Effect of Imaging Markers on Reperfusion Therapy in Basilar Artery Occlusion

Shenqiang Yan, MD [1†] Ying Zhou, PhD [1†] Yuqi Zhao, MD,[1] Feng Wang, MD,[2] Anyang Tao, MD,[3] Lin Zhou, MD,[4] Mengxiong Pan, MD,[5] Genlong Zhong, MD,[6] Lingzhi Hu, MD,[7] Xuanfei Jiang, MD,[8] Xinlei Mao, MD,[9] Huan Tang, MD,[10] Jianwei Wang, MD,[11] Shuxia Qian, MD,[12] Jingping Sun, MD,[13] Xiaoxian Gong, MD,[1] Wansi Zhong, MD [1] and Min Lou, PhD, MD, [1] on behalf of the CASE II investigators

Objective: We aimed to investigate the effectiveness of endovascular therapy (EVT) versus intravenous thrombolysis (IVT) in patients with basilar artery occlusion (BAO), based on the information of advanced imaging.
Methods: We analyzed data of stroke patients with radiologically confirmed BAO within 24 hours. BAO subjects were categorized into "top-of-the-basilar" syndrome (TOBS) and other types. An initial infarct size of <70ml and a ratio of ischemic tissue to infarct volume of ≥1.8 was defined as "target mismatch." The primary outcome was a good outcome, defined as a modified Rankin Scale score of 0 to 3 at 3 months. Propensity score adjustment and inverse probability of treatment weighting (IPTW) propensity score methods were used.
Results: Among 474 BAO patients, 93 (19.6%) were treated with IVT prior to EVT, 91 (19.2%) were treated with IVT alone, 95 (20.0%) were treated with EVT alone, and 195 (41.1%) were treated with antithrombotic therapy. In IPTW analyses, we found no benefit of EVT over IVT for good outcome in either TOBS patients (odds ratio = 1.08, 95% confidence interval [CI] = 0.88–1.31) or those with other types (odds ratio = 1.13, 95% CI = 0.94–1.36). However, in patients with other types, if there existed a target mismatch, EVT was independently related to good outcome (odds ratio = 1.46, 95% CI = 1.17–1.81).
Interpretation: The "target mismatch profile" seems to be a possible candidate selection standard of EVT for those with other types of BAO. Future studies should separate TOBS from other types of BAO, and try to use advanced imaging.

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Although basilar artery occlusion (BAO) accounts for approximately 5 to 10% of acute large vessel occlusion, the case fatality rates are high, and the chances for independent outcomes are low.[1,2] Due to the devastating consequences of acute BAO, clinicians often select more aggressive therapeutic protocols, despite less high-level

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Address correspondence to Dr Lou, Department of Neurology, 2nd Affiliated Hospital of Zhejiang University, School of Medicine, #88 Jiefang Road, Hangzhou, China. E-mail: lm99@zju.edu.cn, loumingxc@vip.sina.com

Members of the CASE II investigators group are available as Table S1.

[†]S.Y. and Y.Zho. contributed equally to this work.

From the [1]Department of Neurology, Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China; [2]Department of Neurology, Taizhou Hospital of Zhejiang Province Affiliated with Wenzhou Medical University, Wenzhou, China; [3]Department of Neurology, Taizhou First People's Hospital, Taizhou, China; [4]Department of Neurology, Zhoushan Hospital of Zhejiang Province, Zhoushan, China; [5]Department of Neurology, First People's Hospital of Huzhou, Huzhou, China; [6]Department of Neurology, Sixth Affiliated Hospital of Wenzhou Medical University, People's Hospital of Lishui, Lishui, China; [7]Department of Neurology, First People's Hospital of Yongkang, Yongkang, China; [8]Department of Neurology, Huzhou Central Hospital, Huzhou, China; [9]Department of Neurology, Wenzhou Central Hospital, Wenzhou, China; [10]Department of Neurology, Shaoxing People's Hospital, Zhejiang University School of Medicine, Shaoxing, China; [11]Department of Neurology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China; [12]Department of Neurology, Second Affiliated Hospital of Jiaxing University, Jiaxing, China; and [13]Department of Neurology, Lishui Hospital of Zhejiang University (Lishui Municipal Central Hospital), Lishui, China

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evidence.[3,4] Recently, both the Basilar Artery Occlusion Endovascular Intervention versus Standard Medical Treatment (BEST) trial[5] and the Basilar Artery International Cooperation Study (BASICS) trial[6] indicated no significant difference between endovascular therapy (EVT) and standard medical therapy for a favorable outcome, which is in contrast with the efficacy of EVT for anterior circulation occlusion.[7] Although we could still look forward to the ongoing Chinese trial on BAO (NCT02737189, beyond 6 hours), it is time to stop and think about the enrollment of BAO patients who would be more likely to benefit from EVT.

Prospective registry studies may provide additional support for decisions about patient selection. Two large ones have been published so far. One is the BASICS registry,[2] which did not support unequivocal superiority of EVT over intravenous thrombolysis (IVT); however, it was concluded >10 years ago, with less modern EVT techniques and without new recanalization devices, and thus is not applicable to the current practice. The other is the Endovascular Treatment for Acute Basilar Artery Occlusion (BASILAR) registry,[8] which indicated that EVT is associated with better functional outcome and reduced mortality; however, it could not explain the neutral results of current randomized trials,[5,6] without using advanced imaging for evaluation.

