Retrospective Cohort Study

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Potential of BMI as a screening indicator for extracranial–intracranial bypass surgery in patients with symptomatic artery occlusion: a post-hoc analysis of the CMOSS trial

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Background: To investigate the association between BMI and the incidence of ischemic stroke in patients with symptomatic artery occlusion, and further to evaluate the utility of BMI as a screening tool for identifying candidates for extracranial–intracranial bypass surgery.
Materials and Methods: The authors analyzed the relationship between BMI and the occurrence of ipsilateral ischemic stroke (IIS) among patients receiving only medical management in the Carotid or Middle cerebral artery Occlusion Surgery Study (CMOSS). Additionally, the authors compared the primary endpoint of CMOSS—stroke or death within 30 days, or IIS after 30 days up to 2 years—among patients with varying BMIs who underwent either surgery or medical treatment.
Results: Of the 165 patients who treated medically only, 16 (9.7%) suffered an IIS within 2 years. BMI was independently associated with the incidence of IIS (hazard ratio: 1.16 per kg/m^2; 95% CI: 1.06–1.27). The optimal BMI cutoff for predicting IIS was 24.5 kg/m^2. Patients with BMI $\geq$24.5 kg/m^2 experienced a higher incidence of IIS compared to those with BMI <24.5 kg/m^2 (17.4 vs. 0.0%, $P<0.01$). The incidence of the CMOSS primary endpoint was significantly different between the surgical and medical groups for patients with BMI $\geq$24.5 kg/m^2 (5.3 vs. 19.8%, $P<0.01$) and those with BMI <24.5 kg/m^2 (10.6 vs. 1.4%; $P=0.02$). Surgical intervention was independently associated with a reduced rate of the CMOSS primary endpoint in patients with BMI $\geq$24.5 kg/m^2.
Conclusion: Data from the CMOSS trial indicate that patients with BMI $\geq$24.5 kg/m^2 are at a higher risk of IIS when treated medically only and appear to derive greater benefit from bypass surgery compared to those with lower BMIs. Given the small sample size and the inherent limitations of retrospective analyses, further large-scale, prospective studies are necessary to confirm these findings.

Keywords: body mass index, bypass surgery, carotid artery occlusion, ischemic stroke, middle cerebral artery occlusion

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Introduction

Intracranial atherosclerotic disease is a leading cause of ischemic stroke worldwide and incurs significant disability and economic burdens, especially in Asian nations[1–3]. Despite intensive medical management and risk factor control, patients with symptomatic internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion and hemodynamic insufficiency face a stroke recurrence risk exceeding 10% annually[4–6]. Both the Carotid Occlusion Surgery Study (COSS)[4] and the recent Carotid or Middle cerebral artery Occlusion Surgery Study (CMOSS)[7] did not show significant benefits of extracranial–intracranial (EC–IC) bypass surgery over medical treatment in these patients. This underscores the importance of identifying more specific risk factors to determine which patients are at high-risk for recurrent ischemic stroke.

Obesity, characterized by abnormal or excessive fat accumulation, is a recognized modifiable risk factor for cardiovascular diseases, especially ischemic heart disease[8,9]. Numerous studies[10–15] have consistently demonstrated a positive correlation between BMI and the incidence of primary ischemic stroke in both Asian and Western populations. A meta-analysis[16] of 13 prospective cohort studies indicated that a 5 kg/m^2 increase in BMI is associated with a 22% increased risk of primary ischemic stroke in European, North American, or Australian populations, and a 35% increased risk in Asian populations. Yet, findings suggest that obesity does not elevate—and may even reduce—the risk of recurrent stroke in patients with previous strokes compared to those of normal weight or who are lean[17,18], a phenomenon often referred to as the 'obesity paradox'[19]. Although the link between obesity and stroke has been extensively explored in the general population, research targeting specific groups, such as patients with symptomatic ICA or MCA occlusion, remains sparse. Determining whether obesity consistently alters the risk of recurrent stroke in this demographic could help in identifying those who might be suitable candidates for revascularization procedures.

In this study, we examined the relationship between BMI levels and the occurrence of subsequent ipsilateral ischemic stroke (IIS) in patients who underwent medical treatment only in the CMOSS trial. We also assessed BMI's potential as a marker to identify those who might benefit from bypass surgery alongside medical treatment.

