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Effect of metabolic syndrome on outcomes in vertebrobasilar artery occlusions following endovascular treatment: findings from the PERSIST registry

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Abstract

Background: Acute vertebrobasilar artery occlusion (VBAO) is associated with severe neurological dysfunction and high mortality rates. Endovascular treatment (EVT) is a highly effective VBAO approach in the initial treatment window. However, predicted factors influencing the outcomes of VBAO patients who undergo EVT remain unknown. Our study aims to assess the impact of metabolic syndrome (Mets) on VBAO after EVT and to determine whether this factor can be influenced by reperfusion time. *Methods:* This retrospective study included a cohort of 569 patients with acute VBAO after EVT, who were enrolled across 21 stroke centers in China. The diagnosis of Mets was determined using the criteria established by the National Cholesterol Education Program (NCEP). The primary outcome was favorable outcome, defined as a modified Rankin Scale score of 0-3 at 90 days post-treatment. To assess the impact of Mets and reperfusion time on the prognosis of VBAO patients, multivariable logistic regression analysis was performed. Safety outcomes, including symptomatic intracranial hemorrhage (sICH), in-hospital mortality, and 1-year mortality, were also evaluated. *Results:* Three hundred and thirty-four (58.70%) were being identified as having Mets in total 569 patients. After adjustment for potential confounding factors, a significant association appeared between Mets and favorable outcome at 90 days (OR, 0.547 [0.371, 0.807], $p = 0.002$). Additionally, the interaction was found between Mets and puncture to reperfusion time (PTR), which co-affects the favorable outcome (p for interaction < 0.001).
Conclusions: VBAO patients with Mets have poor prognosis after being treated with EVT, with this prognosis more sensitive to PTR.

Keywords: Vertebrobasilar artery occlusion, endovascular treatment, metabolic syndrome, puncture to reperfusion

INTRODUCTION

Vertebrobasilar artery occlusion (VBAO) has emerged as the most devastating factor of acute ischemic stroke (AIS) with severe disability and death occurring in about 70% of patients.[1,2] Endovascular treatment (EVT) is a fundamental approach to enhance the recanalization rate in VBAO patients, which provides theoretical

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benefits to achieve direct recanalization and improved VBAO patient outcome.[3] However, the efficacy of EVT is largely contingent upon time to treatment/recanalization in the acute setting.[4]

Time from estimated occlusion to reperfusion (OTR) is generally considered an effective determinant of functional outcome in patients receiving EVT. The likelihood of achieving functional recovery at 90 days decreased from 64.1% to 46.1% when the OTR extended from 180 minutes to 480 minutes.[5] Besides, the puncture to reperfusion time (PTR), which serves as a dependable measure within the hospital's medical records, is associated with the recanalization rate and effectiveness of EVT.[5] The time distributions of OTR and PTR overlap, OTR is equal to the estimated time of occlusion to groin puncture plus PTR. However, the effect of OTR and PTR might be different in EVT. Moreover, even with timely EVT, many patients still do not receive anticipated benefits.[6] It is necessary to further study the prognostic factors to predict the benefits more accurately in VBAO patients following EVT.

Herein, metabolic syndrome (Mets), a significant public health concern worldwide characterized by multifaceted pathophysiological states, evidently exhibits a notable predictive influence in the stroke population.[7,8] Mets encompasses a collection of interconnected metabolic risk factors such as hypertension, dyslipidemia, fasting blood glucose levels exceeding 6.1, and a history of diabetes.[9] Theoretically, patients with Mets are expected to have more vulnerable arteries, resulting in a diminished likelihood of achieving successful reperfusion within an extended timeframe. Mets significantly influence the initial development and subsequent progression of atherosclerosis in the brain-supplying arteries, thereby impeding the recovery process following various apoplexy events.[10] Especially, hypertension and diabetes mellitus were more related to posterior circulation strokes, and Mets was a factor related to intracranial atherosclerosis (ICAS) versus extracranial atherosclerosis (ECAS) only in posterior circulation strokes.[11] However, limited studies directly examine the correlation between Mets and the prognosis of VBAO patients following EVT.

In this study, we aimed to explore the impact of Mets on the prognosis of VBAO after being treated with EVT. Additionally, we sought to determine whether this influence is contingent upon the timing of treatment, potentially influenced by OTR or PTR.