Several imaging parameters had presented good predictive value for clinical outcome. For example, the posterior circulation Acute Stroke Prognosis Early CT score (PC-ASPECTS) was used as a measure of early ischemic changes in patients with vertebrobasilar ischemia.[9] "Top-of-the-basilar" syndrome (TOBS) is a special subtype of BAO,[10] which usually represents distal embolic occlusion and small clot burden, indicating a dramatically high rate of recanalization and good outcome after IVT.[11] There were 3 collateral scales proposed in posterior circulation that were associated with functional outcome.[12–14] In addition, semiquantification and quantification of perfusion deficit may help identify BAO patients with higher risk of disability at an early stage.[15,16] However, none of these indicators was proven to support decision-making for reperfusion therapy. In the current study, we attempt to determine promising candidates to select BAO patients who would benefit from EVT, especially with the help of perfusion imaging.

Subjects and Methods

Study Subjects

The Computer-Based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation (CASE II) is a prospective multicenter registration study that aims to establish an online database of acute stroke patients for stroke management quality evaluation in China (NCT04487340). In the current study, we have obtained permission for data use from 13 comprehensive stroke centers that performed at least 15 thrombectomy procedures with stent retriever devices for BAO annually. To note, the data on underlying etiology and follow-up imaging, such as recanalization and hemorrhagic transformation, are not mandatory requirements for the patients without reperfusion therapy (IVT or/and EVT). We then enrolled patients who (1) were 18 years or older; (2) had a diagnosis of acute posterior circulation stroke confirmed by diffusion-weighted imaging (DWI) or computed tomography (CT); (3) had BAO confirmed by time-of-flight magnetic resonance angiography, CT angiography (CTA), or digital subtraction angiography (DSA); and (4) had time interval within 24 hours from stroke onset to estimated time of BAO. We excluded patients (1) whose image quality was poor due to motion artifacts, (2) who had preexisting disability with a modified Rankin Scale (mRS) score (range = 0–6, with 0 indicating no disability, 3 indicating moderate disability, and 6 indicating death) > 2, and (3) who had neuroimaging evidence of cerebral hemorrhage or anterior circulation stroke.

We retrieved demographic, clinical, and radiological data including age; sex; comorbid conditions such as hypertension, diabetes mellitus, atrial fibrillation, and current smoking; prior antiplatelet use; time interval from stroke onset to treatment (OTT; onset was estimated as the midpoint of sleep for wake-up stroke); treatment approach; stroke etiology; National Institutes of Health Stroke Scale (NIHSS) score; pre- and post-treatment imaging findings, such as clot length and location, hemorrhagic transformation, and recanalization; and mRS score at 3 months, with the scale performed in a structured in-person or telephone interview by investigators who were unaware of the treatment group assignments.

Treatments

Because there is no clear treatment time window for BAO, both IVT and EVT could be suggested by clinicians within 24 hours. Generally, IVT was more often recommended within 4.5 hours, and EVT within 6 hours, referring to the standard of anterior circulation. With the prolongation of OTT, BAO patients were more likely to receive antithrombotic therapy, except for those with TOBS receiving IVT beyond 4.5 hours more frequently due to the potential high recanalization rate. Meanwhile, the performance of reperfusion therapy for BAO usually requires consent from patients or their relatives, who would consider both the cost and potential bleeding risk.

Ethics Statement

This study has been approved by the human ethics committees of Second Affiliated Hospital of Zhejiang University and each subcenter. All clinical investigation has been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained to confirm the acceptance or refusal of reperfusion therapy.

Radiologic and Clinical Assessment

The imaging core laboratory evaluated the findings on baseline and follow-up images. BAOs are classified according to the

3 anatomic segments as proximal, middle, and distal segment by anterior inferior cerebellar artery and superior cerebellar artery. Patients who had clots in the distal segment of the basilar artery with corresponding clinical symptoms were defined as TOBS.[9] PC-ASPECTS was assessed on CTA source images,[9] and on baseline noncontrast CT or DWI if no CTA was available. The posterior circulation collateral score was assessed on baseline angiography.[13] To consistently and easily evaluate vessel recanalization in those without DSA, we used the arterial occlusive lesion scale to define recanalization or no recanalization based on the presence (grades 2 or 3) or absence (grades 0 or 1) of any downstream flow, as this scale is the only grading scale explicitly measuring the degree of recanalization at the target arterial lesion.[17] Hemorrhagic transformation was defined as symptomatic intracranial hemorrhage (sICH) if the patient had clinical deterioration causing an increase on the NIHSS of ≥4 points and if the hemorrhage was likely to be the cause of the clinical deterioration.[18] A target mismatch was then defined in patients with multimodal imaging evaluation as (1) infarct core volume (relative cerebral blood flow < 30% on perfusion CT [compared with anterior circulation territory] or apparent diffusion coefficient $< 620 \times 10^{-6}$ mm^2/s on magnetic resonance imaging) < 70 ml, (2) absolute volume of potentially reversible ischemia (penumbra; hypoperfusion volume [Tmax > 6 seconds] − infarct core volume) > 15 ml, or (3) hypoperfusion volume/infarct core volume > 1.8.[19] Examples are given in Figure 1. The primary outcome was a good outcome, defined as an mRS score of 0 to 3 at 3 months. The main secondary outcomes were functional independence (mRS score ≤ 2), mortality, and ordinal score of mRS (shift analysis) at 3 months.