HIGHLIGHTS

- There was a positive association between BMI levels and incidence of recurrent ischemic stroke in symptomatic artery occlusion patients treated medically only in the Carotid or Middle cerebral artery Occlusion Surgery Study (CMOSS) trial.
- Symptomatic artery occlusion patients with higher BMI levels ($\geq$24.5 kg/m^2) were more likely to experience CMOSS primary endpoint and they tended to benefit more from bypass surgery.
- BMI levels have the potential to identify patients with symptomatic artery occlusion who might be candidates for bypass surgery.

Material and methods

Study population

This study adheres to the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria (Supplemental Digital Content 1, http://links.lww.com/JS9/C722)[20]. It includes all participants from the recently published CMOSS trial[7]. The CMOSS trial, a randomized, multicenter, open-label study with outcome assessor-blinded methodologies, assessed the efficacy of EC–IC bypass surgery in patients with symptomatic ICA or MCA occlusion and related hemodynamic insufficiency. The trial's design and outcomes have been documented previously[7,21]. A total of 324 patients, aged 18–65 years, diagnosed with atherosclerotic ICA or MCA occlusion and experienced either a transient ischemic attack (TIA) or a nondisabling ischemic stroke due to hemodynamic insufficiency—confirmed via computed tomography perfusion imaging—were randomly assigned to two groups: 161 patients underwent EC–IC bypass surgery along with medical treatment, and 163 patients received only medical treatment. The medical regimen included antiplatelet therapy (aspirin 100 mg/day or clopidogrel 75 mg/day) and management of stroke risk factor. The study protocol received approval from the institutional review boards of all 13 participating centers in China, and written informed consent was obtained from all participants. Additionally, the local Institutional Review Board approved the coordination of the CMOSS trial and the post-hoc analysis in this study, under the designation [2013]011.

Data collection

Prior to randomization, all baseline characteristics were collected upon patient admission. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Weight was measured to the nearest 0.1 kg with the patient in minimal clothing using standard scales. Height was measured without shoes to the nearest 0.01 m using standard height measures.

Outcome measures and definitions

IIS was clinically defined as a focal or global disturbance of cerebral function resulting from cerebral ischemia in the region of the symptomatic occluded ICA or MCA, persisting for more than 24 h. This definition encompasses both the ipsilateral primary ischemic stroke in patients who had only experienced a TIA and the ipsilateral recurrent ischemic stroke in patients with a previous ischemic stroke. The CMOSS primary endpoint was defined as the incidence of a composite outcome of any stroke or death within 30 days after randomization, or of an IIS occurring beyond 30 days and up to 2 years after randomization. Follow-up visits were conducted at the neurologic outpatient clinic at 30 days, and at 6, 12, and 24 months postrandomization. In cases where a stroke was suspected, diagnostic confirmation was obtained through brain computed tomography or MRI. An independent outcome committee, along with an imaging core laboratory, assessed the incidence of the endpoints.

Statistical analysis

We utilized univariate and multivariate Cox proportional hazards models to assess whether BMI was independently associated with the incidence of IIS in patients receiving only medical

treatment. Variables with a *P*-value of <0.15 in the univariate analysis were included in the multivariate analysis, which was performed using a backward stepwise selection method. Only those variables that remained significant at a *P*-value of <0.05 were retained in the final model.

The receiver operating characteristic (ROC) curve was constructed to identify the optimal cutoff value for BMI in predicting the incidence of IIS. Patients receiving medical treatment were then categorized into two groups: those with a BMI ≥ the optimal cutoff value and those with a BMI < the optimal cutoff value. The baseline characteristics of these groups were compared using the χ^2 test or Fisher's exact tests for categorical variables, and the *t*-test or Wilcoxon rank test for continuous variables. The risk of time-to-event outcomes was analyzed using Kaplan–Meier curves, with differences between groups evaluated using the log-rank test.

Given that patients with BMI ≥ the optimal cutoff value exhibited an increased risk of IIS during follow-up, we applied the log-rank test to compare the time to reach the CMOSS primary endpoint between surgical and medical groups in patients with BMI ≥ the optimal cutoff value and in patients with BMI < the optimal cutoff value. Furthermore, we utilized both univariate and multivariate Cox proportional hazards models to determine whether the treatment method independently predicted the incidence of the CMOSS primary endpoint in these patient groups.