METHODS

Study population

Retrospectively identified from the Posterior Circulation Ischemic Stroke Registry (PERSIST) were patients who underwent EVT for VBAO. From December 2015 to December 2018, endovascular treatment (EVT) was administered to VBAO patients across 21 stroke centers in China, as encompassed by this registry. Details of the study have been described previously.[12,13] Briefly, the criteria for inclusion and exclusion in this study were as follows: Patients meeting the following criteria were included: 1) older than 18 years old; 2) diagnosed with VBAO based on imaging data, including computed tomographic angiography, magnetic resonance examination, and digital subtracted angiography; 3) underwent EVT within 24-h time window from the estimated occlusion time. The exclusion criteria were: 1) pre-stroke modified Rankin Scale (mRS) > 3; 2) diagnosed with anterior circulation obstruction, aneurysm, or arteriovenous malformation; 3) pregnant or lactating; 4) critical data loss.

Diagnostic criteria of Mets

Mets was identified by the presence of at least two risk factors: (1) elevated blood pressure: systolic blood pressure ⩾130 mmHg, diastolic blood pressure ⩾85 mmHg, or the use of antihypertensive drugs; (2) hyperlipemia; (3) hyperglycemia: FPG ⩾6.1mmol/L or diagnosis of type 2 diabetes previously.[14]

Data collection

Patient characteristics, baseline National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale (GCS) score, posterior circulation-Alberta Stroke Program Early CT score (pc-ASPECT)[15], OTR, PTR and medical history (including hypertension, hyperlipemia, hyperglycemia, and diabetes mellitus) were obtained from the medical record. Laboratory parameters, such as estimated fasting blood glucose (FPG within 24 hours of EVT), admission blood glucose, and modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, were assessed using standard biochemical analysis methods for all participants.[16] The Basilar Artery on Computed Tomography Angiography score (BATMAN)[17] was utilized to evaluate the collateral status of the posterior circulation. Reperfusion status on final angiography was

assessed according to the modified Thrombolysis in Cerebral Infarction (mTICI) scale. Successful recanalization was defined as mTICI grade 2b or 3. Neuroimaging evaluation were executed in a blind manner by two professional neuroradiologists.

Outcome assessment

Functional assessments were conducted via remote communication at 90 days and 1 year. The primary favorable outcome was mRS score ≦ 3. Safety outcomes included the occurrence of symptomatic intracranial hemorrhage (sICH), in-hospital mortality and 1-year mortality. The identification of sICH was based on the radiological-symptomatic classification scheme according to the Heidelberg Bleeding classification, which entailed a neurological deterioration of ≧ 4 points when compared with NIHSS at baseline, or an increase by ≧ 2 points in a NIHSS subcategory.[18]

Statistical analysis

All statistical analyses were performed by SPSS (version 24.0) and R (version 3.4.3). Patients were categorized into two groups: the Mets group and the no-Mets group. Appropriate statistical tests, such as Chi-squared ($\chi 2$) tests, independent t-tests, and analysis of variance (ANOVA) tests, were utilized to compare the baseline characteristics. Binary logistic regression analysis was performed to ascertain the association between Mets (including its components) and outcomes of VBAO underwent EVT. The results, including crude odds ratios (OR) with 95% confidence intervals (CIs), were reported, considering adjusted potential factors such as sex, age, baseline NIHSS, and pc-ASPECT score.

Subgroup analyses were carried out to explore whether there are stratified associations of Mets and the primary outcome between different subgroups. Interactions were examined by adding product terms to the logistic regression model to assess whether sex, age, NIHSS score, time from estimated occlusion to groin puncture and Glasgow coma score modified the association between Mets and outcomes. Additionally, to improve the accuracy of the results, we employed multiple imputations to compensate for the missing values in the OTR and PTR covariates, which exhibited a missing value rate of less than 10%. Subsequently, we conducted univariate and multivariable logistic regression analyses to investigate the association between Mets and no-Mets groups with favorable outcomes. Statistical significance was determined using two-sided p-values < 0.05.