Statistical Analysis

Data are presented as median (interquartile range) or n (%). Fisher exact test was used to compare the dichotomous variables between groups, whereas Mann–Whitney *U* or Kruskal–Wallis test was used for the continuous variables, as appropriate. Variables with a *p* value of <0.1 in univariate analyses were included in a binary or ordinary logistic regression model by using the backward stepwise conditional method, except that the treatment approach was forced into the model. To reduce the effects of potential confounding factors in the between-group comparisons, we used propensity score methods. Propensity score adjustment method (propensity score considered as a covariate in a multivariate logistic regression model) and inverse probability of treatment weighting (IPTW) propensity score method (using stabilized inverse propensity score as weight in a simple logistic regression model) were performed. Multiple imputation was used in the patients with missing essential radiological data. Statistical significance was set at a *p* value of <0.05. All statistical analyses were performed with the SPSS software package (v22.0; IBM, Armonk, NY, USA), and SAS software (v9.4; SAS Institute, Cary, NC, USA) with the use of R software (v4.0.5).

Results

The flowchart of enrollment, treatment, and imaging profile is shown in Figure 2. During the study period, 474 patients (of whom 171 were female [36.1%]; mean age was 68 years) diagnosed as acute BAO were included in the analysis. Among them, 93 (19.6%) patients were treated with IVT bridging with EVT, 91 (19.2%) patients were treated with IVT alone, 95 (20.0%) patients were treated with EVT alone, and 195 (41.1%) patients were treated with antithrombotic therapy. Of patients treated with reperfusion therapy (n = 279), 235 (84.2%) had angiography at between 24 and 48 hours for assessment of recanalization, and 275 (98.6%) had susceptibility-weighted imaging or CT at between 24 and 48 hours for assessment of hemorrhagic transformation. Among all patients, 424 (89.5%) completed follow-up of mRS at 3 months, and perfusion data were available for 133 (28.1%) patients. There were 14 patients for whom EVT was planned, but who had achieved recanalization prior to an EVT attempt.

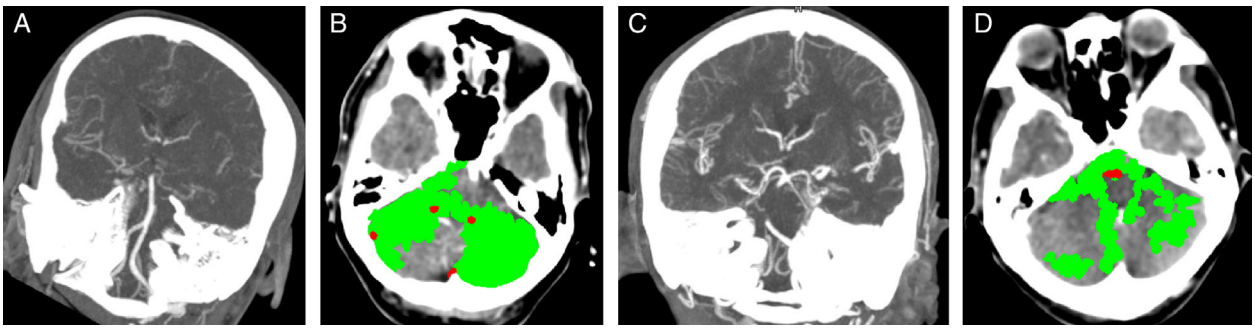

FIGURE 1: Baseline angiography and perfusion images of 2 patients with basilar artery occlusion (BAO) who received reperfusion therapy. (A, B) From Patient 1 with "top-of-the-basilar" syndrome, who received intravenous thrombolysis (IVT). (A) The clot was located in top-of-the-basilar. (B) The presumed infarct core volume was 12ml, and penumbra was 87ml. Patient 1 achieved recanalization 24 hours after IVT, and obtained a modified Rankin Scale (mRS) score of 1 at 3 months. (C, D) From Patient 2, with another type of BAO, who received endovascular treatment (EVT). (C) The clot was located at the midbasilar level. (D) The presumed infarct core volume was 10ml, and penumbra was 66ml. Patient 2 also achieved recanalization 24 hours after EVT, and obtained an mRS score of 1 at 3 months.