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp.) and R version 4.0.2 (R Foundation for Statistical Computing). All probability values were two-tailed, and a *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

In the CMOSS trial, 10 patients initially assigned to the medical treatment group crossed over to undergo surgical procedures, while 12 patients from the surgical group switched to medical treatment only. As a result, the analysis included 165 patients who exclusively received medical treatment to explore the association between BMI levels and the incidence of IIS. Table 1 presents the baseline characteristics of these patients, with a median age of 54.0 years [interquartile range (IQR), 47.0–60.0]. Of these, 134 (81.2%) were male, and the median BMI was 25.3 kg/m^2 (IQR, 23.1–27.0).

Table 1

Baseline characteristics of the cohort and stratified according to BMI levels.

Variables	Total (*n* = 165)	BMI ≥ 24.5 kg/m^2 (*n* = 92)	BMI < 24.5 kg/m^2 (*n* = 73)	*P*
Age, median (IQR)[a], years	54.0 (47.0–60.0)	54.0 (47.0–59.8)	54.0 (46.5–60.0)	0.60
Sex, male, No. (%)	134 (81.2)	79 (85.9)	55 (75.3)	0.09
BMI, kg/m^2	25.3 (23.1–27.0)	–	–	–
Medical history				
Hypertension	92 (55.8)	68 (73.9)	24 (32.9)	< 0.01*
Diabetes mellitus	34 (20.7)	22 (23.9)	12 (16.4)	0.24
Hyperlipidemia	23 (13.9)	18 (19.6)	5 (6.8)	0.02*
Received medication prior to latest qualifying event				
Antiplatelet therapy	144 (87.3)	84 (91.3)	60 (82.2)	0.08
Lipid-lowing therapy	62 (37.6)	41 (44.6)	21 (28.8)	0.04*
Smoking, current or former, No. (%)	90 (54.5)	59 (64.1)	31 (42.5)	< 0.01*
Alcohol consumption, current or former, No. (%)	62 (37.6)	39 (42.4)	23 (31.5)	0.15
Systolic blood pressure, mmHg	130 (120–139)	130 (120–140)	125.0 (118–133)	0.02*
LDL cholesterol level, mmol/l	2.0 (1.6–2.5), *n* = 157	1.9 (1.5–2.4), *n* = 89	2.1 (1.6–2.5), *n* = 68	0.28
HDL cholesterol level, mmol/l	1.1 (0.9–1.3), *n* = 156	(0.9–1.3), *n* = 89	1.1 (1.0–1.4), *n* = 67	0.09
Total cholesterol, mmol/l	3.4 (3.0–4.1), *n* = 157	3.3 (2.9–3.9), *n* = 89	3.6 (3.0–4.2), *n* = 68	0.06
Triglycerides level, mmol/l	1.5 (1.1–1.8), *n* = 157	1.5 (1.2–1.9), *n* = 89	1.3 (0.9–1.7), *n* = 68	0.03*
Glucose level, mmol/l	5.2 (4.7–6.1), *n* = 157	5.2 (4.7–6.0), *n* = 88	5.2 (4.7–6.1), *n* = 69	0.67
Occluded artery, No. (%)				0.35
ICA	102 (61.8)	54 (58.7)	48 (65.8)	
MCA	63 (38.2)	38 (41.3)	25 (34.2)	
Qualifying side, left, No. (%)	90 (54.5)	52 (56.5)	38 (52.1)	0.57
Stroke as the qualifying event, No. (%)	90 (54.5)	46 (50.0)	44 (60.3)	0.19
Qualifying event to randomization, w	9.3 (5.6–16.1)	8.5 (5.3–15.2)	10.6 (6.0–16.9)	0.24
Computed tomography perfusion indexes				
MTT, s	5.8 (4.7–7.6), *n* = 156	5.6 (4.8–7.7), *n* = 89	5.9 (4.4–7.5), *n* = 67	0.97
rCBF	0.61 (0.48–0.83), *n* = 161	0.61 (0.49–0.82), *n* = 90	0.66 (0.46–0.84), *n* = 71	0.65
Admission mRS score, No. (%)				0.06
0	49 (29.7)	31 (33.7)	18 (24.7)	
1	84 (50.9)	49 (53.3)	35 (47.9)	
2	32 (19.4)	12 (13.0)	20 (27.4)	

[a]Data are reported as median (IQR) unless otherwise indicated.

[b]BMI is the weight in kilograms divided by height in meters squared.

HDL, high-density lipoprotein; ICA, internal carotid artery; IQR, interquartile range; LDL, low-density lipoprotein; MCA, middle cerebral artery; mRS, modified Rankin Scale; MTT, mean transit time, qualifying side; rCBF, relative cerebral blood flow, qualifying/contralateral side.

*Statistically significant.

