Body mass index is a risk factor for hemorrhagic transformation in older ischemic stroke patients after intravenous thrombolysis: a single center retrospective study

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Research Article

Keywords: Body mass index, Hemorrhagic transformation, Intravenous thrombolysis, Ischemic stroke, Older patients

Posted Date: February 5th, 2019

DOI: https://doi.org/10.21203/rs.2.293/v1

Abstract

Background: The aim of our study was to determine whether body mass index is a predictor of hemorrhagic transformation in acute ischemic stroke patients after intravenous thrombolysis.

Methods: A retrospective observational study was conducted to recruit 261 participants from a single center in China (67.0% males, median age 65 years). A head computed tomography scan was performed after 24 hours to evaluate hemorrhagic transformation occurrence, and a computed tomography scan was performed immediately in cases of clinical worsening. Multivariate logistic regression was used to estimate the association between risk factors and hemorrhagic transformation in acute ischemic stroke patients after intravenous administration of recombinant tissue plasminogen activator.

Results: Of 261 patients, 40 (15.3%) developed hemorrhagic transformation (55% males, median age 70 years). Body mass index was higher in patients with hemorrhagic transformation than in patients without hemorrhagic transformation (25.7 vs 23.7; *P* value, 0.013). The multivariate logistic regression model showed that body mass index was an independent predictor of hemorrhagic transformation in patients aged ≥ 73 years (odds ratio, 1.74; 95% confidence interval, 1.22-2.49) but not in patients aged < 73 years (odds ratio, 1.01; 95% confidence interval, 0.87-1.18). In addition, the odds ratio was 5.16 (95% confidence interval, 2.21-12.04) when the body mass index was ≥ 25 kg/m2 compared to a body mass index < 25 kg/m2.

Conclusions: The present study demonstrated that body mass index was an independent predictor of hemorrhagic transformation in older acute ischemic stroke patients after intravenous thrombolysis.

Keywords: Body mass index, Hemorrhagic transformation, Intravenous thrombolysis, Ischemic stroke, Older patients.

Background

Stroke is one of the leading causes of death and the most common cause of severe disability in adults worldwide [1, 2]. Recombinant tissue plasminogen activator (r-tPA) treatment is an effective therapy for acute ischemic stroke [3, 4]. However, treatment with r-tPA is accompanied by a serious complication known as hemorrhagic transformation (HT), occurring in 13-43% patients [3], which is related to higher mortality, early neurological deterioration, and poorer long-term functional outcome for stroke patients [3]. Asian individuals are thought to have a 2.12-fold increased risk of r-tPA-related intracranial hemorrhage compared to non-Asian individuals [5]. HT is a complex and multifactorial phenomenon that is not fully understood and is only partially predictable. Therefore, identifying risk factors that are predisposing to HT may lead to new preventive strategies.

Body mass index (BMI) is reportedly an independent predictor for ischemic stroke with a 4% risk increase for each unit augmentation in BMI [6]. Previously, we found that BMI (≥ 25 kg/m^2) was associated with an increased risk of ischemic stroke [7]. However, the relationship between BMI and the risk of HT

remains unclear. Some studies showed no associations between BMI and the risk of HT [8-10]. while others found inverse associations [11] or positive associations between body weight and HT in ischemic stroke with thrombolysis [12, 13]. The aim of our study was to determine whether BMI is associated with HT in consecutive acute ischemic stroke patients with thrombolytic therapy in China.

Methods

Study Population

This retrospective cohort study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University between April 2014 and August 2018. All of the patients had a clinical diagnosis of acute ischemic stroke according to the World Health Organization (WHO) criteria and were further confirmed by head computed tomography (CT). Among 309 eligible patients, we excluded 8 patients who had missing data at admission (2.6%) and 40 who underwent intra-arterial thrombolysis or intravenous r-tPA treatment combined with mechanical thrombectomy (12.9%). After exclusion, 261 patients were included in the final analysis of the current study (Figure 1). All the data were extracted from the patients' medical charts. This retrospective study was reviewed and approved by the Institutional Review Board at Xi'an Jiaotong University. The need for patient consent was waived by the same ethics committee.

Baseline Data Collection

The baseline demographic, clinical and laboratory information collected included age, gender, BMI, current smoking status, fasting plasma glucose, triglyceride, low-density lipoprotein cholesterol, uric acid, platelet count, use of antiplatelet agents before enrollment, systolic and diastolic blood pressures, the National Institutes of Health Stroke Score (NIHSS) on admission, onset-to-needle time, and history of hypertension, diabetes mellitus and atrial fibrillation.

