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Article

Long-Term Protective Association of Elevated Body Mass Index With Survival in Intracerebral Hemorrhage: A 2-Year Cohort Study Revealing the Obesity Paradox

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Abstract

Aims/Background: The 'obesity paradox' has been reported in intracerebral hemorrhage (ICH), but evidence on long-term mortality remains limited. We investigated the association between body mass index (BMI) and long-term all-cause mortality in a hospital-based ICH cohort. **Methods:** This retrospective cohort study included adult patients with primary ICH admitted within 48 h between 1 November 2016 and 28 February 2021. Patients with secondary ICH, neurosurgical procedures, isolated intraventricular hemorrhage, severe pre-existing disability, or loss to follow-up were excluded. Patients were categorised based on World Health Organization BMI criteria as follows: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). The primary outcome was all-cause mortality. Associations between BMI and mortality were assessed using Cox proportional hazards models, and potential nonlinearity was evaluated by modeling BMI with a spline term within the Cox proportional hazards framework. **Results:** Of the 947 screened patients, 839 were included (underweight n = 66; normal weight n = 465; overweight n = 261; obese n = 47). Median follow-up time varied across BMI groups (25.5–43.0 months). BMI demonstrated an inverse association with all-cause mortality in an exploratory multivariable model excluding age (hazard ratio (HR): 0.923, 95% confidence interval (CI): 0.864–0.985; $p = 0.016$). However, this association was attenuated and no longer statistically significant after adjustment for age (HR: 0.958, 95% CI: 0.898–1.022; $p = 0.190$), suggesting important age-related confounding. Restricted cubic spline analysis showed no evidence of nonlinearity ($p = 0.475$). Kaplan–Meier curves showed higher survival in overweight and obese groups than in underweight and normal-weight groups. BMI was also negatively associated with hematoma volume; this relationship remained after log transformation. **Conclusion:** An apparent inverse association between BMI and long-term mortality was observed after primary ICH; however, this association was substantially influenced by age. These findings highlight the complex relationship between BMI, aging, and hemorrhagic stroke characteristics and should be interpreted cautiously given the observational design. **Clinical Trial Registration:** ClinicalTrials.gov (NCT04803292).

Keywords: stroke; cerebral hemorrhage; body mass index; death; cohort studies; patient outcome assessment

1. Introduction

According to the World Health Organization, obesity is characterised by detrimental levels of body fat accumulation and represents a significant global public health challenge. In the past few decades, obesity has increasingly spread and is currently considered a global epidemic [1,2]. Abnormal pathophysiological states such as inflammatory response and metabolic dysfunction correlate with a wide range of disorders, including diabetes, hypertension, mood disorders, dementia, osteosclerosis, chronic kidney disease, cerebrovascular disease, and cancer [1,3,4,5,6,7]. Usually, obesity development accelerates the disease process and exacerbates prognosis.

However, for intracerebral hemorrhage (ICH), the second most common type of stroke, studies have reported a unique association with obesity. Patients with ICH with higher body mass index (BMI) tend to have lower mortality and better functional outcomes than those with ischemic stroke [8,9,10]. This protective ability of obesity on ICH outcomes was labeled as the 'obesity paradox' [8]. Thus far, the positive, no, or negative association between obesity and ICH remains controversial. However, most of the existing literature has focused on short-term functional outcomes, usually 3-month outcomes measured using the modified Rankin Scale (mRS), thus lacking long-term follow-up. In this study, we reexamine the association between BMI and ICH mortality in a cohort with a median follow-up time of 2 years to elucidate the long-term effect of BMI.

2. Methods

2.1 Study Design and Patients

This study was a retrospective analysis of patients with ICH visiting the Second Affiliated Hospital of Zhejiang University from 1 November 2016 to 28 February 2021. The study was registered at ClinicalTrials.gov (registration number: NCT04803292). We enrolled adult patients (age ≥18 years) who satisfied the following conditions: (1) admitted for primary ICH within 48 h; (2) underwent CT scan; and (3) had a BMI record. Exclusion criteria comprised the following: (1) secondary ICH due to trauma, intracranial tumors, or systemic disorders or isolated intraventricular hemorrhage (IVH) [11,12]; (2) pre-existing disability with mRS >3 before ICH onset, as documented in medical records or reported by caregivers; (3) treated with neurosurgical procedures.

2.2 Clinical Data

We retrieved the following data: (i) demographic characteristics (e.g., age and sex); (ii) admission BMI; (iii) vascular risk factors and past history (including hypertension, diabetes, atrial fibrillation (AF), coronary heart disease, kidney disease and prior hemorrhagic or ischemic stroke or transient ischemic attack) using a standardised format [13]; (iv) medication before admission; (v) neurological function assessment with Glasgow Coma Score (GCS) [14] and National Institute of Health Stroke Scale (NIHSS) [15] on admission. In our institution, GCS and NIHSS are routinely assessed at presentation by emergency physicians as part of the standardised stroke evaluation protocol. The data used in this study were retrospectively extracted from the medical records. Additional clinical and imaging variables were also collected. Time from onset to initial CT (OCT) and time from onset to magnetic resonance imaging (MRI) (OMT) were recorded as time intervals in hours or days, as appropriate. ICH location was classified as lobar, deep, cerebellar, or brainstem based on neuroimaging findings. Intraventricular extension and subarachnoid hemorrhage (SAH) were determined from baseline CT scans. Cerebral microbleeds (CMB) and cortical superficial siderosis (cSS) were assessed on susceptibility-weighted imaging and defined based on established criteria [16,17]. Susceptibility-weighted imaging (SWI) was routinely performed in all patients with ICH during the study period. All patients included in the SWI-based analyses had complete assessments for CMB and cSS, and no missing data were present for these variables. Laboratory parameters, including international normalised ratio (INR), platelet (PLT), admission blood glucose, and serum creatinine, were obtained from blood samples collected at admission as part of routine clinical evaluation.

2.3 BMI Classification

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI categories were defined according to the World Health Organization (WHO) [18] classification for adults to facilitate comparison with previous international studies investigating the association between BMI and outcomes after ICH: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2) [8,19]. Height was self-reported or provided by proxies, and weight was usually recorded as bed weight at admission.