Table 2

The univariate and multivariate analyses of factors associated with the incidence of ipsilateral ischemic stroke (IIS) in patients treated medically in the CMOSS trial.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, median, per year	1.02 (0.97–1.08)	0.43		
Sex, male	0.69 (0.22–2.15)	0.53		
BMI[a], per kg/m^2	1.13 (1.05–1.21)	<0.01*	1.16 (1.06–1.27)	<0.01*
Medical history				
Hypertension	2.58 (0.83–8.01)	0.10	–	–
Diabetes mellitus	0.92 (0.26–3.24)	0.90		
Hyperlipidemia	2.18 (0.70–6.74)	0.18		
Received medication prior to latest qualifying event				
Antiplatelet therapy	2.25 (0.30–17.01)	0.43		
Lipid-lowing therapy	2.97 (1.08–8.19)	0.04*	3.85 (1.33–11.10)	0.01*
Smoking, current or former	1.08 (0.40–2.89)	0.88		
Alcohol consumption, current or former	0.39 (0.11–1.37)	0.14	–	–
Systolic blood pressure, per mmHg	1.00 (0.97–1.03)	0.96		
Stroke as the qualifying event	0.50 (0.83–1.38)	0.18		
Occluded artery, MCA	0.99 (0.36–2.71)	0.98		
Qualifying side, left	1.07 (0.40–2.87)	0.90		
Qualifying event to randomization, per week	1.00 (0.95–1.05)	0.92		
Computed tomography perfusion indexes				
MTT, per sec	1.17 (1.02–1.35)	0.03*	1.23 (1.06–1.42)	<0.01*
rCBF	0.26 (0.03–2.34)	0.23		
LDL cholesterol level, per mmol/l	0.55 (0.25–1.22)	0.14	–	–
HDL cholesterol level, per mmol/l	1.13 (0.23–5.65)	0.88		
Total cholesterol, per mmol/l	0.57 (0.29–1.14)	0.11	–	–
Triglycerides level, per mmol/l	1.16 (0.73–1.85)	0.53		
Glucose level, per mmol/l	0.71 (0.42–1.20)	0.20		

HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MCA, middle cerebral artery; MTT, mean transit time, qualifying side; rCBF, Relative cerebral blood flow, qualifying/contralateral side.

[a]BMI is the weight in kilograms divided by height in meters squared.

*Statistically significant.

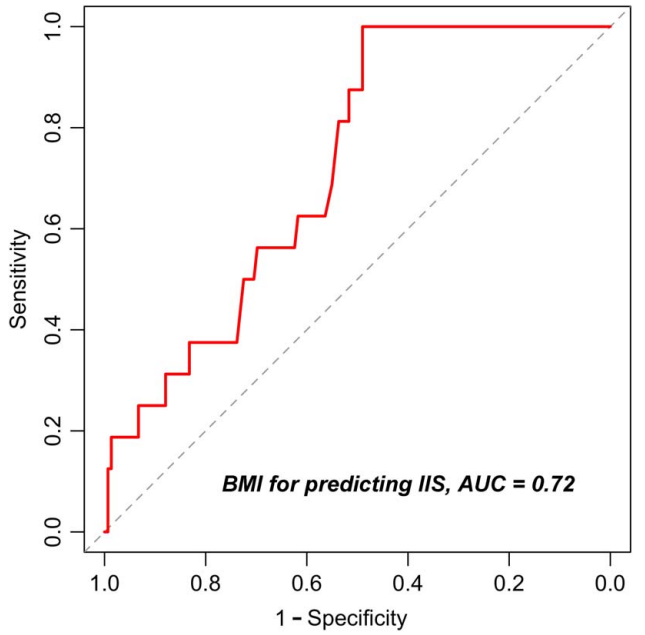

Figure 1. ROC curve of BMI for predicting incidence of IIS. The AUC is 0.72 (95% CI: 0.62–0.83; $P < 0.01$) and the optimal cutoff value for predicting IIS is identified as 24.5 kg/m^2. Under this threshold, the sensitivity is 100.0% and specificity is 49.0%. AUC, area under the curve; IIS, ipsilateral ischemic stroke; ROC, receiver operating characteristic.