RESULTS

Patient characteristics

Among 609 patients in this study, a total of 569 patients were included in the final analytic population. The characteristics of the included patients were shown in Table 1. Specifically, the prevalence of Mets reached 58.7% in the baseline. As anticipated, patients with Mets exhibited a higher likelihood of developing hypertension (82.1% vs 46.2%, $p < 0.001$), hyperlipidemia (54.4% vs 27.8%, $p < 0.001$), and hyperglycemia (50.9% vs 15.7%, $p < 0.001$), along with lower BATMAN score (4 vs 5, $p = 0.008$) compared to non-Mets patients. Moreover, patients with Mets displayed a higher prevalence of large artery atherosclerosis according to the TOAST Classification (73.1% vs 53.6%, $p < 0.001$). There was no significant difference observed between the two groups regarding the probability of reperfusion (as indicated by mTICI score 2b/3), acceptance of intravenous thrombolysis, and the OTR.

Mets (including individual components) and outcomes

Table 2 showcased the connections between Mets (including its constituents) and clinical outcomes. Mets emerged as a standalone prognosticator of poorer neurological recovery within a 90-day (OR = 0.547, [0.371, 0.807], $p = 0.002$) and one-year (OR = 0.554, [0.382, 0.804], $p = 0.002$) timeframe after adjustment for potential confounding factors. While Mets also being significantly associated with in-hospital mortality (OR = 1.857, [1.201, 2.872], $p = 0.005$), relevance disappeared facing with mortality in 1 year and sICH. Mets showed a significant correlation with a favorable outcome of 90 days in the unadjusted model (OR = 0.558, [0.396, 0.786], $p = 0.001$). However, significance was attenuated (OR = 0.547, [0.371, 0.807], $p = 0.002$) when accounting for Mets and sex, age, baseline NIHSS score, time from estimated occlusion to groin puncture, GCS score covariates, indicating that these covariates may be important confounders that had been overlooked in previous studies. Independent association between hypertension (component of Mets) and in-hospital mortality was less significant ((OR = 0.892, [0.667, 1.593], $p = 0.005$). after being controlled for other risk factors.

Subgroup analysis

Subgroup analysis was prespecified for the

Table 1: Comparison between patients with Mets and those without Mets

		All (n=569)	NO Mets (n=235)	Mets (n=334)	P
Male, n (%)		164 (28.8)	62 (26.4)	102 (30.5)	0.302
Age (mean (SD))		63.56 (12.93)	62.52 (14.37)	64.29 (11.79)	0.107
CHD, n (%)		55 (9.7)	20 (8.5)	35 (10.5)	0.474
Estimated FBG (median [IQR])		6.95 [6.16, 8.22]	6.00 [5.84, 6.79]	7.43 [6.47, 8.70]	<0.001
Hyperglycemia, n (%)		220 (43.4)	58 (27.8)	162 (54.4)	<0.001
Hypertension, n (%)		383 (67.3)	108 (46.2)	275 (82.1)	<0.001
Hyperlipidemia, n (%)		207 (36.4)	37 (15.7)	170 (50.9)	<0.001
Previous stroke or TIA, n (%)		114 (20.0)	45 (19.1)	69 (20.7)	0.672
Smoking, n (%)		177 (31.1)	81 (34.5)	96 (28.7)	0.168
Baseline NIHSS (median [IQR])		23.00 [14.00, 29.00]	23.00 [13.00, 28.00]	23.00 [15.00, 29.00]	0.579
BATMAN Score (median [IQR])		5.00 [3.00, 7.00]	5.00 [3.00, 7.00]	4.00 [3.00, 6.00]	0.008
Glasgow Coma Score (median [IQR])		8.00 [6.00, 12.00]	8.00 [6.00, 12.00]	7.00 [6.00, 11.00]	0.470
Baseline pc-ASPECT Score (median [IQR])		9.00 [8.00, 10.00]	9.00 [8.00, 10.00]	9.00 [8.00, 10.00]	0.160
Collateral status, n (%)	ASITN/SIR grade 0-1	433 (76.1)	176 (74.9)	257 (76.9)	0.775
	ASITN/SIR grade 2	90 (15.8)	38 (16.2)	52 (15.6)	
	ASITN/SIR grade 3-4	46 (8.1)	21 (8.9)	25 (7.5)	
TOAST Classification, n (%)	Large artery atherosclerosis	370 (65.0)	126 (53.6)	244 (73.1)	<0.001
	Cardio-embolism	118 (20.7)	60 (25.5)	58 (17.4)	
	Others	81 (14.2)	49 (20.9)	32 (9.6)	
Time from estimated occlusion to groin puncture, (median [IQR]), min		340.00 [230.00, 512.00]	342.00 [230.00, 549.00]	330.00 [230.00, 493.75]	0.425
Time from puncture to reperfusion, (median [IQR]), min		110.00 [72.00, 160.00]	110.00 [69.50, 170.00]	105.00 [75.25, 150.00]	0.404
Intravenous thrombolysis, n (%)		104 (18.3)	37 (15.7)	67 (20.1)	0.226
mTICI score 2b or 3, n (%)		486 (85.4)	203 (86.4)	283 (84.7)	0.630