BMI was calculated as weight in kilograms divided by height squared in meters. Body weight and height were measured by nurses or obtained from the patient or relatives or – if not available – from estimates made by the attending stroke physician [8-10].

All blood samples were collected from patients after at least 8 hours of fasting but within 24 hours of hospital admission. Biochemical analysis was performed in the clinical laboratory of the First Affiliated Hospital of Xi'an Jiaotong University. All laboratory indicators were measured using an automatic biochemistry analyzer (BJ-G188; Hitachi, Tokyo, Japan).

Thrombolysis Method

All patients were treated with r-tPA within 4.5 hours post onset. Intravenous r-tPA (alteplase, 0.9 mg/kg up to a maximum of 90 mg) was used with 10% of the total dose as a bolus, followed by a 60-min infusion of the remaining dose.

Ascertainment of Hemorrhage Transformation

On admission, all patients underwent a CT scan within the first 4.5 hours of stroke onset. CT was repeated 24 hours after intravenous r-tPA, and another CT scan was performed immediately in cases of rapid neurological deterioration to evaluate the presence of HT. HT after intravenous r-tPA was identified by the presence of hyperdensity on noncontrast CT [14]. Symptomatic intracranial hemorrhage (sICH) was defined as any type of intracranial hemorrhage on any posttreatment imaging after thrombolysis start and an increase in NIHSS by 4 points from baseline, or death; asymptomatic intracranial hemorrhage (aSICH) was defined as any type of intracranial hemorrhage on any posttreatment imaging after thrombolysis start but not accompanied by neurological deterioration (the European Cooperative Acute Stroke Study II, ECASS II) [15].

Statistical Analysis

Descriptive analysis was conducted with continuous variables described as medians with interquartile range (IQR) or as the means with standard deviation (SD) if the variables had normal distributions. Categorical variables are presented as numbers (percentages). Baseline demographic and clinical characteristics were compared by Student's t-test for continuous variables and the Chi-square test for categorical variables. The association between risk factors and HT was estimated by odds ratio (OR) and 95% confidence interval (CI) using multivariate logistic regression models. Variables significant in the univariable analysis were included in the multivariable modeling. Statistical analysis was performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Two-tailed significance values were applied, and statistical significance was defined as $P < 0.05$.

Results

The study included 261 patients treated with thrombolysis. The median age was 65 years old (range, 27-93), and 67.0% (N = 175) of this group was male. The baseline NIHSS median score was 6.0 (IQR, 4.0-12.0), and the fasting plasma glucose median level at admission was 5.8 (IQR, 4.8-7.5). The baseline characteristics of the study population are presented in Table 1. Among 261 patients, HT occurred in 40 patients (15.3%; 22 male and 18 female). Of these 40 patients, 14 (5.36%) were defined as sICH. In general, participants with HT were older and had higher BMI levels than participants without HT. In addition, participants with HT were more likely to have a medical history of atrial fibrillation and use of antiplatelet agents, as well as a higher fasting plasma glucose level and NIHSS score on admission, than those without HT.

In the univariate statistical analysis of demographic data, stroke risk factors and components directly related to treatment, variables significantly affecting the HT proved to be age ($P = 0.011$), NIHSS scores at admission ($P < 0.001$), BMI (≥ 25 kg/m^2) ($P = 0.002$), fasting plasma glucose ($P < 0.001$) and atrial fibrillation ($P < 0.001$)). Multivariate analysis demonstrated that compared to participants in the non-HT group, those in the HT group had an OR (95% CI) of 5.16 (2.21-12.04) for BMI (≥ 25 kg/m^2), 2.78 (1.18-6.57) for atrial fibrillation, 1.14 (1.07-1.22) for NIHSS score and 1.20 (1.06-1.37) for fasting plasma

glucose (Table 2). No differences were found regarding age and sex evaluated in either group in the multivariate analysis.

In addition, when BMI was identified as a continuous variable, the association between BMI and HT was significant in patients ≥ 73 years with an OR (95% CI) of 1.74 (1.22-2.49) but not in patients < 73 years with an OR (95% CI) of 1.01 (0.87-1.18) (Table 2 and Figure 2). Furthermore, of those patients ≥ 73 years, BMI was significantly associated with sICH (OR, 2.11; 95% CI, 1.16-3.83) as well as with aSICH (OR, 1.64; 95% CI, 1.08-2.48) after adjustment for fasting plasma glucose, atrial fibrillation, and NIHSS score on admission (Table 3).