2.4 Neuroimaging

Computed tomography (CT) images used in data analysis were acquired within 48 h after symptom onset in all patients. CT scans were routinely interpreted by licensed radiologists as part of standard clinical practice. Analyses were performed on images in Digital Imaging and Communications in Medicine format. Hematoma volumes were independently measured by two investigators (Yujia Jin and Yu Deng) who were blinded to clinical information and outcomes using ITK-SNAP software (University of Pennsylvania, Philadelphia, USA; https://www.itksnap.org) based on semi-automated segmentation, followed by manual correction when necessary. If the absolute difference between the two measurements exceeded 10 mL, the images were re-evaluated by both investigators to reach consensus. This 10-mL discrepancy threshold was prespecified at the beginning of the study based on previous experience with hematoma volume measurements. Although relative differences may provide additional information, particularly for small hematomas, an absolute threshold was adopted for practical reproducibility, as discrepancies requiring reassessment were mainly observed in larger or irregularly shaped hematomas. Minor absolute differences in very small hematomas were considered less likely to substantially affect clinical interpretation. Inter-rater reliability was assessed using the intraclass correlation coefficient (ICC), which demonstrated excellent agreement (ICC = 0.92, 95% CI: 0.89–0.95). The mean value of the two measurements was used for statistical analysis.

2.5 Follow-Up

Follow-up was conducted by the study investigators, all of whom are trained clinicians, with patients approximately evenly distributed among them. Follow-up was performed via face-to-face visits or standardised telephone interviews. Follow-up assessments were performed by study team members who were reassigned to patients after partial masking of baseline clinical and imaging information by a dedicated research assistant. Only limited information required for patient identification (e.g., patient name and admission date) was retained during follow-up procedures. Therefore, the follow-up investigators were blinded to baseline imaging measurements and detailed exposure data during outcome assessment. Functional status was assessed using the mRS at 3 months after ICH onset. Survival time was calculated from the date of ICH onset to the date

of death or the last available follow-up. Patients who survived at the end of follow-up were considered censored observations at their last confirmed follow-up date. Follow-up was censored on 31 December 2023. To ensure the completeness of follow-up to the greatest extent possible, we collected at least one phone number upon admission, and most patients had two phone number records (the patient's and their relatives' phone numbers). Loss to follow-up was defined as failure to ascertain the survival status of a patient after more than five unsuccessful telephone attempts and the absence of confirmation via hospital records or collaborating local physicians. When telephone contact could not be established, survival status was further verified via available hospital records or collaborating local physicians whenever possible.

2.6 Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. Comparisons among BMI groups were performed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Homogeneity of variance was evaluated using the Levene test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was applied when the expected cell count was less than 10. All-cause mortality was defined as death from any cause during the follow-up period. The potential nonlinear association between BMI and all-cause mortality was assessed using restricted cubic spline (RCS) functions within a Cox proportional hazards regression model. Four knots were used for the RCS analysis. The presence of nonlinearity was evaluated by comparing the model incorporating the restricted cubic spline term with a model including BMI as a linear continuous variable using a likelihood ratio test. Candidate variables were first examined using univariable Cox proportional hazards analyses. Variables with $p < 0.01$ were subsequently entered into the multivariable Cox regression model. Two multivariable Cox proportional hazards models were constructed, namely an exploratory model excluding age and an age-adjusted model including age as an additional covariate. Given the strong association between age and both BMI and mortality, an additional exploratory model excluding age was performed to evaluate the potential influence of age-related confounding on the association between BMI and all-cause mortality. To further explore the potential modifying effect of age on the association between BMI and all-cause mortality, prespecified subgroup analyses stratified by age were performed. Patients were categorized into two age groups: <65 years and ≥65 years [20]. Multicollinearity among variables was assessed using the variance inflation factor (VIF), with a threshold of VIF <5 indicating no significant multicollinearity. We further analyzed the association between BMI and mortality using Kaplan–Meier curves. Survival differences among BMI categories were compared using the log-rank test. A two-sided p value < 0.05 was considered statistically significant. The association between BMI and baseline hematoma volume was evaluated using Pearson correlation analysis. Because baseline hematoma volume exhibited a markedly right-skewed distribution, an additional analysis was performed after a logarithmic transformation of hematoma volume to evaluate the robustness of the observed association between BMI and hematoma volume. In addition, the distribution of 3-month functional outcomes across BMI categories was presented. Differences in BMI between patients with and without individual risk factors were compared using independent-samples t tests or Mann–Whitney U tests, as appropriate, based on data distribution.

Missing data were minimal for variables included in the primary analyses. Specifically, missingness was below 0.5% for all variables entered into the multivariable Cox regression models. Therefore, complete-case analysis was performed, and no imputation procedures were applied. The primary outcome variables (all-cause mortality and follow-up time) had complete data.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA), Empower ® (X&Ysolutions, Inc., Boston, MA, USA), and R (https://www.R-project.org/). We designed this study following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [21].

3. Results

3.1 Patient Selection and Baseline Characteristics

A total of 947 patients with primary ICH were initially screened. After applying the predefined exclusion criteria, 108 patients were excluded due to secondary causes (n = 75), neurosurgical procedures (n = 10), severe pre-existing disability (modified Rankin Scale >3, n = 4), IVH (n = 13), and loss to follow-up (n = 6) (Fig. 1). The final cohort comprised 839 patients.

Patients were categorised based on BMI: underweight (n = 66, 7.9%), normal weight (n = 465, 55.4%), overweight (n = 261, 31.1%), and obese (n = 47, 5.6%). Baseline demographic and clinical characteristics are presented in Table 1.

Baseline demographic, clinical, and imaging characteristics stratified by BMI category are presented in Table 1. Several variables exhibited statistically significant differences across the four groups. Age demonstrated a progressive decline with increasing BMI category, from a mean of 69.45 years in the underweight group to 52.85 years in the obese group ($p < 0.001$). The proportion of female sex also differed significantly, being highest in the underweight group (48.5%) and lower in the overweight and obese groups (28.4% and 29.8%, respectively; $p = 0.004$). A positive association was observed between BMI category and the prevalence of both hypertension (ranging from

Table 1. Patient characteristics.