SD, standard deviation; IQR, interquartile range; CHD, coronary heart disease; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; BATMAN, Basilar Artery on Computed Tomography Angiography; GCS, Glasgow Coma Scale Score; pc-ASPECT score, posterior circulation-Alberta Stroke Program Early CT Score; TOAST, Trial of Org 10172 in Acute Stroke Treatment; mTICI, modified Thrombolysis in Cerebral Infarction Score.

Table 2: Multivariable analysis of the associations between Mets (including its components) and the favorable outcomes

Outcomes		Unadjusted model				Adjusted model			
		OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P
favorable outcome at 90 days	Mets	0.558	0.396	0.786	0.001	0.547	0.371	0.807	0.002
	Hypertension	0.789	0.552	1.128	0.194	0.894	0.592	1.35	0.594
	Hyperlipidemia	1.135	0.8	1.61	0.478	0.926	0.623	1.376	0.703
	Estimated FBG (>6.1)	0.892	0.556	1.431	0.635	0.978	0.892	1.072	0.631
favorable outcome at 1 year	Mets	0.552	0.393	0.774	0.001	0.554	0.382	0.804	0.002
	Hypertension	0.665	0.468	0.947	0.023	0.746	0.503	1.105	0.144
	Hyperlipidemia	1.111	0.788	1.567	0.549	0.906	0.619	1.326	0.611
	Estimated FBG (>6.1)	0.922	0.578	1.471	0.733	0.971	0.889	1.061	0.515
In-hospital mortality	Mets	1.798	1.18	2.739	0.006	1.857	1.201	2.872	0.005
	Hypertension	2.081	1.304	3.321	0.002	2.009	1.238	3.258	0.005
	Hyperlipidemia	0.868	0.573	1.314	0.503	1.031	0.667	1.593	0.892
	Estimated FBG (>6.1)	1.754	0.943	3.263	0.076	1.084	0.989	1.188	0.083
Mortality in 1 year	Mets	1.262	0.895	1.779	0.185	1.235	0.855	1.784	0.261
	Hypertension	1.354	0.942	1.948	0.102	1.2	0.811	1.776	0.361
	Hyperlipidemia	0.774	0.544	1.102	0.155	0.901	0.617	1.315	0.589
	Estimated FBG (>6.1)	0.997	0.62	1.602	0.989	1.023	0.94	1.113	0.603
sICH	Mets	0.965	0.495	1.88	0.917	0.928	0.474	1.815	0.826
	Hypertension	1.207	0.585	2.489	0.611	1.153	0.554	2.4	0.704
	Hyperlipidemia	0.903	0.452	1.806	0.774	0.98	0.485	1.983	0.956
	Estimated FBG (>6.1)	0.81	0.335	1.961	0.641	0.984	0.832	1.165	0.855

Adjusted by sex, age, Mets, hypertension, hyperlipidemia, hyperglycemia, estimated FBG, baseline NIHSS score, pc-ASPECT score.
OR, odds ratio; CI, confidence interval; sICH, symptomatic intracranial hemorrhage; FBG, fasting blood glucose; mRS, modified Rankin Scale.

favorable outcomes at 90 days based on the sex (male and female), age (<70 years, >70 years), severity of deficit (mild, NIHSS score <20; and severe, >20), estimated occlusion to groin puncture time (<6 hours, >6 hours), Glasgow coma score (severe, <8; mild, >8). For favorable outcome at 90-days, the interaction effect between age (p for interaction = 0.045), NIHSS score (p for interaction < 0.001), and estimated time of occlusion to groin puncture (p for interaction = 0.002), and Glasgow coma score (p for interaction = 0.014) was significant, suggesting that those groups had an obvious impact on Mets patients. Nevertheless, no evidence of interaction effects between sex and Mets was found (Figure 1).