Association between BMI and IIS incidence

Among the 165 patients who received only medical treatment, 16 (9.7%) experienced IIS during the 2-year follow-up. Patients with IIS exhibited a significantly higher BMI than those without, with a median BMI of 26.4 kg/m² (IQR, 25.3–29.9) compared to 24.8 kg/m² (IQR, 23.0–26.8; $P < 0.01$). Table 2 details the results from the univariate analysis of risk factors for IIS in this patient group. IIS occurred in 10 of 102 patients (9.8%) with ICA occlusion and 6 of 63 patients (9.5%) with MCA occlusion, where the hazard ratio (HR) for MCA occlusion related to IIS was 0.99 (95% CI: 0.36–2.71; $P = 0.98$). Seven variables with a *P*-value of <0.15 were included in the multivariate model. In the multivariate analysis, only BMI, mean transit time (MTT), and lipid-lowering therapy prior to the latest qualifying event were independently associated with the incidence of IIS. The adjusted HR for BMI in relation to IIS was 1.16 per kg/m^2 (95% CI: 1.06–1.27; $P < 0.01$).

The ROC analysis indicated that BMI had an area under the curve of 0.72 (95% CI: 0.62–0.83; $P < 0.01$; Fig. 1) for predicting IIS, identifying 24.5 kg/m^2 as the optimal cutoff. At this threshold, the sensitivity was 100.0% and the specificity 49.0%.

Using the established optimal BMI cutoff of 24.5 kg/m^2, the 165 patients were categorized into two groups: one with BMI ≥24.5 kg/m^2 ($n = 92$) and the other with BMI <24.5 kg/m^2 ($n = 73$). Table 1 outlines the baseline characteristics of these groups. The prevalence of hypertension, hyperlipidemia, smoking, and lipid-lowering therapy prior to the latest qualifying event was higher in patients with BMI ≥24.5 kg/m^2 compared to those with BMI <24.5 kg/m^2. Additionally, patients with BMI ≥24.5 kg/m^2 also showed higher systolic blood pressure and triglyceride levels. No significant differences were observed in MTT or relative cerebral blood flow between the groups. During the follow-up, six patients (3.6%) were either lost to follow-up ($n = 4$) or died from nonstroke causes ($n = 2$) at 6, 6, 9, 12, 13, and 22 months. IIS occurred in 16 (17.4%) of the 92 patients with BMI ≥24.5 kg/m^2, but in none (0%) of the 73 patients with BMI <24.5 kg/m^2. The incidence of IIS was significantly higher in the higher BMI group ($P < 0.01$), as illustrated in Figure 2.

Bypass surgery versus medical treatment in patients with varying BMIs

Group randomization revealed that 76 patients (47.2%) with BMI ≥24.5 kg/m^2 were in the surgical group, and 91 patients (55.8%) were in the medical group, out of 161 and 163 total patients, respectively ($P = 0.12$), indicating no significant difference. Among

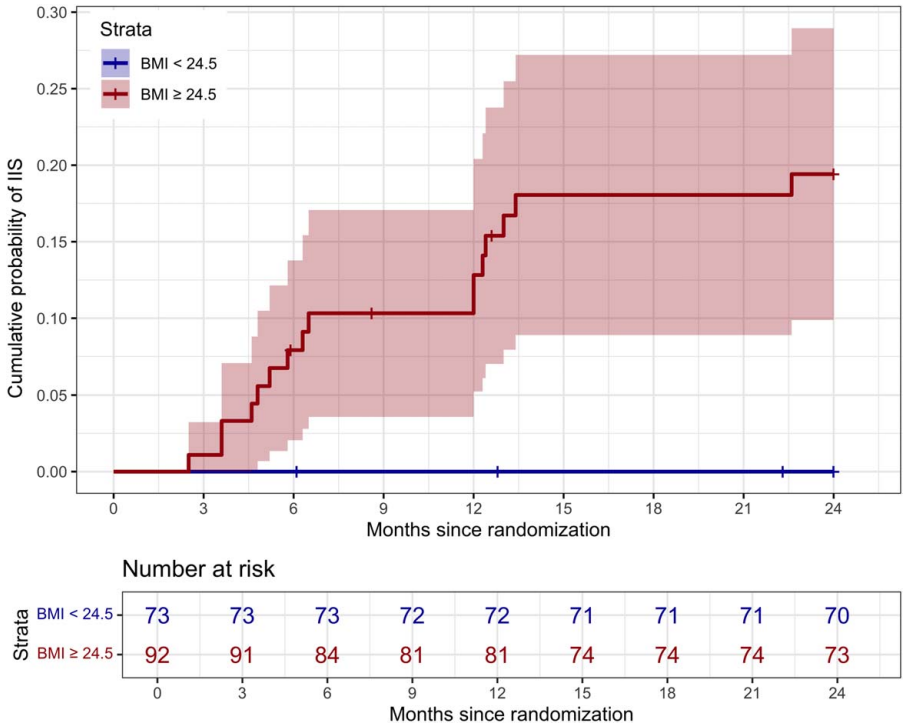

Figure 2. Cumulative probability of IIS in patients with different BMI levels. Stratified based on BMI ≥24.5 kg/m^2 and BMI <24.5 kg/m^2 ($P < 0.01$, log-rank test). The shading represents the 95% CI. IIS, ipsilateral ischemic stroke.

