our results with strong generalizability. Nonetheless, our findings merit further investigation with prospectively collected data matched by ICH severity.

In conclusion, our study demonstrated that a higher BMI is associated with decreased mortality, improved functional outcomes, and better self-reported health status at 90 days, thus supporting the existence of an obesity paradox in patients with ICH. Notably, the survival benefit among overweight and obese patients was only documented at 90 days, suggesting that the paradoxical effect of obesity may not be immediate but instead operate over a more extended period following ICH occurrence. In addition, our results demonstrate

that patients' race/ethnicity and sex do not seem to influence the effect of BMI on ICH outcomes, whereas age may play a significant role on patients' long-term functional outcomes. Further studies investigating the mechanisms behind this paradox are key to explore and develop potential treatment targets for patients with ICH patients.

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Douglas J. Mayson, MD	Department of Neurology, MedStar Georgetown University Hospital, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nicole Gonzales, MD	Department of Neurology, University of Colorado School of Medicine, Aurora	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jacob L. McCauley, PhD	John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, FL	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Appendix 1 *(continued)*

Name	Location	Contribution
Marc Malkoff, MD	Departments of Neurology and Neurosurgery, University of Tennessee Health Sciences, Memphis	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christiana E. Hall, MD, MS	Department of Neurology, University of Texas Southwestern, Dallas	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Michael R. Frankel, MD	Department of Neurology, Emory University, Grady Memorial Hospital, Atlanta, GA	Major role in the acquisition of data
Michael L. James, MD	Departments of Anesthesiology and Neurology, Duke Clinical Research Institute, Duke University, Durham, NC	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christopher D. Anderson, MD, MMSc	Henry and Allison McCane Center for Brain Health and Center for Genomic Medicine, Massachusetts General Hospital, Boston	Major role in the acquisition of data
Jaroslaw Aronowski, MD, PhD	Department of Neurology, The University of Texas Health Science Center at Houston	Drafting/revision of the manuscript for content, including medical writing for content
Sean I. Savitz, MD	Department of Neurology, The University of Texas Health Science Center at Houston	Drafting/revision of the manuscript for content, including medical writing for content
Daniel Woo, MD	Department of Neurology, University of Cincinnati, OH	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Ching-Jen Chen, MD	Department of Neurosurgery, The University of Texas Health Science Center at Houston	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Jennifer Osborne, RN, BSN	Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, OH	Site Investigator	Supervision of personnel and technical assistance
Jonathan Rosand, MD, MSC	Henry and Allison McCance Center for Brain Health and Center for Genomic Medicine, Massachusetts General Hospital, Boston	Site Investigator	Technical assistance and data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Mark W. Brown, MA	Wake Forest University School of Medicine, Winston-Salem, NC	Site Investigator	Technical assistance
Eric W. Rademacher, PhD	University of Cincinnati, College of Medicine, Cincinnati, OH	Site Investigator	Technical assistance and data collection
Salina Waddy, MD	National Institute of Neurological Disorders and Stroke, Bethesda, MD	Site Investigator	Data collection
Jamie N. Roberts, MA, CCRP	National Institute of Neurological Disorders and Stroke, Bethesda, MD	Site Investigator	Data collection
Lee Birnbaum, MD, MS	Department of Neurology, University of Texas-San Antonio	Site Investigator	Major role in acquisition of data
Bruce Coull, MD	Department of Neurology, University of Arizona, Tucson, AZ	Site Investigator	Major role in acquisition of data
Ji Y. Chong, MD	New York Presbyterian Lower Manhattan Hospital, New York, NY	Site Investigator	Major role in acquisition of data
Tanya Warwick, MD	University of California San Francisco, Fresno, CA	Site Investigator	Major role in acquisition of data
Latisha K. Ali, MD	Department of Neurology and Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio	Site Investigator	Major role in acquisition of data
Floyd Jones, CCRC	University of Texas Health Science Center at San Antonio, TX	Site Investigator	Major role in acquisition of data
Tiffany Watson	University of Maryland School of Medicine, Baltimore, MD	Site Investigator	Technical assistance and data collection
Anne Leonard, MPH, RN	University of Texas Health Science Center at San Antonio, TX	Site Investigator	Technical assistance and data collection
Rebecca Martinez, RN, BS	University of Texas Medical School, Houston, TX	Site Investigator	Major role in acquisition of data
Ralph I. Sacco, MD	University of Miami, Miller School of Medicine, Miami, FL	Site Investigator	Major role in acquisition of data
Carl D. Langefeld, PhD	Wake Forest University School of Medicine, Winston-Salem, NC	Site Investigator	Technical assistance

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