	Underweight (BMI <18.5 kg/m^2)	Normal weight (BMI 18.5–24.9 kg/m^2)	Overweight (BMI 25.0–29.9 kg/m^2)	Obese (BMI ≥30.0 kg/m^2)	*p* value	F, H, or χ^2 values
	n = 66	n = 465	n = 261	n = 47		
Age, year	69.45 ± 12.77	62.54 ± 12.21	57.90 ± 11.83	52.85 ± 15.93	<0.001	24.901
Female, n (%)	32 (48.5%)	180 (38.7%)	74 (28.4%)	14 (29.8%)	0.004	13.339
Hypertension, n (%)	41 (62.1%)	327 (70.3%)	228 (87.4%)	43 (91.5%)	<0.001	39.997
Diabetes, n (%)	2 (3.0%)	72 (15.5%)	54 (20.7%)	6 (12.8%)	0.005	
Atrial fibrillation, n (%)	3 (4.5%)	9 (1.9%)	4 (1.5%)	0 (0.0%)	0.342	
Coronary heart disease, n (%)	3 (4.5%)	20 (4.3%)	9 (3.4%)	1 (2.1%)	0.875	
Ischemic stroke or TIA, n (%)	5 (7.6%)	47 (10.1%)	31 (11.9%)	2 (4.3%)	0.420	
Previous ICH, n (%)	4 (6.1%)	36 (7.7%)	17 (6.5%)	2 (4.3%)	0.832	
Kidney disease, n (%)	4 (6.1%)	18 (3.9%)	9 (3.4%)	1 (2.1%)	0.723	
Smoking, n (%)	17 (25.8%)	149 (32.0%)	96 (36.8%)	13 (27.7%)	0.256	4.048
Alcohol intake, n (%)	25 (37.9%)	148 (31.8%)	82 (31.4%)	10 (21.3%)	0.316	3.537
Previous medication						
Antiplatelet drugs, n (%)	6 (9.1%)	47 (10.1%)	29 (11.1%)	4 (8.5%)	0.960	
Statins, n (%)	4 (6.1%)	36 (7.7%)	19 (7.3%)	2 (4.3%)	0.947	
Baseline GCS	15 (13–15)	15 (14–15)	15 (14–15)	15 (14–15)	0.281	3.834
Baseline NIHSS	5 (2–12)	4 (2–10)	4 (2–9)	3 (2–9)	0.299	3.673
Imaging data						
OCT, h	5.00 (2.00–7.75)	5.00 (2.50–9.00)	5.00 (2.50–11.00)	5.00 (2.00–9.50)	0.623	1.761
Baseline hematoma volume, mL	14.39 (7.84–31.84)	8.28 (3.00–16.62)	8.53 (2.70–17.00)	9.90 (4.23–14.80)	<0.001	19.415
CMB burden						
Lobar CMB count, median (IQR)	0 (0–4)	0 (0–3)	0 (0–3)	0 (0–2)	0.521	2.256
Deep CMB count, median (IQR), n	1 (0–3)	1 (0–3)	1 (0–4)	1 (0–4)	0.292	3.732
cSS, n (%)	22 (33.3%)	86 (18.5%)	40 (15.3%)	5 (10.6%)	0.006	
ICH location						
Lobar ICH, n (%)	31 (47.0%)	88 (18.9%)	37 (14.2%)	7 (14.9%)	<0.001	
Deep ICH, n (%)	29 (43.9%)	307 (66.0%)	183 (70.1%)	32 (68.1%)	0.001	16.260
Cerebellum ICH, n (%)	8 (12.1%)	33 (7.1%)	15 (5.7%)	2 (4.3%)	0.305	
Brainstem ICH, n (%)	1 (1.5%)	40 (8.6%)	29 (11.1%)	6 (12.8%)	0.049	
Intraventricular extension, n (%)	24 (36.4%)	125 (26.9%)	71 (27.2%)	12 (25.5%)	0.428	2.774
SAH, n (%)	16 (24.2%)	41 (8.8%)	13 (5.0%)	4 (8.5%)	<0.001	
OMT, day	5 (4–7)	5 (4–6)	5 (3–6)	5 (4–7)	0.142	5.443
INR	1.02 (0.96–1.08)	1.00 (0.96–1.04)	0.99 (0.95–1.02)	1.01 (0.96–1.04)	0.006	12.444
PLT, 10^9/L	166 (133–212)	191 (153–234)	203 (170–238)	215 (174–261)	<0.001	23.918
Admission blood glucose, mmol/L	5.78 (5.18–6.70)	5.46 (4.90–6.63)	5.87 (5.15–6.86)	6.10 (5.54–7.58)	0.001	15.885
Cr, μmol/L	58.50 (49.50–73.00)	61.00 (51.00–73.00)	64.40 (54.00–75.53)	66.00 (53.50–77.50)	0.099	6.272
Follow-up time, months	25.50 (12.00–48.00)	36.00 (12.00–51.00)	41.00 (12.00–50.00)	43.00 (24.50–51.00)	0.081	6.735

BMI, body mass index; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; GCS, Glasgow Coma Score; NIHSS, National Institute of Health Stroke Scale; OCT, time from onset to first CT; CMB, cerebral microbleeds; cSS, cortical superficial siderosis; SAH, subarachnoid hemorrhage; OMT, time from onset to MRI; INR, international normalised ratio; PLT, platelet; Cr, creatinine; IQR, interquartile range. Values are presented as mean ± SD or median (IQR) as appropriate. Group comparisons were performed using ANOVA, Kruskal–Wallis test, Fisher's exact test, or chi-square test. Percentages were calculated using available data for each variable. Therefore, denominators may vary slightly because of occasional missing values. ICH location categories were not mutually exclusive because some patients had hemorrhages involving multiple anatomical locations. Therefore, percentages may sum to more than 100%. Missing data were present for NIHSS (n = 1), INR (n = 2), and admission blood glucose (n = 5). Percentages were calculated based on available data for each variable.

62.1% in underweight to 91.5% in obese patients; $p < 0.001$) and diabetes mellitus ($p = 0.005$). With respect to neuroimaging and hemorrhage characteristics, baseline hematoma volume was significantly larger in the underweight group (median 14.39 mL, IQR 7.84–31.84) than in the other groups ($p < 0.001$). The distribution of hemorrhage location varied significantly, with lobar ICH being more frequent in the underweight group (47.0%) than in the normal weight (18.9%), overweight (14.2%), and obese (14.9%) groups ($p < 0.001$). Correspondingly, deep ICH was less frequent in the underweight group (43.9%) than in the other groups (66.0%, 70.1%, and 68.1%, respectively; $p = 0.001$). The prevalence of brainstem ICH also differed across BMI categories ($p = 0.049$). The presence of cSS and concurrent SAH both exhibited statistically significant variation across BMI groups (cSS: 33.3% underweight vs. 10.6% obese, $p = 0.006$; SAH: 24.2% underweight vs. 5.0–8.5% in higher BMI groups, $p < 0.001$). Several laboratory parameters, including INR ($p = 0.006$), platelet count ($p < 0.001$), and admission blood glucose ($p = 0.001$), also differed significantly across BMI categories. By contrast, no statistically significant differences were observed among the four BMI groups for the following characteristics: AF, coronary heart disease, prior ischemic stroke or transient ischemic attack, previous ICH, kidney disease, smoking status, alcohol intake, pre-admission use of antiplatelet agents or statins, baseline Glasgow Coma Score, baseline NIH Stroke Scale score, time from onset to first CT, cerebral microbleeds burden (lobar or deep), presence of cerebellar, intraventricular extension, time from onset to MRI, serum creatinine, and duration of follow-up (all $p > 0.05$).