the patients with BMI ≥24.5 kg/m^2, 4 (5.3%) of 76 patients in the surgical group experienced the CMOSS primary endpoint (two cases each of IIS and periprocedural intracranial hemorrhages); whereas 18 (19.8%) of 91 patients in the medical group experienced the CMOSS primary endpoint (16 cases of IIS and 2 of periprocedural intracerebral hemorrhages) ($P < 0.01$, Fig. 3A). Univariate and multivariate analyses assessing the association between treatment type and the incidence of the CMOSS primary endpoint for patients with BMI ≥24.5 kg/m^2 are detailed in Supplemental Table S1 (Supplemental Digital Content 2, http://links.lww.com/JS9/C723). Bypass surgery was identified as an independent variable, associated with a HR of 0.12 (95% CI: 0.03–0.45; $P < 0.01$). MTT was another independent variable, with a HR of 1.27 (95% CI: 1.15–1.40; $P < 0.001$).

Conversely, among patients with BMI <24.5 kg/m^2, nine (10.6%) in the surgical group reached the CMOSS primary

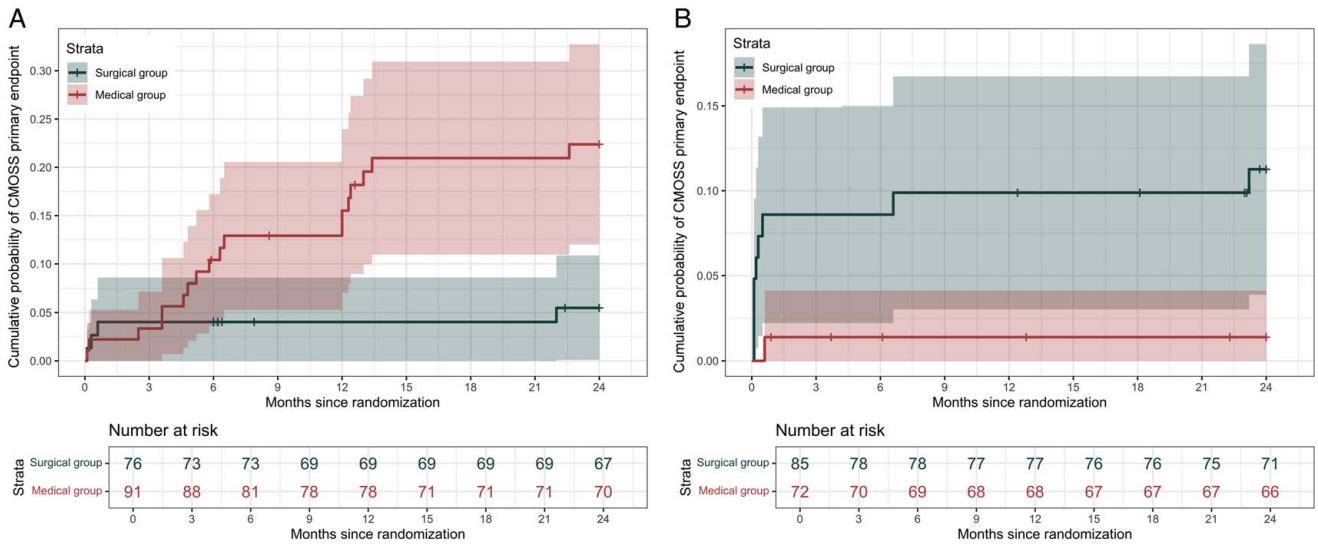

Figure 3. Cumulative probability of the CMOSS primary endpoint in patients with different BMI levels. There are significant differences between the surgical and medical groups with (A) BMI ≥24.5 kg/m^2 ($P < 0.01$, log-rank test) and (B) BMI <24.5 kg/m^2 ($P = 0.02$, log-rank test). The shading represents the 95% CI.

endpoint—seven cases of IIS and two periprocedural intracranial hemorrhages, compared to only one patient (1.4%) in the medical group who experienced a periprocedural intracerebral hemorrhage ($P = 0.02$, Fig. 3B). The analyses of factors associated with the incidence of the CMOSS primary endpoint in this BMI category are available in Supplemental Table S2 (Supplemental Digital Content 2, http://links.lww.com/JS9/C723). Factors independently associated included antiplatelet therapy prior to the latest qualifying event and systolic blood pressure upon admission. The impact of the treatment method was no longer statistically significant, with a HR for bypass surgery of 6.93 (95% CI: 0.87–55.39; $P = 0.07$).