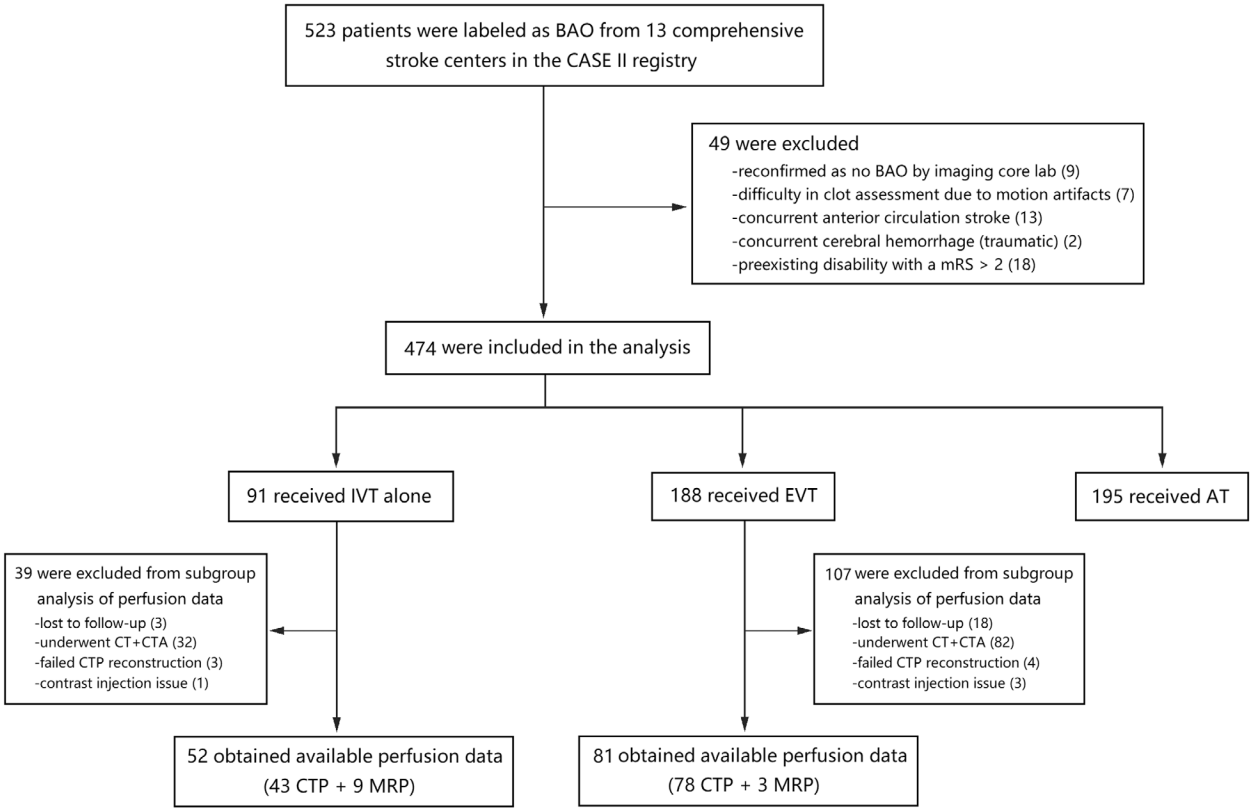

FIGURE 2: Flowchart of enrollment, treatment, and imaging profile. AT = antithrombotic treatment; BAO = basilar artery occlusion; CASE = Computer-Based Online Database of Acute Stroke Patients for Stroke Management Quality Evaluation; CT = computed tomography; CTA = CT angiography; CTP = CT perfusion; EVT = endovascular treatment; IVT = intravenous thrombolysis; MRP = magnetic resonance perfusion; mRS = modified Rankin Scale.

Comparison of Clinical Outcome between Patients with and without Reperfusion Therapy

Table 1 shows the comparison of characteristics between patients who were treated with and without reperfusion therapy. Patients in the group of reperfusion therapy had a lower proportion of hypertension and diabetes mellitus, significantly higher baseline NIHSS score, significantly shorter OTT, and higher proportion of TOBS. After propensity score weighting, all baseline variables were balanced between the two groups. As Table 2 shows, patients with reperfusion therapy were more likely to achieve mRS ≤ 3 (odds ratio = 2.00, 95% confidence interval [CI] = 1.12–3.56), after adjusting for potential confounders. This difference remained marginally significant (odds ratio = 1.72, 95% CI = 0.99–2.97) when propensity score adjustment was used, but became nonsignificant (odds ratio = 1.02, 95% CI = 0.87–1.21) when IPTW was used. Similar findings were presented for lower mRS score and mortality rate.

Comparison of Clinical Outcome between Patients with EVT and with IVT Alone

Table 3 shows the comparison of characteristics between patients who were treated with EVT and with IVT alone. Patients with EVT had a lower proportion of atrial fibrillation, significantly higher baseline NIHSS score, longer OTT, lower proportion of TOBS, and significantly higher rate of recanalization. After propensity score weighting, all baseline variables were balanced between the two groups. As Table 4 shows, patients with EVT were more likely to achieve recanalization, and had a lower mortality rate, but developed similar rates of sICH, and had similar rates of mRS ≤ 3 and mRS ≤ 2, compared with those received IVT alone. Figure 3 shows the results of subgroup analyses in BAO patients who received reperfusion therapy based on the IPTW propensity score method. We found a significantly better effect of IVT in those with cerebral blood volume PC-ASPECT < 8, and better effect of EVT in those with thrombus length > 10mm.

Comparison of Characteristics between Patients with TOBS and Other Types of BAO

Among all enrolled patients, 177 (37.3%) patients were classified as TOBS and 297 (62.7%) as other types of BAO. Patients with TOBS had a higher proportion of females (43.5% vs 31.6%, $p = 0.010$), higher rate of atrial fibrillation (28.2% vs 13.5%, $p < 0.001$), lower rate of hypertension (60.5% vs 79.5%, $p < 0.001$) and diabetes mellitus (12.4% vs 24.6%, $p = 0.001$), and shorter OTT (461 ± 392 vs 583 ± 453 minutes, $p = 0.003$) than

TABLE 1. Univariate Comparison of Characteristics Stratified by Exposure to Reperfusion Therapy in Unweighted and Propensity Score-Weighted Patients