Discussion

In the present study, we demonstrated that BMI is a predictor of HT in older patients (≥ 73 years) with ischemic stroke treated with intravenous thrombolysis. In addition, fasting plasma glucose, atrial fibrillation, and NIHSS score at admission are also predictors of HT.

HT is a life-threatening complication in acute ischemic stroke patients treated with intravenous thrombolysis, which can worsen the clinical course and outcome. Furthermore, HT occurs in approximately 10% to 43% of patients after thrombolysis [16, 17]. In the present study, the rate of HT after thrombolysis was 15.3%, which was consistent with the findings of a previous investigation in China [17].

BMI is an established risk factor for stroke. Previously, we found that BMI (≥ 25 kg/m^2) was associated with an increased risk of ischemic stroke [7]. However, its impact on HT after acute ischemic stroke is unclear. The present study indicates that a higher BMI can increase the risk of HT and its subtype (sICH and aSICH) after intravenous thrombolytic therapy in patients older than 73 years. In addition, patients with BMI ≥ 25 kg/m^2 had an approximately 5.16-fold increased risk of developing HT compared to patients with BMI < 25 kg/m^2, and this association was independent of age, fasting plasma glucose, atrial fibrillation and NIHSS score. In agreement with our findings, in the Safe Implementation of Treatments in Stroke symptomatic intracerebral hemorrhage risk score (The SITS SICH risk score), body weight was a predictor for sICH [12]. Moreover, Diedler J et al reported that the risk of sICH significantly increased in patients weighing > 100 kg who accepted intravenous r-tPA thrombolysis compared to those weighing ≤ 100 kg [13]. However, a meta-analysis across three studies in Europe reported that obesity (BMI ≥ 30 kg/m^2 vs. BMI < 30 kg/m^2) was not related to sICH risk with 3-month follow-up [8, 9], while others found inverse associations that may be related to obese patients receiving an intravenous r-tPA dose < 0.9 mg/kg [11]. These seemingly discrepant observations might be explained by differences in race, length of follow-up, sample size, or definition and subtype of HT. In one large study, body weight independently increased the risk of sICH when using the SITS-MOST (Safe implementation of thrombolysis in stroke-monitoring study) definition but not when using the ECASS II definition [9, 12]. When race was included in the GRASPS score, Asian race was an independent predictor of sICH [18].

Furthermore, our study showed a relationship among HT and different factors, such as NIHSS score, atrial fibrillation and fasting plasma glucose values, confirming the results of previous studies [4]. A higher NIHSS score was shown to increase the risk of HT in many studies [19, 20]. Severe ischemic stroke is reflected by large areas of injured brain tissue, including injured blood vessels, which are prone to bleeding after r-tPA treatment. Atrial fibrillation was also reported as an independent predictor of HT and sICH in many studies [4, 21]. This finding was confirmed in the present and our previous study assessing Chinese patients. Hyperglycemia is common in patients during the acute phase of stroke; however, the association between HT and blood glucose is controversial. In a meta-analysis of 11 studies on the associations between blood glucose and post r-tPA intracranial hemorrhage, the pooled OR associated with a per mmol/L increase in glucose level among patients treated with r-tPA was 1.10 (95% CI, 1.05-1.14) [4]. A previous Chineses study showed that elevated serum glucose on admission places a patient at increased risk for sICH following rt-PA [22]. In the present study, we confirmed that fasting plasma glucose was a predictor of HT in acute ischemic stroke patients after r-tPA treatment.

Although the mechanism of HT is not fully understood, several explanations may account for the observed association between these risk factors and HT in acute ischemic stroke after r-tPA treatment. First, obesity has been shown to be associated with a proinflammatory state, and participants with obesity more frequently had cardiovascular risk factors. The present study found that patients with higher BMI were likely to have lower platelet count. Certainly, the mechanism underlying this phenomenon requires further research. Second, interactions of multiple pathogenic factors, including hyperglycemia-mediated vascular oxidative stress and inflammation, ischemic insult, and r-tPA neurovascular toxicity, in concert, contribute to the blood-brain barrier damage-intracerebral hemorrhagic transformation process. The development of combination approaches targeting multiple pathological cascades may help to attenuate hemorrhagic complications [23].