Discussion

In this study, through the inclusion of participants in the CMOSS, we identified a strong positive correlation between BMI levels and the incidence of IIS in patients with symptomatic ICA or MCA occlusion who received only medical treatment. This correlation persisted independently of hemodynamic and other clinical factors. The optimal cutoff value for BMI as a predictor of IIS was established at 24.5 kg/m^2. When analyzed at this threshold, based on randomization groups, the rates of the CMOSS primary endpoint were significantly higher in medically treated patients with higher BMI levels (≥ 24.5 kg/m^2) and in surgically treated patients with lower BMI levels (< 24.5 kg/m^2). Bypass surgery was also found to be independently associated with a reduced rate of the CMOSS primary endpoint in patients with BMI ≥ 24.5 kg/m^2. These findings suggest that BMI levels could potentially be used to identify patients who might benefit from bypass surgery.

Prospective studies investigating the indicators for screening patients who might benefit from bypass surgery in cases of symptomatic MCA or ICA occlusion remain scarce. Grubb *et al*.[5] examined the relationship between hemodynamic factors and the risk of subsequent stroke in 81 patients with carotid occlusion who had a history of TIA or nondisabling stroke. Over a mean follow-up period of 31.5 months, 13 patients suffered an IIS; the analysis indicated that stage II hemodynamic failure and age were independently associated with a recurrent ischemic stroke. Another prospective cohort study[22] involving 117 patients found that stroke recurrence in patients with ICA occlusion was associated with age, symptoms, and leptomeningeal collaterals. Consistent with these studies, our research also demonstrated that MTT, a measure of hemodynamics, was an independent factor associated with the recurrence of ischemic stroke in patients with symptomatic artery occlusion. However, no prior studies, including the COSS trial[4] and its post-hoc analyses, have explored the relationship between BMI levels and the recurrence of ischemic stroke in patients with carotid or intracranial artery occlusion, nor the potential of BMI as a screening tool for candidates for bypass surgery.

Numerous prospective cohort studies[10,12,14–16,23] across diverse populations have established a strong correlation between BMI and the risk of ischemic stroke, regardless of sex, age, or geographic region. Furthermore, Mendelian randomization studies[24,25] suggest a causal relationship between adiposity and stroke. Our study is the first to demonstrate that BMI levels are also independently associated with the incidence of recurrent stroke in patients with symptomatic ICA or MCA occlusion, showing a particularly robust association. Among the 165 patients in the medical group of the CMOSS trial, none with BMI < 24.5 kg/m^2 experienced an IIS over a 2-year follow-up period, whereas 16 patients (17.4%) with BMI ≥ 24.5 kg/m^2 did during the same period.

Our findings have significant implications for both public health and clinical practice. Firstly, since BMI is a modifiable factor, should future prospective studies validate a causal link between BMI levels and the recurrence of ischemic stroke in patients with symptomatic artery occlusion, controlling BMI alongside aggressive medical treatment may help mitigate the risk of recurrent ischemic stroke. Secondly, this study has identified BMI as a simple and convenient clinical tool for identifying high-risk patients with symptomatic ICA or MCA occlusion. The cost-effectiveness of using BMI is particularly notable given the complexity and risks associated with measuring traditional hemodynamic indicators, or their unavailability in certain contexts. Moreover, our analysis initially supports the potential use of BMI as a screening tool for identifying candidates for EC–IC bypass surgery. The risk of the CMOSS primary endpoint was considerably higher in medically treated patients with BMI ≥ 24.5 kg/m^2 compared to those in the surgical group. If corroborated by future research, integrating BMI levels with traditional hemodynamic indicators could enhance the screening strategy for identifying patients who might benefit from EC–IC bypass surgery or other revascularization therapies.