	Unweighted			Propensity Score-Weighted		
Variable	With Reperfusion Therapy, n = 279	Without Reperfusion Therapy, n = 195	*p*	With Reperfusion Therapy, W = 244.3	Without Reperfusion Therapy, W = 238.1	*p*
Age, yr	68 ± 12	68 ± 13	0.997	67 ± 12	65 ± 13	0.243
Female, n (%)	99 (35.5)	72 (36.9)	0.771	35.5	34.6	0.919
Comorbid conditions, n (%)						
Hypertension	187 (67.0)	156 (80.0)	0.002[a]	69.7	62.7	0.437
Diabetes mellitus	42 (15.1)	53 (27.2)	0.002[a]	16.7	16.6	0.977
Atrial fibrillation	53 (19.0)	37 (19.0)	1.000	18.8	16.3	0.621
Smoking history	85 (30.5)	68 (34.9)	0.320	29.0	33.2	0.631
Clinical variables						
Baseline NIHSS score	24 (13–35)	6 (2–15)	<0.001[a]	18 (7–32)	20 (8–31)	0.953
Onset to treatment, min	349 ± 264	806 ± 488	<0.001[a]	431 ± 335	450 ± 428	0.696
Prior antiplatelet use, n (%)	44 (15.8)	43 (22.1)	0.092	16.0	17.7	0.789
TOBS, n (%)	120 (43.0)	57 (29.2)	0.003[a]	41.4	47.7	0.476

For categorical variables, only the percentages of each group are presented after propensity score weighting.
[a]Statistically significant.
NIHSS = National Institutes of Health Stroke Scale; TOBS = "top-of-the-basilar" syndrome; W = sum of weights calculated from the propensity score model in each group.

TABLE 2. Odds Ratios (95% Confidence Intervals) for the Association between Clinical Outcomes and Reperfusion Therapy

Clinical Outcome	With Reperfusion Therapy, n = 279	Without Reperfusion Therapy, n = 195	Model 1	Model 2	Model 3
Primary outcome					
mRS ≤ 3, n (%)	114/258 (44.2)	84/166 (50.6)	2.00 (1.12–3.56)	1.72 (0.99–2.97)	1.02 (0.87–1.21)
Secondary outcomes					
mRS	3.7 ± 2.2	3.3 ± 2.3	0.56 (0.35–0.90)	0.59 (0.37–0.95)	0.87 (0.48–1.59)
mRS ≤ 2, n (%)	87/258 (33.7)	73/166 (44.0)	1.47 (0.83–2.62)	1.45 (0.82–2.54)	0.96 (0.81–1.13)
Death, n (%)	83/258 (32.2)	48/166 (28.9)	0.45 (0.25–0.83)	0.54 (0.30–0.95)	0.92 (0.79–1.08)

The propensity score model included age, sex, hypertension, diabetes mellitus, atrial fibrillation, smoking history, baseline NIHSS score, onset to treatment, prior antiplatelet use, and TOBS. Model 1 adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, smoking history, baseline NIHSS score, onset to treatment, prior antiplatelet use, and TOBS in the raw data. Model 2 adjusted for propensity score. Model 3 was weighted by propensity score.
mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TOBS = "top-of-the-basilar" syndrome.

TABLE 3. Univariate Comparison of Characteristics Stratified by Exposure to EVT in Unweighted and Propensity Score-Weighted Patients with Reperfusion Therapy

	Unweighted			Propensity Score-Weighted		
Variable	**With EVT, n = 188**	**IVT Alone, n = 91**	***p***	**With EVT, W = 186.8**	**IVT Alone, W = 95.9**	***p***
Age, yr	67 ± 12	69 ± 12	0.278	68 ± 12	65 ± 14	0.465
Female, n (%)	64 (34.0)	35 (38.5)	0.506	36.3	34.9	0.866
Comorbid conditions, n (%)						
Hypertension	125 (66.5)	62 (68.1)	0.892	67.0	60.1	0.491
Diabetes mellitus	28 (14.9)	14 (15.4)	1.000	16.0	14.4	0.776
Atrial fibrillation	28 (14.9)	25 (27.5)	0.015[a]	18.1	18.4	0.956
Smoking history	61 (32.4)	24 (26.4)	0.333	29.3	32.3	0.775
Clinical variables						
Baseline NIHSS score	28 (14–35)	19 (7–29)	<0.001[a]	23 (13–35)	24 (15–35)	0.782
Onset to treatment, min	375 ± 281	295 ± 215	0.017[a]	352 ± 264	343 ± 255	0.730
Prior antiplatelet use, n (%)	31 (16.5)	13 (14.3)	0.727	15.5	11.5	0.400
Image variables						
TOBS, n (%)	67 (35.6)	53 (58.2)	<0.001[a]	42.8	41.5	0.876
Thrombus length, mm	10 (6–15)	5 (1–10)	<0.001[a]	8 (4–13)	10 (3–17)	0.617
PC-ASPECTS	9 (8–10)	10 (9–10)	0.055	9 (9–10)	9 (8–10)	0.635
PC-CS	6 (4–7)	6 (4–7)	0.848	6 (5–7)	6 (4–7)	0.607
CBV PC-ASPECTS	9 (7–10)	9 (7–10)	0.779	9 (7–10)	9 (7–9)	0.834
Stroke etiology, n (%)			0.037[a]			0.362
LAA	66 (35.1)	21 (23.1)		31.8	20.2	
Cardioembolism	52 (27.7)	37 (40.7)		28.9	33.4	
Other	3 (1.6)	4 (4.4)		1.2	2.6	
Undetermined	67 (35.6)	29 (31.9)		38.0	43.7	