There are some limitations of our study. First, the present study used a retrospective design, so some confounders were not available for control in our multivariate analyses. Second, the study included a single center-based sample and a relatively small sample size, which might have limited the statistical power of the study. Third, body weight and height were self-reported by patients or caregivers in part, but these data were reassessed by the attending stroke physician.

Conclusions

Our findings suggest that BMI is a predictor for HT in older (≥ 73 years) ischemic stroke patients after intravenous thrombolysis. In addition, fasting plasma glucose, atrial fibrillation, and NIHSS score at admission are also predictors of HT in ischemic stroke patients after intravenous thrombolysis. Future studies with a prospective design and larger sample size are needed to confirm the results from the present study.

Abbreviations

r-tPA: Recombinant tissue plasminogen activator; HT: Hemorrhagic transformation; BMI: Body mass index; WHO: World Health Organization; CT: Computed tomography; NIHSS: National institutes of health stroke score; sICH: Symptomatic intracranial hemorrhage; aSICH: Asymptomatic intracranial hemorrhage; ECASS II: the European Cooperative Acute Stroke Study II; IQR: Interquartile range; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; The SITS SICH: The Safe Implementation of Treatments in Stroke symptomatic intracerebral hemorrhage; SITS-MOST: Safe implementation of thrombolysis in stroke-monitoring study; FPG: fasting plasma glucose.

Declarations

Acknowledgments

Not applicable.

Funding

This work was supported by the Natural Science Foundation of Shaanxi Province of China (2014JM4107, 2017JM8150) and the Key Science and Technology Program of Shaanxi Province, China (2018SF-089).The funders had no role in the design of the study and collection, analysis, interpretation of data or in writing the manuscript.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YRZ contributed to the conception and design of the study and to the analysis and interpretation of the data. CQM and XYY contributed to the collection, analysis and the drafting of the article. CYM, YQ and GGL collected the data and revised the article critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at Xi’an Jiaotong University. The need for patient consent was waived by the same ethics committee.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of study participants.

Characteristic	Total (n = 261)	HT (n = 40)	without HT (n = 221)	P value
Demographic data				
Age (year) (median, IQR)	65 (56-73)	70 (62-75)	64 (55-73)	0.017
Male, n (%)	175 (67.0)	22 (55.0)	153 (69.2)	0.078
BMI (kg/m^2) (median, IQR)	24.0 (22.2-26.0)	25.7 (22.7-26.4)	23.7 (22.1-25.4)	0.013
Current smoking, n (%)	100 (38.4)	15 (37.5)	85 (38.5)	0.566
Medical history, n (%)				
Diabetes mellitus	67 (25.7)	14 (35.0)	53 (24.0)	0.142
Atrial fibrillation	70 (26.8)	23(57.5)	47(21.3)	0.000
Hypertension	174 (66.7)	29(72.5)	145(65.6)	0.395
Laboratory tests				
FPG (mg/dL) (median, IQR)	5.8 (4.8-7.5)	7.9 (5.9-10.0)	5.6 (4.7-7.0)	0.000
TG (mmol/L) (median, IQR)	1.27 (0.86-1.82)	1.52 (0.96-1.95)	1.22 (0.86-1.80)	0.112
LDL-C (mmol/L) (mean±SD)	2.45 ± 0.82	2.53 ± 0.89	2.44 ± 0.80	0.565
UA (μmol/L) (mean±SD)	303.0 ± 86.9	301.4 ± 85.4	303.2 ± 87.4	0.988
PLT count (10^9/L) (median, IQR)	176 (148-223)	170 (133-204)	179 (149-225)	0.120
Parameters on admission				
Systolic BP (mmHg) (median, IQR)	150 (134-167)	153 (139-175)	150 (134-167)	0.635
Diastolic BP (mmHg) (median, IQR)	85 (75-100)	81 (69-100)	85 (75-99)	0.308
NIHSS score (median, IQR)	6 (4-12)	13 (7-17)	5 (3-10)	0.000
ONT (hour) (median, IQR)	3.0 (2.5-4.0)	3 (2-3.6)	3.0 (2.5-4.0)	0.070
Antiplatelet therapy, n (%)	60 (23.0)	15 (37.5)	45 (20.4)	0.057

Notes: Continuous variables are expressed as the median (interquartile range) or as the mean with SD; categorical variables are expressed as frequency (percent).

Abbreviations: HT, hemorrhagic transformation; IQR, interquartile range; BMI, body mass index; FPG, fasting plasma glucose; NIHSS, National Institutes of Health Stroke Scale; ONT, symptom onset to treatment.