It is important to note that our study, being a post-hoc analysis of the CMOSS trial with a limited sample size and a low event rate, suggests only an association between BMI levels and the incidence of IIS in medically treated patients with symptomatic artery occlusion, rather than definitively establishing a causal relationship. Although some research has indicated that increased prothrombotic factors[26,27] and inflammatory markers[28–30] commonly observed in overweight or obese individuals may contribute to their elevated risk of ischemic stroke, the potential causal link between BMI levels and the recurrence of ischemic stroke in these patients necessitates further exploration through additional prospective clinical trials and comprehensive pathophysiological investigations.

This study has additional limitations that should be acknowledged. Firstly, the sample size was modest, and multiple comparisons were conducted, potentially leading to both type I and II errors in our analysis. Secondly, the follow-up period was relatively short, and the small number of endpoint events might not have been adequate to identify clinically significant differences between the groups. Thirdly, since all participants included in the CMOSS are Chinese, there is uncertainty regarding the generalizability of our findings to other populations, and even if similar findings are observed in diverse populations, it is plausible that the optimal BMI threshold for predicting stroke recurrence may vary. It is well-documented that Asians exhibit a more central distribution of body fat, particularly visceral fat, compared to other populations with similar BMI values[31,32]. The cutoff points for being overweight (> 23.0 kg/m^2) and obese (> 25.0 kg/m^2) among Asians are lower than those established by the WHO criteria. In individuals of Chinese descent, the risk of developing diabetes, hypertension, and dyslipidemia begins to escalate at a BMI of approximately 23 kg/m^2, which is below the BMI threshold recommended by the WHO for Europeans as an indicator of increased risk of morbidity[33]. Additionally, our results indicated that patients with lower BMI levels (< 24.5 kg/m^2) undergoing surgical treatment experienced a higher primary

endpoint rate in the CMOSS trial compared to those receiving medical treatment. This disparity was primarily due to a higher incidence of stroke during the perioperative period. However, the underlying causes were not investigated further in this study. Therefore, prospective cohort studies with extended follow-up durations and diverse regional populations are necessary to corroborate our findings and to explore more thoroughly the impact of BMI levels on the incidence of stroke during the perioperative period for EC–IC bypass surgery in patients with symptomatic artery occlusion.

Conclusion

In this post-hoc analysis of the CMOSS trial, our results revealed that BMI of ≥ 24.5 kg/m^2 was associated with an increased risk of subsequent IIS when treated medically in patients with symptomatic atherosclerotic ICA or MCA occlusion combined with hemodynamic insufficiency. These patients appeared to benefit from bypass surgery. These findings suggest that BMI levels may identify patients with symptomatic artery occlusion who could be candidates for bypass surgery. However, considering the limited sample size and the retrospective nature of this analysis, prospective studies with large samples are required to further confirm the relationship between BMI and stroke recurrence in patients with symptomatic artery occlusion and to better clarify the role of BMI in guiding the selection of patients for revascularization therapy.

Ethical approval

The study procedures were approved by Ethics Committee of Xuanwu Hospital, Capital Medical University No. [2013]011.

Consent

This is a post-hoc analysis of the Carotid or Middle cerebral artery Occlusion Surgery Study (CMOSS) trial. Written informed consent was provided by all participants for the CMOSS trial and informed consent was waived for its retrospective design of the present study.

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Author contribution

G.-D.L., T.W., F.Y., Y.M., S.L., and L.-Q.J.: concepts/study design; G.-D.L., T.W., F.Y., X.-Y.S., R.-J.Y., and J.-C.L.: data analysis/ interpretation; X.-Y.S., R.-J.Y., J.-C.L., X.-G.T., Y.-X. G., J.-Y.W., Z.-Y.T., D.K., Y.-L.C., J.R., D.-H.W., L.D., A.M., C.-H.H., and J.-S.Y.: data collection; G.-D.L., F.Y., X.-Y.S., R.-J. Y., and J.-C.L.: manuscript drafting; T.W., Y.M., S.L., and L.-Q.J.: critical revision of the article; G.-D.L. and T.W.: statistical analysis; L.-Q.J., S.L., and Y.M.: overall responsibility. All authors contributed in reading and approving the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

ClinicalTrials.gov, Identifier: NCT01758614.
This is the registration number of the CMOSS study.

Guarantor

Liqun Jiao, Sheng Liu, and Yan Ma.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Additional data can be made available via the corresponding author to qualified researchers upon reasonable request. [liqunjiao@sina.cn].

Provenance and peer review

Uninvolved.

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Presentation

None.

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