For categorical variables, only percentages for each group are presented after propensity score weighting.
[a]Statistically significant.
CBV = cerebral blood volume; EVT = endovascular therapy; IVT = intravenous thrombolysis; LAA = large artery atherosclerosis; NIHSS = National Institutes of Health Stroke Scale; PC-ASPECTS = posterior circulation Acute Stroke Prognosis Early CT score; PC-CS = posterior circulation collateral score; TOBS = "top-of-the-basilar" syndrome; W = sum of weights calculated from the propensity score model in each group.

those with other types of BAO. Among BAO patients receiving reperfusion therapy, those with TOBS were more likely to achieve recanalization (88.8% vs 77.3%, $p = 0.025$), mRS ≤ 3 (60.9% vs 31.8%, $p < 0.001$), and mRS ≤ 2 (47.3% vs 23.6%, $p < 0.001$), and had a lower mortality rate (23.6% vs 38.5%, $p < 0.001$). To note, 15.2% (12/79) of patients with TOBS for whom EVT was planned had achieved recanalization prior to an EVT attempt, whereas only 1.6% (2/123) of patients with other types of BAO were found to achieve recanalization.

Efficacy of EVT versus IVT Alone in Patients with TOBS and Other Types of BAO

In patients with TOBS and reperfusion therapy, those who received EVT achieved a higher rate of recanalization (98.3% vs 76.6%, $p < 0.001$), and developed a similar

TABLE 4. Odds Ratios (95% Confidence Intervals) for the Association between Radiological and Clinical Outcomes and EVT

Outcome	With EVT, n = 188	IVT Alone, n = 91	Model 1	Model 2	Model 3
Radiological outcomes, n (%)					
Recanalization	150/163 (92.0)	44/72 (61.1)	34.20 (10.03–116.61)	19.45 (6.64–56.93)	1.63 (1.35–1.98)
sICH	13/184 (7.1)	6/91 (6.6)	0.66 (0.20–2.23)	0.75 (0.24–2.35)	1.00 (0.94–1.07)
Clinical outcomes					
Primary outcome					
mRS ≤ 3, n (%)	68/170 (40.0)	46/88 (52.3)	1.46 (0.73–2.93)	1.41 (0.74–2.70)	1.10 (0.93–1.31)
Secondary outcomes					
mRS	3.8 ± 2.1	3.4 ± 2.3	0.56 (0.32–0.99)	0.64 (0.37–1.12)	0.53 (0.25–1.15)
mRS ≤ 2, n (%)	50/170 (29.4)	37/88 (42.0)	1.11 (0.55–2.23)	1.13 (0.59–2.14)	1.07 (0.93–1.22)
Death, n (%)	52/170 (30.6)	31/88 (35.2)	0.36 (0.18–0.75)	0.39 (0.20–0.78)	0.80 (0.65–0.97)

The propensity score model included age, sex, hypertension, diabetes mellitus, atrial fibrillation, smoking history, baseline NIHSS score, onset to treatment, prior antiplatelet use, TOBS, thrombus length, PC-ASPECTS, PC-CS, and CBV PC-ASPECTS. Model 1 adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, smoking history, baseline NIHSS score, onset to treatment, prior antiplatelet use, TOBS, thrombus length, PC-ASPECTS, PC-CS, and CBV PC-ASPECTS. Model 2 adjusted for propensity score. Model 3 was weighted by propensity score.
CBV = = cerebral blood volume; EVT = endovascular therapy; IVT = intravenous thrombolysis; mRS = modified Rankin Scale; NIHSS =National Institutes of Health Stroke Scale; PC-ASPECTS = posterior circulation Acute Stroke Prognosis Early CT score; PC-CS = posterior circulation collateral score; sICH = symptomatic intracranial hemorrhage; TOBS = "top-of-the-basilar" syndrome.

rate of sICH (6.0% vs 7.5%, $p = 0.731$) compared to those with IVT alone. In IPTW analyses, we found no benefit of EVT over IVT for mRS ≤ 3 (odds ratio = 1.08, 95% CI = 0.88–1.31) in TOBS patients (n = 120), and still no benefit of EVT over IVT (odds ratio = 0.91, 95% CI = 0.67–1.23) in those with target mismatch (n = 42).

In patients with other types of BAO and reperfusion therapy, those who received EVT achieved a significantly higher rate of recanalization (88.3% vs 32.0%, $p < 0.001$), and developed a similar rate of sICH (7.7% vs 5.3%, $p = 1.000$) compared to those with IVT alone. In IPTW analyses, we found no benefit of EVT over IVT for mRS ≤ 3 (odds ratio = 1.13, 95% CI = 0.94–1.36) in patients with other types of BAO (n = 159), but a significantly better effect of EVT for mRS ≤ 3 (odds ratio = 1.46, 95% CI = 1.17–1.81) in those with target mismatch (n = 42), whereas there was still no benefit of EVT over IVT (odds ratio = 1.25, 95% CI = 0.92–1.69) in those without target mismatch (n = 34).

Discussion

In the current study, we found that BAO patients receiving reperfusion therapy achieved better clinical outcome than those who received antithrombotic therapy. The procedure of EVT decreased mortality rate but did not increase the proportion of good outcome compared with IVT. In addition, the presence of target mismatch profile was associated with good outcome after EVT in patients with other types of BAO, but not in those with TOBS, indicating that the combination of mismatch profile and clot location may assist in selecting eligible BAO patients for EVT.