Table 2. Associations of BMI with HT.

Variables	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis OR (95% CI)	*P* value
BMI (per kg/m^2)	1.00 (0.88-1.14)	0.975	1.10 (0.87-1.17)	0.905
18-73 years	1.26 (1.03-1.54)	0.022	2.07 (1.28-3.33)	0.003
≥ 73 years				
BMI (2 categories, kg/m^2) (≥ 25 vs. < 25)	3.04 (1.53-6.06)	0.002	5.16 (2.21-12.04)	<0.001
NIHSS	1.15 (1.09-1.22)	<0.001	1.14 (1.07-1.22)	<0.001
FPG	1.26 (1.13-1.41)	<0.001	1.20 (1.06-1.37)	0.004
Atrial fibrillation	5.01 (2.48-10.14)	<0.001	2.78 (1.18-6.57)	0.020

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; FPG, fasting plasma glucose; NIHSS, National Institutes of Health Stroke Scale.

Multivariate analysis: adjusted for age, FPG, atrial fibrillation, and NIHSS score on admission.

Table 3. Associations of BMI in older patients (≥73 years) with aSICH and sICH.

VVariables	aSICH OR (95% CI) (n = 7)		sICH OR (95% CI) (n = 6)	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
BMI (per kg/m^2)	1.93 (0.95-1.50)	1.64 (1.08-2.50)*	1.25 (0.97-1.60)	2.11 (1.16-3.83) *

Abbreviations: sICH, symptomatic intracranial hemorrhage; OR, odds ratio; CI, confidence interval; BMI, body mass index.
Multivariate analysis: adjusted for fasting plasma glucose, atrial fibrillation, and NIHSS score on admission. *$P <$ 0.05.

Figures

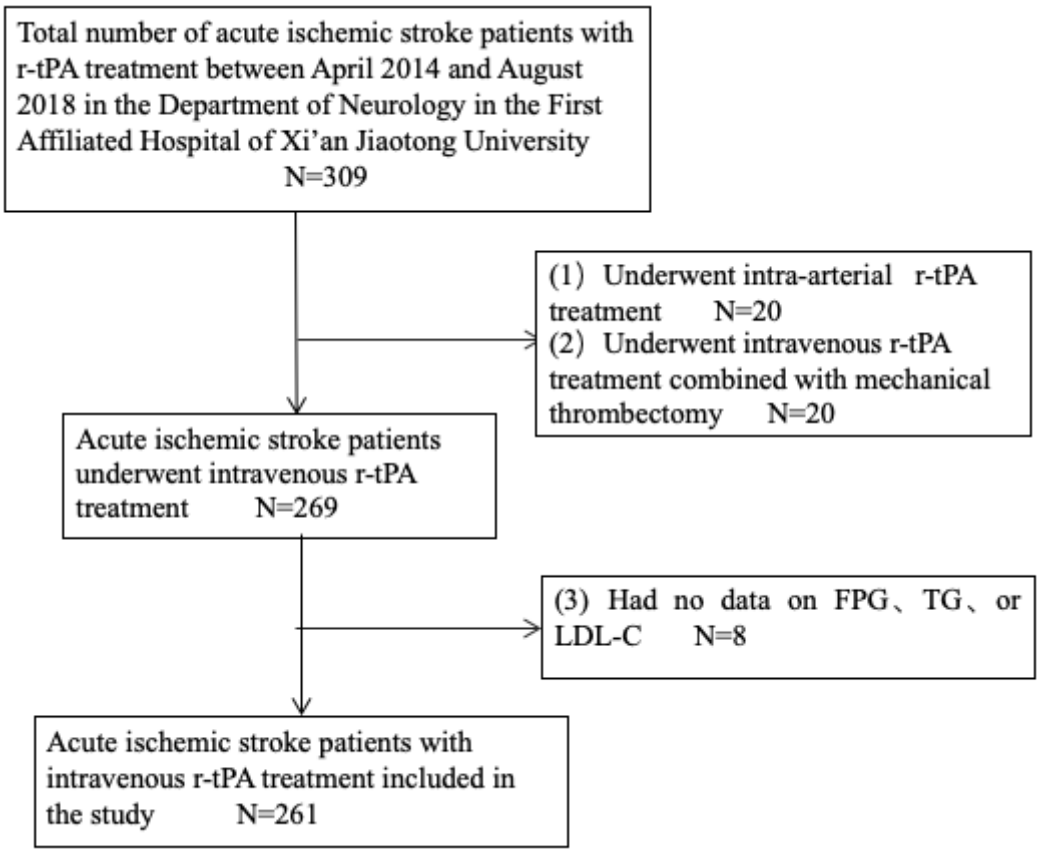

Figure 1

Reasons for exclusion from 309 cases of acute ischemic stroke patients receiving intravenous r-tPA treatment.