Interactions between Mets and PTR in predicating functional outcomes

To examine the impact of Mets, OTR, and PTR on patient outcomes, a multivariable analysis was conducted (Table 3). The findings indicated that Mets, OTR, and PTR exhibited statistically significant predictive capabilities for outcomes (Table 3). Upon meticulous examination, no significant interaction was observed between Mets and OTR, implying that the collective influence on

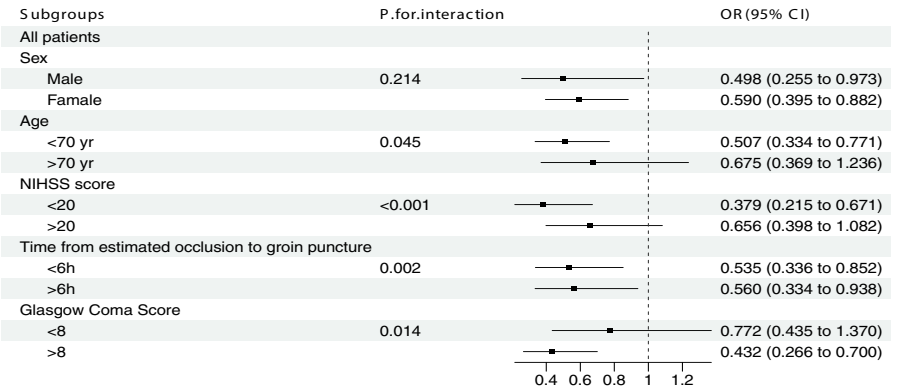

Figure 1. Subgroup analysis of forest plot
Interaction between Mets and sex, age, baseline NIHSS score, time from estimated occlusion to groin puncture, GCS score on 90 days favorable outcome.

clinical outcomes could potentially be independent or insignificant. This finding underscores the complexity of Mets and OTR's limited impact in influencing treatment responses. Figure 2 provided a clear depiction of the prediction of favorable outcomes in patients with Mets compared to those without Mets, considering the variable PTR. The interaction plot demonstrates a categorical relationship, indicating the presence of an inflection point at (21.45, 0.48). When the PTR descends below this threshold, the anticipated likelihood of a favorable outcome in the Mets group significantly diminishes in comparison to the no-Mets group. Moreover, the presented interaction plot effectively demonstrates the simultaneous correlation between patients with Mets or no-Mets and PTR. Specifically, it elucidates that the probability of a positive outcome among patients with Mets diminishes at a higher rate as PTR increases.

DISCUSSION

In the present study, the associations between Mets and clinical outcome have, for the first time, been demonstrated: (1) Mets also indicated poor prognosis in VBAO with a direct time-dependent manner following EVT, (2) emphasized the essential role of prioritizing early detection of Mets and the differences among time windows before EVT.

The research conducted on the impact of Mets on AIS outcomes has yielded inconsistent results, with most studies focusing on anterior circulation rather than posterior circulation. In line with our hypothesis, our study successfully validated the predictive role of Mets in determining poor prognosis in VBAO stroke patients after undergoing EVT. Specifically, a total of 58.7% of participants in our study developed Mets, a rate slightly exceeding that reported in previous

Table 3: Multivariable analysis of the 90 days favorable outcomes (mRS 0-3) and unfavorable outcomes (mRS 4-6)

	All patients (n=569)	Unfavorable outcome (n=349)	Favorable outcome (n=220)	P
Mets, n (%)	334 (58.7)	224 (64.2)	110 (50.0)	0.001
PTR, (median [IQR]), min	110.00 [72.00, 160.00]	115.00 [80.00, 170.00]	103.00 [65.75, 143.25]	0.006
OTR, (median [IQR]), min	460.00 [345.00, 650.00]	480.00 [350.00, 679.00]	413.50 [336.50, 591.25]	0.032
Hypertension, n (%)	383 (67.3)	242 (69.3)	141 (64.1)	0.200
Hyperlipidemia, n (%)	207 (36.4)	123 (35.2)	84 (38.2)	0.531
Estimated FBG (median [IQR])	6.95 [6.16, 8.22]	6.95 [6.16, 8.22]	6.95 [6.16, 8.06]	0.478

Adjusted by sex, age, Mets, hypertension, hyperlipidemia, hyperglycemia, estimated FBG, baseline NIHSS score, pc-ASPECT score.
IQR, interquartile range; mRS, modified Rankin scale.