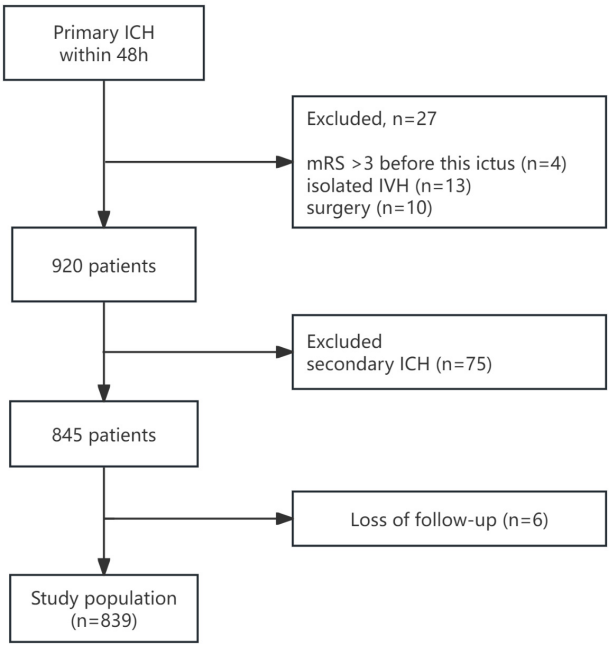

Fig. 1. Flowchart of patient selection and inclusion.

3.2 Association Between BMI and Long-Term Mortality

Restricted cubic spline analysis based on the Cox proportional hazards model revealed an overall inverse trend between BMI and all-cause mortality (Fig. 2). However, the nonlinearity test was not statistically significant ($p = 0.475$), indicating no strong evidence of a nonlinear association. Therefore, BMI was modeled as a linear continuous variable in the Cox regression analysis.

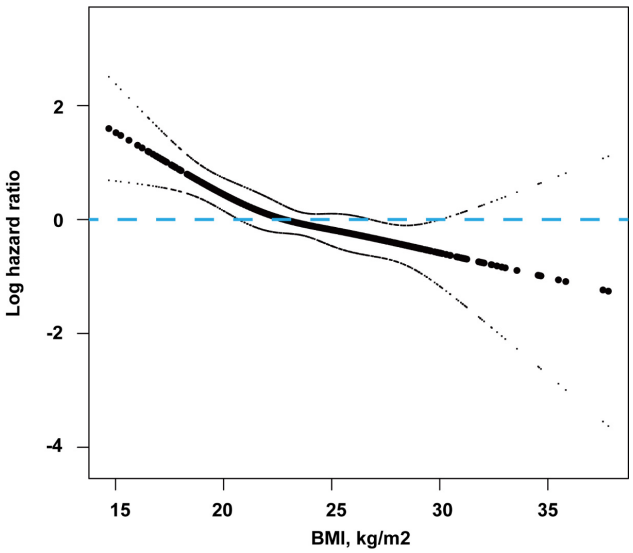

Fig. 2. Restricted cubic spline curve illustrating the unadjusted association between body mass index (BMI) and all-cause mortality. The curve was generated from a Cox proportional hazards model including BMI as the sole predictor. Age and other covariates were not included in this analysis. The horizontal dashed line indicates the centered reference level of the spline term. The thick line in the middle represents the estimated log hazard ratio, and the dashed lines represent the 95% confidence intervals. Therefore, the horizontal dashed line at log(HR) = 0 corresponds to the average predicted effect rather than a specific BMI reference value. No significant nonlinearity was detected ($p = 0.475$). Estimates at extreme BMI ranges should be interpreted cautiously because of limited sample size.

In an exploratory multivariable Cox proportional hazards model excluding age, BMI was inversely associated with all-cause mortality. However, after age was included in the multivariable model, this association was attenuated and no longer statistically significant.

Multivariable Cox proportional hazards analysis demonstrated that BMI was inversely associated with all-cause mortality after adjustment for variables identified in the univariable analyses ($p < 0.01$). These variables include hypertension, AF, previous ICH, baseline hematoma volume, lobar ICH, intraventricular extension, SAH, GCS score, CMB, and cSS (**Supplementary Table 1**; Table 2). No significant multicollinearity was detected among the variables included in the multivariable model (all VIF val-

Table 2. Multivariable Cox regression analysis of all-cause mortality (exploratory model excluding age).

Exposure	Male (n = 539)		Female (n = 300)		Total cohort (n = 839)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
BMI	0.931 (0.858, 1.010)	0.087	0.901 (0.798, 1.017)	0.093	0.923 (0.864, 0.985)	0.016
Hypertension	0.458 (0.261, 0.801)	0.006	0.481 (0.190, 1.214)	0.121	0.425 (0.268, 0.676)	<0.001
Atrial fibrillation	6.914 (2.154, 22.198)	0.0012	3.692 (0.432, 31.546)	0.233	6.358 (2.439, 16.576)	<0.001
Previous ICH	2.141 (1.017, 4.510)	0.045	2.251 (0.706, 7.173)	0.170	2.218 (1.219, 4.035)	0.009
Baseline hematoma volume, mL	1.005 (0.988, 1.023)	0.550	0.999 (0.966, 1.032)	0.942	1.002 (0.987, 1.017)	0.775
Lobar ICH	1.118 (0.542, 2.305)	0.763	2.456 (0.752, 8.019)	0.137	1.357 (0.750, 2.456)	0.313
Intraventricular extension	1.336 (0.717, 2.488)	0.361	1.468 (0.565, 3.815)	0.430	1.374 (0.843, 2.238)	0.202
SAH	1.334 (0.591, 3.016)	0.488	1.648 (0.548, 4.954)	0.374	1.455 (0.773, 2.736)	0.245
GCS	0.883 (0.773, 1.007)	0.064	0.860 (0.733, 1.008)	0.062	0.876 (0.797, 0.964)	0.007
Lobar CMB	1.024 (0.998, 1.051)	0.074	1.036 (1.019, 1.053)	<0.001	1.029 (1.018, 1.041)	<0.001
cSS	1.881 (1.020, 3.467)	0.043	1.190 (0.400, 3.540)	0.754	1.796 (1.078, 2.993)	0.025

