Ischemic Stroke Mortality Is More Strongly Associated with Anemia on Admission Than with Underweight Status

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Background: Underweight patients have recently been reported as a group with a high risk of poststroke death. Anemia also increases mortality rates in stroke patients. However, the causal associations between body weight and anemia resulting in stroke-related death remain unclear. We examined the association of weight status and hemoglobin levels with 3-month mortality after ischemic stroke. *Methods:* The study enrolled all consecutive patients with acute ischemic stroke and no history of stroke admitted to our hospital between January 2010 and December 2013. The patients were categorized into 4 body mass index (BMI) categories (underweight, normal-weight, overweight, and obese). Anemia was evaluated according to the World Health Organization criteria (men, <13 g/dL; women, <12 g/dL). *Results:* A total of 1733 acute ischemic stroke patients (149 underweight, BMI < 18.5 kg/m^2; 1076 normal-weight, BMI = 18.5-24.9 kg/m^2; 436 overweight, BMI = 25-29.9 kg/m^2; and 72 obese, BMI > 30 kg/m^2) were included. Death within 3 months occurred in 65 patients (underweight, 10.1%; normal-weight, 3.4%; overweight, 2.3%; and obese, 5.6%). Compared to nonanemic patients, those with anemia (n = 329, 19.0%) had lower BMI (21.8 kg/m^2 versus 23.7 kg/m^2, $P < .001$) and higher mortality rates (9.1% versus 2.5%, $P < .001$). Underweight status was associated with 3-month mortality after adjusting for age, sex, comorbidities, and initial stroke severity. However, in the models that included laboratory findings, it was anemia status (odds ratio, 2.81; 95% confidence interval, 1.46-5.43), not underweight status, that was

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independently associated with 3-month mortality. *Conclusion:* Anemia on admission was associated with stroke mortality independent of underweight status.
Key Words: Anemia—underweight status—ischemic stroke—mortality.

Introduction

The risk of ischemic stroke is known to increase with excess body weight, independent of other vascular risk factors.[1] Obesity is also one of the causes of hypertension, diabetes mellitus, and dyslipidemia, which are among the classical vascular risk factors.[2] However, some reports have indicated that obesity may not increase the risk of stroke recurrence.[3,4] On the other hand, the potential association between obesity and stroke-related mortality is still under debate. A few studies reported that being underweight also leads to poor stroke outcomes.[5-8] Therefore, the causal association between body mass index (BMI) and stroke mortality remains unclear.

Anemia has also been reported to worsen stroke outcomes.[9,10] Although there is no consensus yet regarding the potential association between anemia and BMI, anemia has been shown to have a higher incidence in underweight individuals.[11,12] A recent meta-analysis has found that anemia increases the mortality risk in patients with stroke.[13] However, few studies have investigated whether anemia remains associated with stroke mortality after adjusting for BMI or nutritional status. Indeed, it has been reported that serum albumin levels are associated with stroke mortality.[9,14]

The aims of the present study were to elucidate the relationship among BMI status, anemia, and ischemic stroke mortality, and to assess the influence of hypoalbuminemia on this relationship.

Methods

This was a single-center, hospital-based, retrospective study that received approval from the hospital's institutional review board. The study included consecutive patients with no history of stroke who were admitted with acute ischemic stroke to the Brain Attack Center at Ota Memorial Hospital between January 2010 and December 2013. Patients with prior stroke history, as well as those admitted later than 7 days after stroke onset and those who received acute stroke management with intravenous recombinant tissue plasminogen activator treatment, endovascular therapy, or any operation, were excluded from the present study. Ischemic strokes were classified according to the criteria laid down by the Trial of Org 10172 in Acute Stroke Treatment.[15] The following baseline clinical characteristics were recorded at admission: age; sex; BMI; classical vascular risk factors including hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease (CKD), daily alcohol intake (>40 g), and smoking habit; laboratory findings including hemoglobin and serum albumin levels; and the National Institutes of Health Stroke Scale (NIHSS) score as a measure of neurological severity. Hypertension was defined as the use of antihypertensive medications before admission, or as a confirmed blood pressure of 140/90 mmHg or higher at rest 2 weeks after stroke onset. Diabetes mellitus was defined as a glycated hemoglobin level of 6.5% or higher, a fasting blood glucose level of 126 mg/dL or higher, or the use of antidiabetic medication. Dyslipidemia was defined as a total cholesterol level of 220 mg/dL or higher, a low-density lipoprotein cholesterol level of 140 mg/dL or higher, a high-density lipoprotein cholesterol level of less than 40 mg/dL, a triglyceride level of 150 mg/dL or higher, or the use of antihyperlipidemic medication. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2. In the Japanese population, eGFR is calculated using the following equation[16]:

$$\mathrm{eGFR} = 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-.287}\ (\times .739 \text{ for women}).$$

Each patient was assigned to 1 of 4 BMI categories (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; or obese, BMI ≥ 30.0 kg/m^2) according to the classification laid down by the World Health Organization. Anemia was also defined according to the World Health Organization criteria as a hemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women.[17] Statistical analysis was performed using the JMP v12.0.1 software (SAS Institute, Inc., Cary, NC). For continuous variables, data were expressed either as means ± standard deviations or medians (25th and 75th percentiles). Discrete variables are expressed as frequencies and percentages. The statistical significance of intergroup differences was assessed by χ^2, unpaired *t*, Mann–Whitney *U*, and Kruskal-Wallis tests, as appropriate. Multivariate logistic analyses were performed to identify the indicators (model 1: age, sex, underweight, hypertension, diabetes mellitus, dyslipidemia, CKD, daily alcohol intake, smoking habit, cardioembolic stroke and NIHSS scores; model 2: anemia and serum albumin added to the indicators of model 1) for stroke mortality using a backward selection procedure with a *P* value greater than .10 as the exclusion criterion for the likelihood ratio test.

Results

Baseline Characteristics According to BMI Categories or Anemia Status

A total of 1733 patients (age, 72 ± 12 years; women, 37.6%) were included. The mean BMI was 23.3 ± 3.7 kg/m^2,