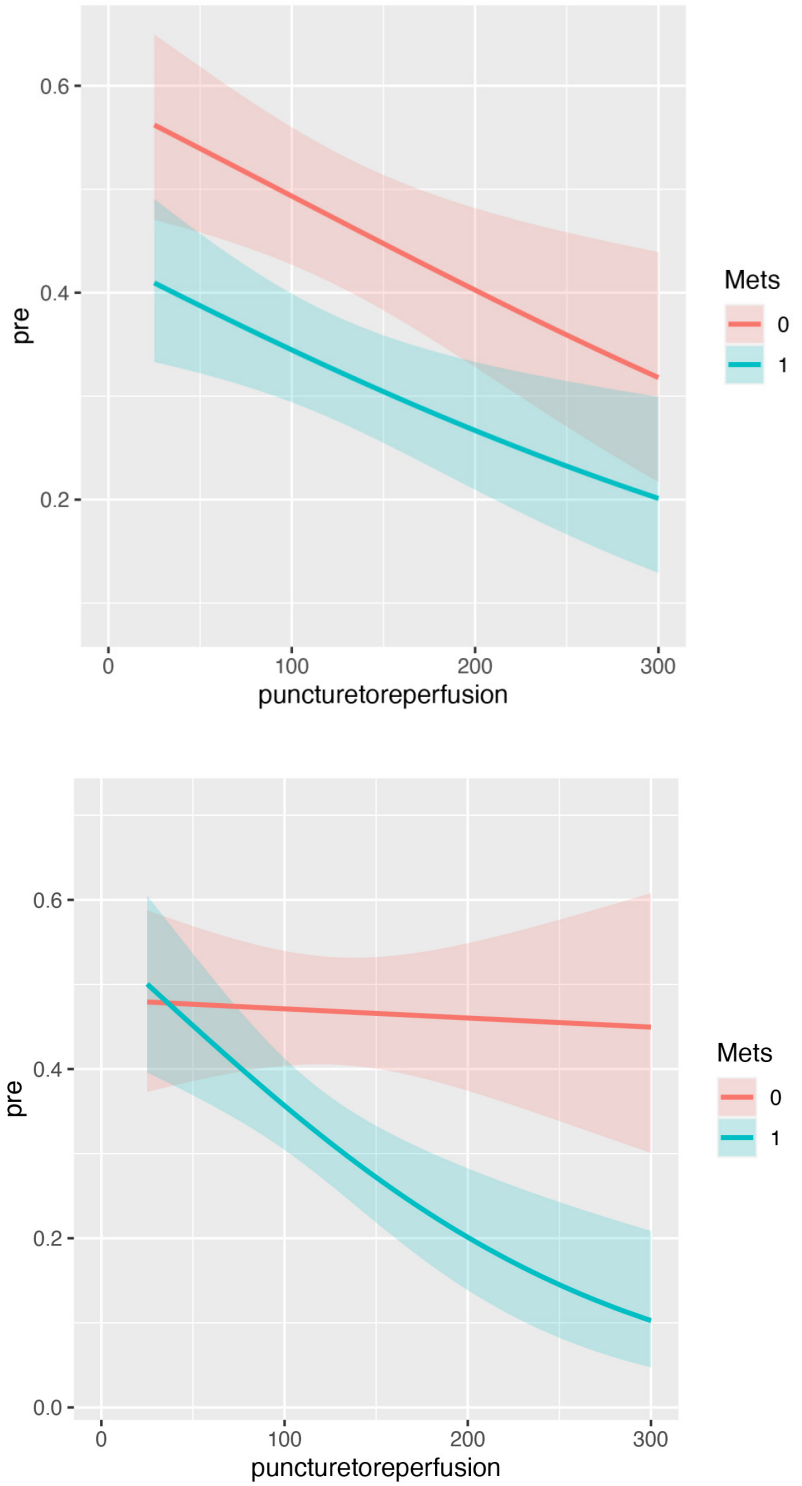

Figure 2. Prediction of Mets according to puncture to reperfusion time with and without interaction term Prediction of Mets patients (blue plot) according to baseline puncture to reperfusion time (x axis) compared to no Mets patients (red plot) with and without the interaction term.