BMI, body mass index; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; GCS, Glasgow Coma Score; CMB, cerebral microbleeds; cSS, cortical superficial siderosis. "Deep ICH" was not simultaneously included in the multivariable model because "Deep ICH" and "Lobar ICH" are mutually exclusive variables in the majority of cases, which may introduce redundancy and potential collinearity.

ues <5). In the total cohort, in the multivariable Cox regression model including age, BMI was not significantly associated with all-cause mortality (overall BMI: hazard ratio (HR) = 0.958, 95% CI = 0.898–1.022; $p = 0.190$), whereas age was independently associated with mortality (overall: HR = 1.066, 95% CI = 1.043–1.089; $p < 0.001$; **Supplementary Table 2**). In an exploratory model excluding age, BMI was significantly associated with reduced mortality risk (HR: 0.923, 95% CI: 0.864–0.985; $p = 0.016$, Table 2). These findings show that the association between BMI and mortality is attenuated after adjustment for age, indicating that age may serve as an important confounder. Sex-stratified multivariable Cox regression analyses exhibited similar directional trends; however, statistical significance was not reached (male: HR: 0.931, 95% CI: 0.858–1.010; $p = 0.087$; female: HR 0.901, 95% CI 0.798–1.017; $p = 0.093$) (Table 2).

3.3 Age-Stratified Analyses

To further explore the association between BMI and all-cause mortality across different age groups, we performed stratified analyses (<65 vs. ≥65 years) (**Supplementary Tables 3,4**). In age-stratified analyses, an inverse association between BMI and all-cause mortality was observed in men aged <65 years (HR: 0.834, 95% CI 0.699–0.997; $p = 0.046$), whereas no statistically significant associations were observed in women (HR 1.161, 95% CI 0.859–1.569; $p = 0.331$) or in the overall subgroup (HR: 0.894, 95% CI: 0.770–1.038; $p = 0.141$). (**Supplementary Table 3**). In patients aged ≥65 years, BMI was not significantly associated with all-cause mortality (**Supplementary Table 4**).

3.4 Kaplan–Meier Survival Analysis

Unadjusted Kaplan–Meier survival curves demonstrated significant differences in long-term survival across BMI categories (Fig. 3). Patients in the overweight and obese groups exhibited higher survival probabilities than underweight and normal-weight patients. The log-rank test indicated a statistically significant difference among the BMI groups ($p < 0.0001$).

3.5 Association Between BMI and Hematoma Volume and Functional Outcome

We analyzed the association of BMI with baseline hematoma volume and 3-month mRS. A weak inverse association was observed between BMI and baseline hematoma volume, with a very small correlation coefficient, suggesting limited clinical relevance (correlation coefficient: –0.116, $p = 0.0008$; Fig. 4). Because of the right-skewed distribution of hematoma volume, logarithmic transformation was applied before regression analysis. The association between BMI and hematoma volume remained substantially unchanged after transformation (**Supplementary Fig. 1**), indicating that the findings were robust to the skewed distribution of hematoma volume. Fig. 5 descriptively illustrates the distribution of 3-month mRS scores across BMI categories, with lower BMI groups exhibiting a higher proportion of unfavorable functional status.

3.6 BMI Distribution Across Clinical Subgroups

BMI distributions across clinical subgroups are presented in Fig. 6 (Ref. [17]). No statistically significant difference in BMI was observed between patients with and without AF ($p = 0.0578$). Significant differences in BMI were observed between non-CAA and probable CAA patients ($p < 0.0001$), between patients with and without cSS ($p = 0.0002$), and between non-lobar and lobar ICH groups ($p < 0.0001$).

4. Discussion

Our findings show an apparent inverse association between BMI and long-term mortality after ICH; however, this association was substantially attenuated after adjust-