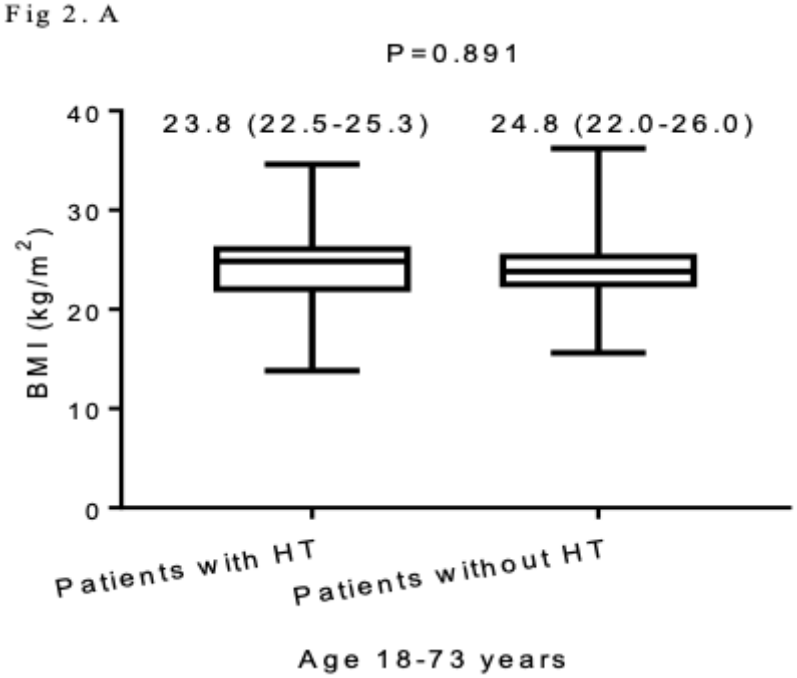

Figure 2

Comparison of BMI in patients with and without HT. A: Adult patients (ages between 18 and 73 years) (P = 0.891).

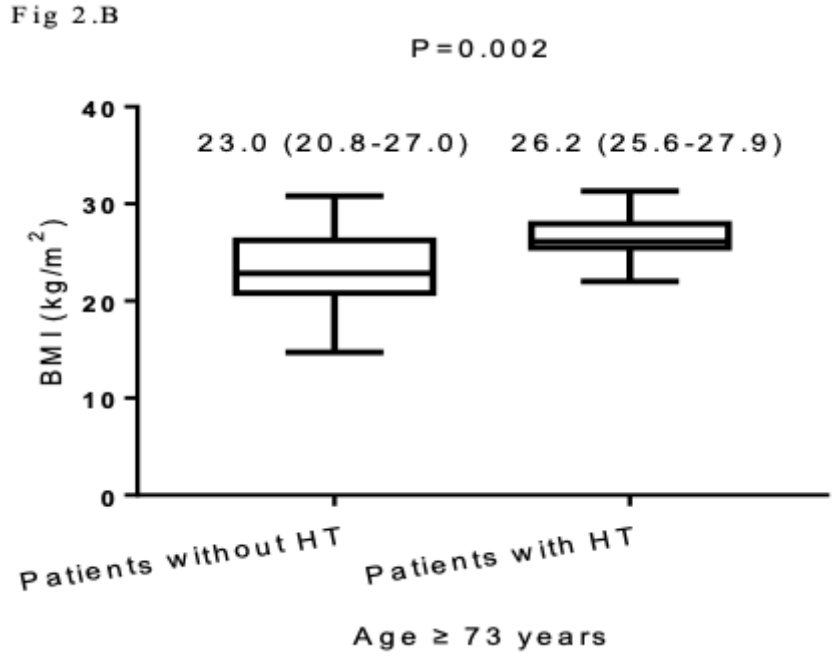

Figure 3

Comparison of BMI in patients with and without HT. B: Patients over 73 years (P = 0.002). HT: hemorrhagic transformation, BMI: body mass index.