studies.[10,19-21] This variance can be attributed to the unique emphasis of our study on the posterior circulation. This finding suggested that individuals diagnosed with Mets may have an increased propensity for the development of VBAO, underscoring the importance of investigating the predictive role of Mets in clinical outcome of VBAO population. Though we proved the association between Mets and the outcome of VBAO, the mechanism remained unknown. One plausible explanation is that VBAO is linked to more intricate and severe neurological impairments owing to the crucial regions that these arteries supply. As a result, any difference will influence the outcome due to the magnitude of harm or the engagement of essential cerebral structures.[17,22] An alternative explanation could be that disease progresses rapidly and infarct growth is most sensitive to ischemic duration because collateral circulation is rapidly failing and the vertebrobasilar arteries are more fragile. in the context of Mets.[23]

Previous studies of AIS have consistently highlighted the importance of timely EVT in achieving arterial recanalization for a favorable outcome[4,24], but a significant number of patients still have poor outcomes. It should be considered that EVT carries the risk of bleeding and subsequent intracranial hemorrhage, primarily attributed to reperfusion following vascular recanalization and the associated restoration of blood pressure. The procedure itself may also pose a potential threat to blood vessel integrity. These considerations are especially pertinent in patients with Mets, a specific population that stands to derive significant benefit from expeditious reperfusion therapy.

Previous studies have shown that OTR in intra-arterial therapy is a major determinant in predicting good outcomes.[25] Every additional hour between arrival at the emergency department and the initiation of groin puncture was associated with a 22% reduction in successful reperfusion.[26] Among the temporal variables that influence OTR, PTR is the primary determinant of good prognosis in the Mets group, which may be a more practical temporal indicator when considering EVT. Therefore, there is an urgent need for reliable baseline biomarkers to develop treatment strategies for Mets patients that weigh their harms and benefits and can prospectively guide thrombus removal or vascular repair.

Our study represents the first multicenter investigation to identify a notable interaction between Mets and PTR concerning functional outcomes in VBAO. Importantly, the two curves of Mets group and no-Mets group in the interaction plot intersect at (21.45, 0.48), suggesting that the prognosis of Mets group will be worse than that of no-Mets group if the PTR exceeds 21.45 minutes. This result revealed that ischemic regions within the Mets group exhibited a time-dependent vulnerability to reperfusion injury. The actions displayed by the Mets are contributing to the development of proinflammatory and prothrombotic pathophysiological conditions, potentially leading to heightened resistance to clot lysis. The complex interplay between platelet activation, comprised endogenous fibrinolytic capacity, endothelial dysfunction, and Mets, exacerbating neuronal injury after EVT.[27,28] Furthermore, patients who undergo EVT at a later stage may experience blood flow stagnation and the formation of new blood clots, thereby augmenting the overall thrombus burden.[29] Consequently, the composition and characteristics of these thrombi in the Mets contribute to a progressive pattern of reperfusion failure during the initial intervention, potentially prolonging the duration of post-thrombolysis reperfusion.[30]

The present study still has several important limitations. Firstly, it is crucial to acknowledge the inconsistent definitions of Mets in previous studies. Additionally, the generalizability of our findings to other racial or ethnic groups may be limited. Secondly, data generation in this study was driven by clinical factors rather than being systematically generated. Furthermore, the absence of standardized meals may have implications for the accuracy of estimated glucose levels. Thirdly, our statistical adjustments for clinical differences in patients may be inadequate due to the potential existence of unmeasured or residual confounding variables. In addition to the deficiency, this study encompasses inherent flaws in retrospective analysis.

In conclusion, our study provides an initial theoretical basis for managing VBAO patients with Mets. In patients with VBAO after EVT, Mets is associated with an adverse effect on 90-day outcomes and can serve as a valuable prognostic marker for identifying refractory patients. Streamlining workflows to reduce surgical delays in intravascular therapy requires special attention to Mets patients. PTR serves as a reliable time indicator linked to Mets' impact on outcomes, reflecting their predictive effect. Optimal treatment effect relies on early control from puncture to reperfusion. Early attention should be given to VBAO patients with Mets

requiring EVT to modify in-hospital reperfusion delays.

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DISCLOSURE

Ethics: The study was approved by the ethics committee of the First Affiliated Hospital of the University of Science and Technology of China (USTC), Hefei, China. Individual consent was waived as this study was retrospective.

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Data availability: Data are available upon reasonable request.

Conflict of interest:
The authors declare that they have no conflicts of interest.

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