In the BASICS registry, BAO patients with a severe deficit had better clinical outcome after EVT or IVT, compared with antithrombotic treatment, whereas outcomes were similar after treatment with EVT or IVT.[2] To note, the benefit of EVT might be limited to outdated techniques, such as intra-arterial thrombolysis without mechanical recanalization, and the use of first-generation devices.[2] In the BASILAR registry, EVT administered within 24 hours of estimated occlusion time was associated with better clinical outcome and reduced mortality in patients with acute BAO.[8] However, the recent randomized controlled trials could not verify these findings,[5,6] which might be due to the following two reasons: (1) there was a lack of equipoise of sample size between groups of EVT and standard medical treatment; and (2) only 20% of the enrolled patients received IVT, which was much lower than that in the BASICS trial (almost 80%).[6] A

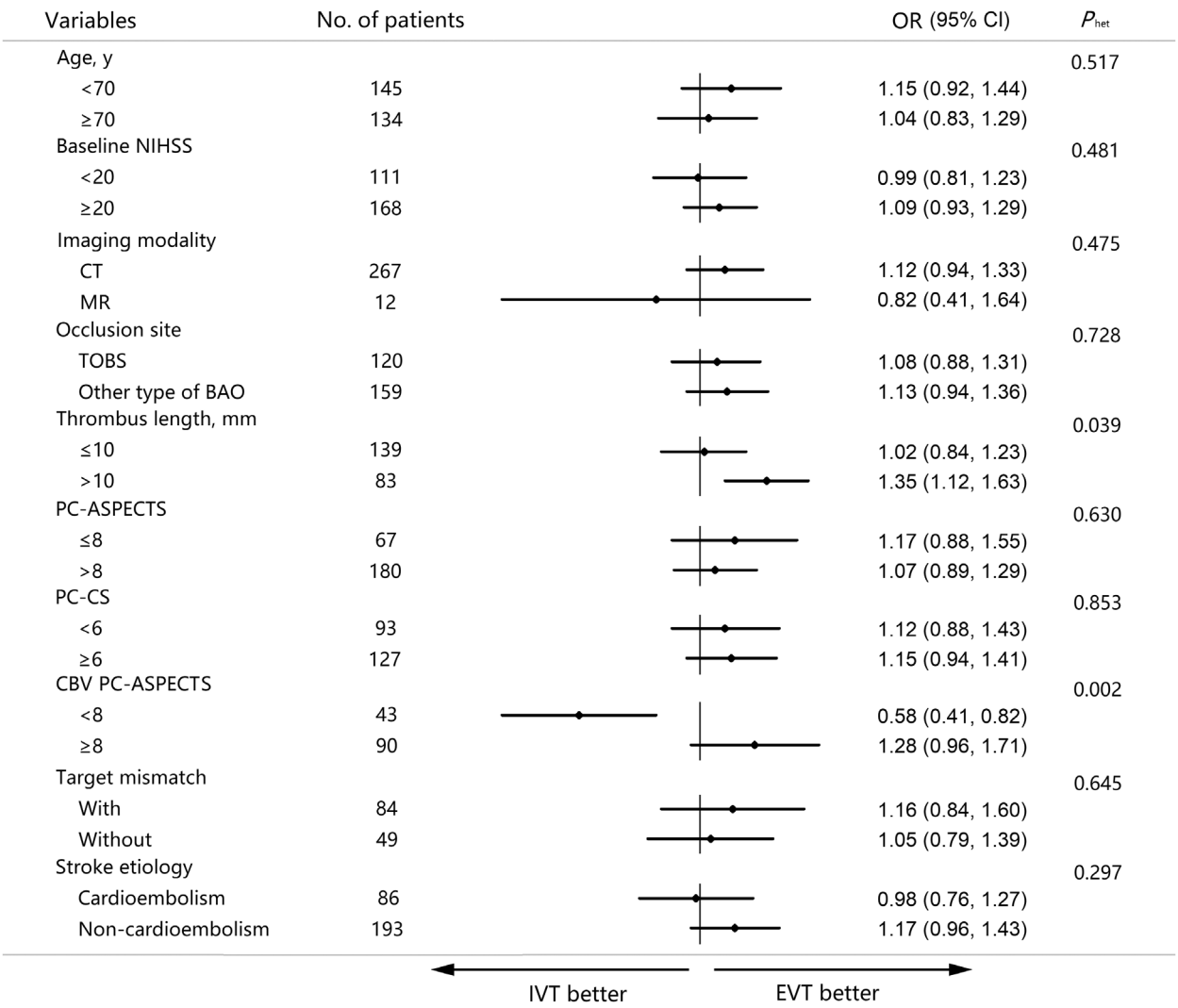

FIGURE 3: Forest plot shows the odds ratios (ORs) and 95% confidence intervals (CIs) for the primary outcome (a modified Rankin Scale score of 0–3) according to subgroups based on the inverse probability of treatment weighting propensity score method. BAO = basilar artery occlusion; CBV = cerebral blood volume; CT = computed tomography; MR = magnetic resonance; NIHSS = National Institutes of Health Stroke Scale; PC-ASPECTS = posterior circulation Acute Stroke Prognosis Early CT score; PC-CS = posterior circulation collateral score; TOBS = "top-of-the-basilar" syndrome.

recent meta-analysis showed that endovascular thrombectomy was a superior approach to IVT for decreasing mortality rate, but not for achieving good clinical outcome,[20] which is consistent with our findings in the current study.