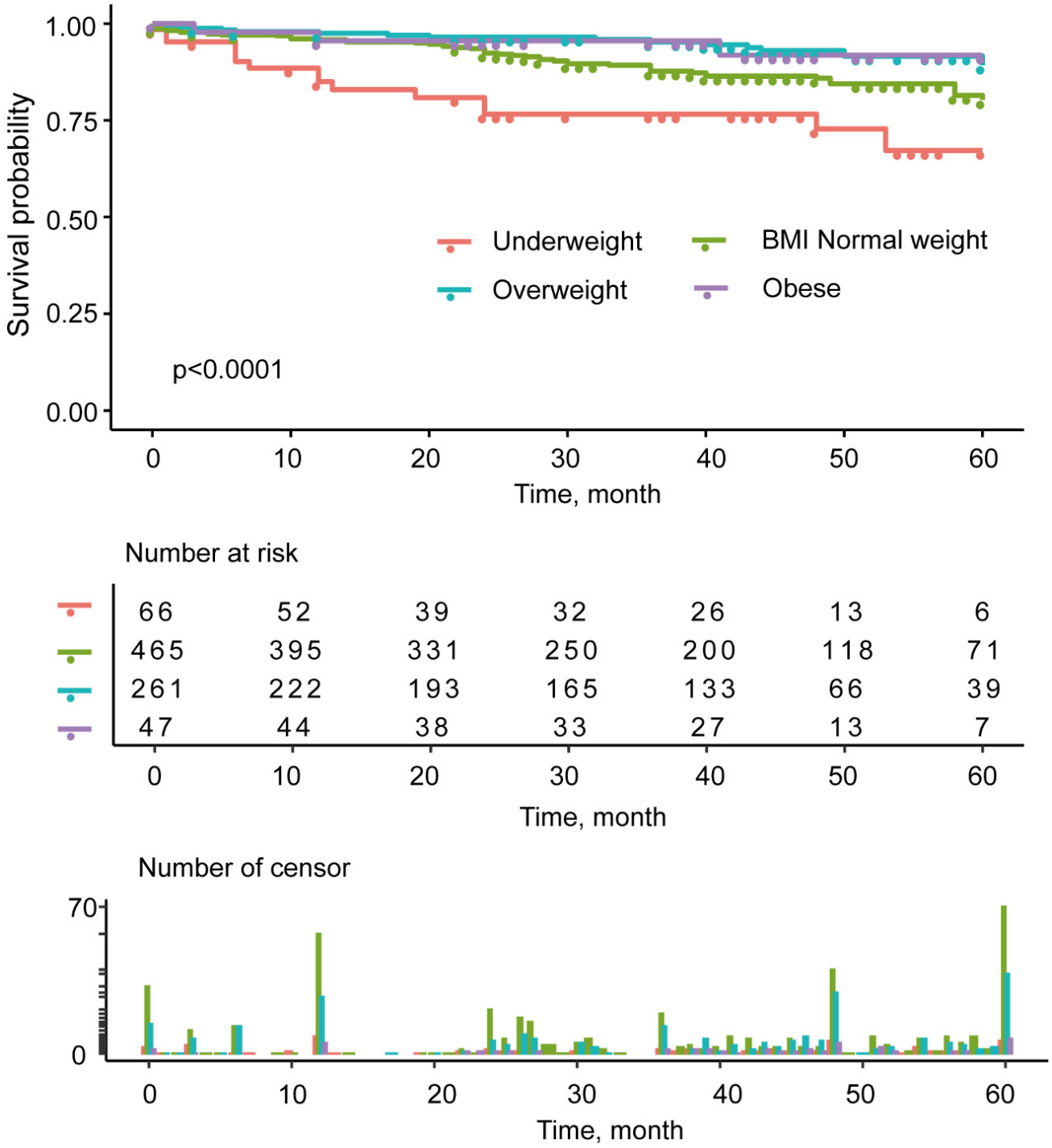

Fig. 3. Unadjusted Kaplan–Meier survival curves for all-cause mortality stratified by BMI categories.

ment for age, indicating that the observed survival difference may be partly explained by age-related confounding. In addition, higher BMI was associated with smaller baseline hematoma volume and a lower prevalence of several adverse imaging phenotypes, including probable CAA, cSS, and lobar ICH. The 3-month mRS distribution was presented descriptively and should not be interpreted as evidence of an independent association between BMI and functional outcome.

An important finding of the present study is the substantial influence of age on the observed association between BMI and mortality. Although higher BMI was associated with lower long-term mortality in unadjusted and exploratory analyses, this association was attenuated and no longer statistically significant after adjustment for age. This finding indicates that age may be a major confounding factor underlying the apparent ‘obesity paradox’ in ICH. Notably, patients with lower BMI in our cohort were generally older and more likely to exhibit imaging features associated

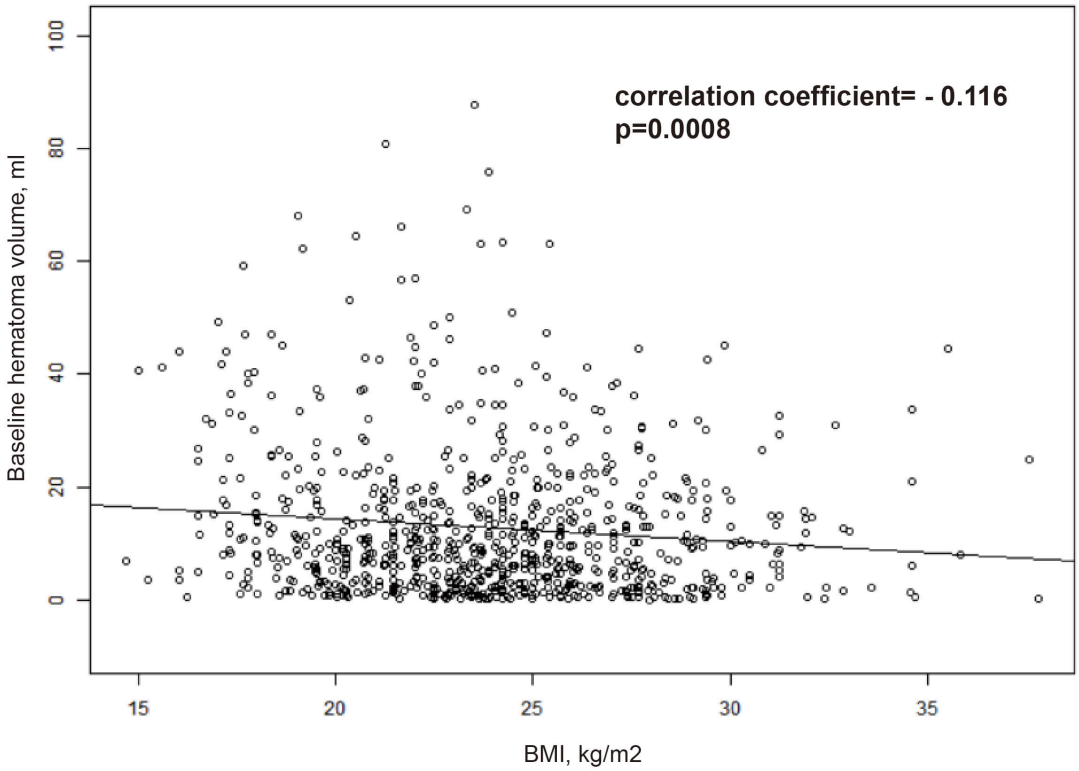

Fig. 4. Scatter plot showing the association between BMI and baseline hematoma volume.

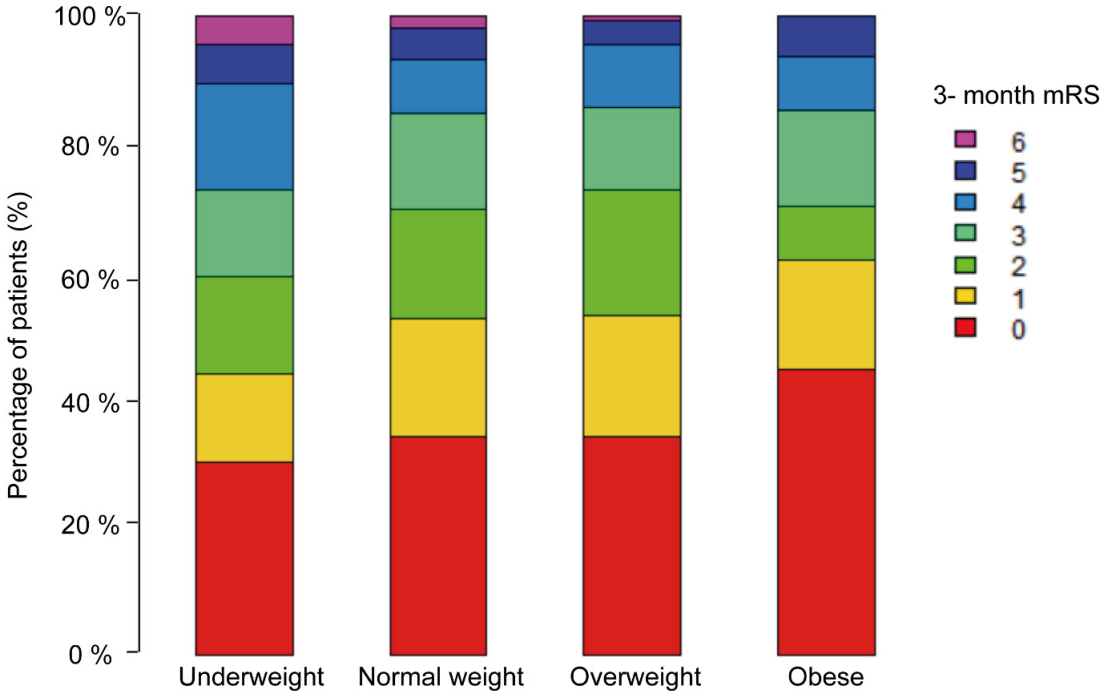

Fig. 5. Distribution of 3-month modified Rankin Scale (mRS) scores across BMI categories. Values represent the percentage of patients in each mRS category (0–6).