Leaving aside the uncertain evidence of efficacy of EVT, the superiority of IVT over antithrombotic treatment beyond 4.5 hours still remains unclear. If we have not been able to confirm the efficacy of EVT over IVT for BAO patients in randomized trials, trials of IVT beyond the regular time window should be considered, even without the use of multimodal imaging. Patients with acute BAO might respond to reperfusion therapy even in a very late time window. In a prospective, single-center cohort of 184 BAO patients with IVT, recanalization of BAO up to 24 hours was independent of OTT, and the extended treatment window (even up to 48 hours) did not lead to poor outcome, without extensive ischemic changes.[21] In some instances, the initial thrombus may not lodge to the basilar tip but rather floats on this arterial reflux; thus, a pistonlike clot movement can generate blood flow between the clot and arterial wall, which in turn maintains brittle patency of the brainstem perforator vasculature.[22]

Our study confirmed the huge differences between TOBS and other types of BAO, in aspects of both recanalization (76.6% vs 32.0%) and good outcome (63.5% vs 36.1%) after IVT. Fifteen percent of TOBS patients who planned for EVT had achieved recanalization during DSA examination in our study. Two possible mechanisms may explain the high recanalization rate of TOBS after IVT. First, as the clot was located at the top of the basilar

artery, persistent blood flow of posterior cerebral artery in most cases of TOBS increased the surface area of clot exposed to tissue plasminogen activator (t-PA), which may increase the opportunity of the clot to be dissolved. Second, red thrombi, which showed a higher response rate to t-PA, are likely to be the main component of emboli in TOBS. The extremely high rate of recanalization and good outcome after IVT limited the benefit of EVT in the patients with TOBS. We encourage clinicians to give priority to IVT for TOBS, even in a very late time window. Additional need for DSA evaluation is still recommended in the case of IVT failure, but cost efficiency should be taken into consideration. Moreover, the procedure of EVT significantly improved recanalization rate compared to IVT in patients with occlusion sites other than TOBS. Unfortunately, the increased recanalization did not result in better outcomes, which might be due to the extent of early ischemic injury and small proportion of salvageable brainstem. New devices and optimal strategies of EVT,[23,24] advanced imaging techniques for patient selection, and neuroprotective agents should be investigated to avoid futile recanalization in patients with other types of BAO.

Trials have demonstrated that EVT in anterior circulation ischemic stroke patients with target mismatch profile was related to good outcome.[7] Previous case reports or case series also put forward the possible benefit of reperfusion therapy in isolated cerebellar infarction with mismatch profiles,[25] but data from randomized trials or register studies are lacking for BAO. Our data revealed that, in patients with other types of BAO, the procedure of EVT was related to better outcome than IVT alone in those with target mismatch, but not in those without. This finding is encouraging, and provides a possible candidate selection standard of EVT for BAO in future trials. In contrast, this selection standard seems invalid in patients with TOBS, in which the threshold of "penumbra" and the definition of "target mismatch" might be affected by the pistonlike clot movement of thrombi and good collateral status. Currently, there is no commercial software solution for quantitative perfusion CT measurement available for the posterior circulation, as no prospective imaging protocols and standardized thresholds for the identification of perfusion deficit lesion have been applied. In this study, we tested a mismatch profile used in anterior circulation as a preliminary attempt. Notably, the infarct core was defined based on the anterior circulation territory as a control. The accurate threshold of CT perfusion (CTP) parameters for both "core" and "penumbra," and the appropriate mismatch profile in BAO, remain unclear and need further investigation. Fewer than 8% of patients failed to obtain perfusion images due to motion artifacts and contrast injection issues, which still encouraged other investigators to perform perfusion imaging in BAO more often.

Our study is observational and has all the inherent limitations of a nonrandomized study. There is no standard treatment protocol, as clinicians have complex reasons for selecting a specific treatment option. Multivariate analyses and propensity score matching cannot adjust completely for systematic differences between groups, which is the aim of randomization in clinical trials. Propensity score matching analysis was not performed in some subgroups due to the relatively small sample size, and the corresponding 95% CIs were excessively large, indicating the need of further confirmation. Most patients without EVT were diagnosed with BAO on the basis of noninvasive imaging; thus, the possibility of false-positive CTA or magnetic resonance angiography could not be excluded. In addition, the accurate threshold of CTP parameters for "core" and "penumbra" and the appropriate mismatch profile in BAO remain unclear, requiring further investigation.

In conclusion, IVT is associated with a high recanalization rate and good outcome rate for TOBS, suggesting it should always be offered when indicated in the 4.5-hour time window. Given these findings, future trials of IVT in the late time window should include TOBS. More studies are needed with the latest technology and optimal procedural approach to evaluate EVT in BAO more proximally.

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Author Contributions

S.Y., Y.Zho., and M.L. contributed to conception and design of the study; all authors contributed to acquisition, analysis, and interpretation of data; S.Y., Y.Zho., Y.Zha., and M.L. contributed to drafting/revising a significant portion of the manuscript or preparing figures.

Potential Conflicts of Interest

Nothing to report.

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