with cerebral amyloid angiopathy and frailty-related hemorrhagic phenotypes, including lobar ICH, cSS, and larger hematoma volume. Therefore, BMI may partly function as a surrogate marker of biological aging, frailty, and hemorrhagic small vessel disease burden rather than exerting a directly protective effect. These findings highlight the importance of cautious interpretation of the obesity paradox in observational ICH studies.

The paradoxical association between elevated BMI and improved survival was first described in

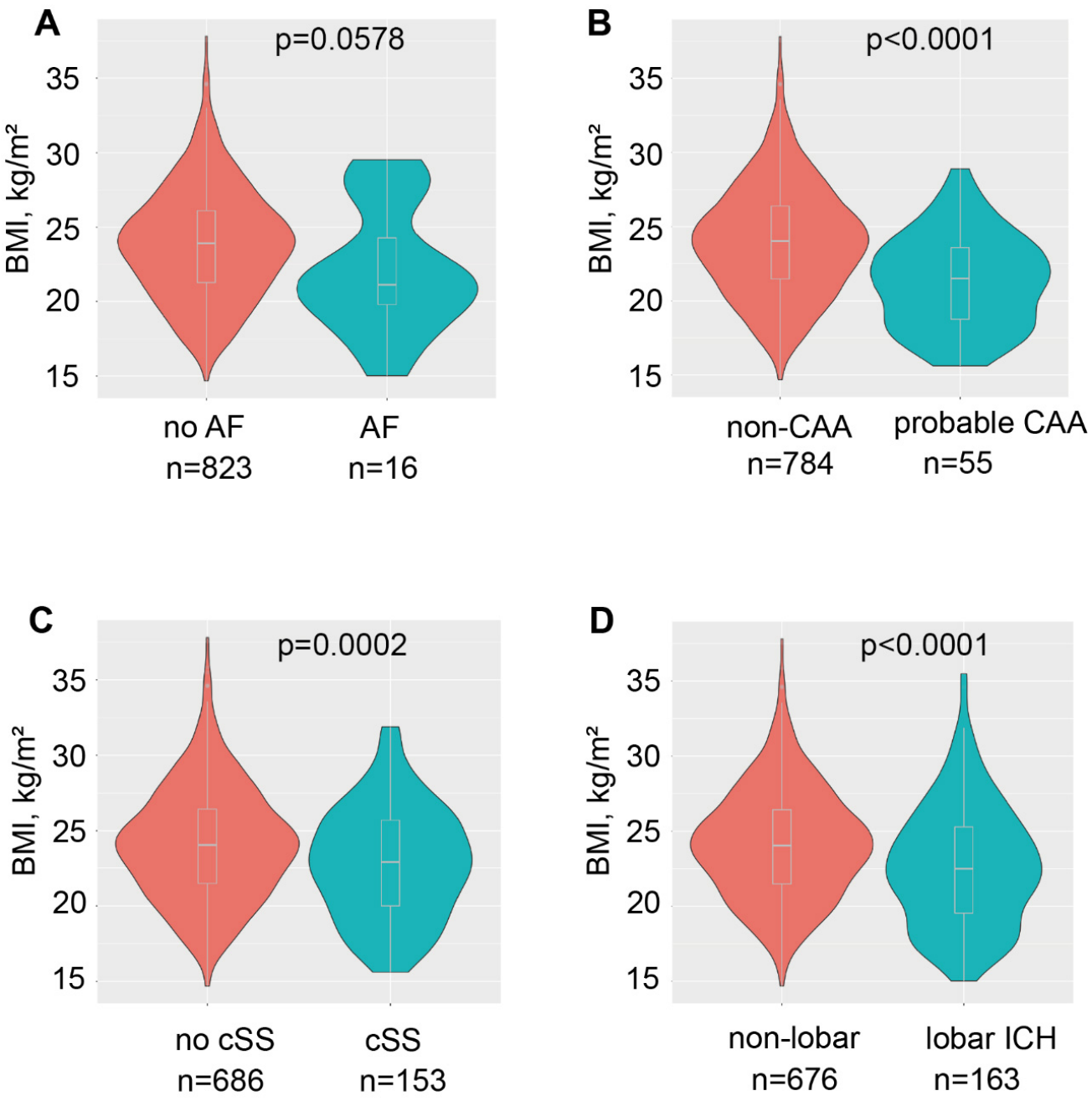

Fig. 6. Correlation between body mass index and atrial fibrillation, cerebral amyloid angiopathy, cortical superficial siderosis and lobar intracerebral hemorrhage. (A) Correlation between BMI and atrial fibrillation (AF). (B) correlation between BMI and CAA. (C) correlation between BMI and cSS. (D) correlation between BMI and lobar ICH. Probable CAA was evaluated based on the modified Boston criteria [17]. BMI, body mass index; CAA, cerebral amyloid angiopathy; cSS, cortical superficial siderosis; ICH, intracerebral hemorrhage.

patients with heart failure and has subsequently been reported in multiple chronic and acute diseases [22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40]. Previous observational studies investigating BMI and outcomes after ICH have also suggested a possible obesity paradox, although the findings remain inconsistent [8,41,42,43,44,45,46,47,48,49,50,51]. In the present study, overweight and obese patients exhibited lower long-term mortality in unadjusted and exploratory analyses. Similar findings have been reported by Dangayach et al. [52], who observed lower 3-month mortality and severe disability rates among overweight and obese patients with ICH. Sun et al. [45] likewise reported lower mortality and more favorable functional outcomes in obese patients during a 12-month follow-up. Several additional studies and meta-analyses have also demonstrated inverse associations between elevated BMI and mortality after ICH [42,43,48,53]. However, our findings further indicate

that this association is substantially influenced by age, suggesting that at least part of the apparent obesity paradox may reflect differences in biological aging, frailty, and hemorrhagic phenotype distribution across BMI categories. Interestingly, previous geriatric studies have similarly suggested that overweight status in older adults does not necessarily increase mortality risk and may partly reflect reduced frailty [54]. Further multicenter prospective studies are required to elucidate the independent contribution of BMI to long-term outcomes after ICH.

Given the substantial influence of age observed in our analyses, the potential mechanisms underlying the apparent obesity paradox should be interpreted cautiously. The observed association may partly reflect age-related frailty and differences in hemorrhagic phenotypes rather than a direct protective effect of adiposity. In our cohort, patients with higher BMI tended to have smaller hematoma volumes and lower prevalence of lobar ICH, probable CAA, and cSS, all of which are generally associated with older age and worse hemorrhagic outcomes. These findings show that differences in underlying hemorrhagic small vessel disease patterns may partly contribute to the observed BMI–mortality association. Nevertheless, several biological hypotheses proposed in previous studies may also be relevant. Obesity has been associated with elevated circulating coagulation factors, including factor VII, factor VIII, fibrinogen, and higher platelet activity, which could theoretically facilitate hemostasis after hemorrhagic events [55]. Interestingly, we also observed differences in baseline INR and platelet counts across BMI categories in the present study, although causal relationships cannot be established from our observational data. Additional hypotheses include greater metabolic reserve, altered inflammatory responses, and differences in vascular or endothelial function in overweight individuals [27,44,56,57]. However, these mechanisms remain speculative and require further mechanistic investigation.

This study is unique in that it evaluated the follow-up results of patients for up to 60 months, whereas most previous research data were often limited to hospitalisation, discharge, and 3-month outcomes. In addition, the study considered multiple baseline features, which can help adjust for potential confounding factors. This study has some limitations. This is a retrospective study on a single racial population, which limits the generalisability of the research results. In our institution, such patients are typically triaged to the neurosurgery service at presentation, whereas this cohort was established within the neurology department and therefore mainly included conservatively managed cases. As surgical candidates are generally more severely ill, this may have introduced selection bias and resulted in a relatively less severe study population. Furthermore, surgical decision-making in ICH is complex and influenced by multiple factors, including clinical severity, physician judgment, patient and family preferences, and perioperative considerations. These factors cannot easily be adjusted completely in observational analyses. Therefore, the generalisability of our findings to all ICH patients should be interpreted with caution. Further evaluation may be necessary for patients of other races. In addition, height was self-reported or provided by proxies in some patients, as accurate measurement was not always feasible during the acute phase of ICH. This may introduce measurement error or recall bias in BMI estimation, which should be considered when interpreting the results. We did not collect information on waist and hip circumference. BMI cannot distinguish between muscle and fat mass, leading to a relatively qualitative analysis of obesity. Currently, some studies show that BMI may not be the best indicator of obesity, and waist circumference and hip circumference are more closely related to research results than BMI alone [58]. The loss of statistical significance in sex-stratified analyses likely reflects reduced statistical power because of smaller subgroup sample sizes rather than true absence of association. In subgroup analyses, the direction of effect was generally similar across most strata; however, some heterogeneity was observed in the age <65 subgroup, where the hazard ratio of women was in the opposite direction to that of men, suggesting potential effect modification. Interestingly, hypertension was associated with lower mortality in the multivariable analysis; this appears counterintuitive. This finding has also been reported in previous studies and may be explained by several factors. First, patients with hypertension are more likely to receive regular medical care and early intervention, which may improve outcomes. Second, selection and survival biases may contribute to this observation, as hypertensive patients included in hospital-based cohorts may represent a relatively stable subgroup. Third, differences in underlying ICH mechanisms may also contribute; hypertensive ICH is more often located in deep brain regions, whereas non-hypertensive ICH, such as cerebral amyloid angiopathy-related hemorrhage, is associated with worse prognosis. Moreover, residual confounding cannot be excluded. Therefore, this finding should be interpreted with caution. Finally, although variables included in the multivariable Cox models were selected based on univariable analyses, this data-driven approach may not fully capture clinically relevant confounders identified from previous literature. Reliance on statistical screening thresholds may also increase the risk of model instability or overfitting, and future studies with larger sample sizes and externally validated models are needed to confirm these findings.

Summarily, our study observed an apparent inverse association between BMI and long-term mortality after primary ICH. However, this association was substantially attenuated after adjustment for age, suggesting an important influence of age-related confounding. Higher BMI was also associated with smaller hematoma volume and lower prevalence of several adverse hemorrhagic imaging phenotypes. These findings may contribute to improved understanding of prognostic heterogeneity in ICH, although the underlying mechanisms require further investigation.

5. Conclusion

Our study identified an apparent inverse association between BMI and long-term mortality after primary ICH; however, this association was substantially influenced by age. Higher BMI was also associated with smaller hematoma volume and lower prevalence of several adverse imaging phenotypes. These findings highlight the complex relationship between BMI, aging, and hemorrhagic stroke characteristics. Further multicenter prospective studies are needed to clarify the independent role of BMI in long-term ICH outcomes.

Key Points

• In this single-center cohort study on patients with intracerebral hemorrhage, BMI exhibited an inverse association with all-cause mortality in unadjusted and exploratory analyses; however, this association was attenuated and no longer significant after adjustment for age, suggesting a major confounding effect of age.

• BMI was also associated with several hemorrhagic imaging phenotypes, including hematoma location, hematoma volume, CMB, cSS, and probable CAA, although most associations were weak and should be interpreted cautiously.

• Lower BMI was more frequently observed in patients with probable cerebral amyloid angiopathy, cortical superficial siderosis, and lobar ICH.

• Higher BMI was associated with improved survival in exploratory analyses; however, this association was attenuated after age adjustment, suggesting that the obesity paradox in intracerebral hemorrhage requires further validation.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

YD: Conceptualization, Data curation, Formal analysis, Writing original draft. YJJ: Conceptualization, Investigation, Validation, Methodology, Writing original draft, Funding acquisition. YTS: Data curation, Formal analysis. DYC, TBX, KFQ, YYC: Data curation. MSW: Investigation, Resources, Software, Validation, Writing – review & editing. JW: Conception, Design, Project administration, Supervision, Writing – review & editing, Funding acquisition. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was conducted in compliance with the principles set forward by the Declaration of Helsinki. Written consent was obtained for each patient. The ethical approval have been obtained for Human Ethics Committee Board of the Second Affiliated Hospital of Zhejiang University School of Medicine ((2021) Lunshenyan No.(0015)). This study was a retrospective analysis of routinely collected clinical data. Ethical approval for the use of these data for research purposes was obtained in 2021 before data extraction and analysis.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM58250.

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