CHALLENGES IN POSTERIOR CIRCULATION ISCHEMIC STROKE

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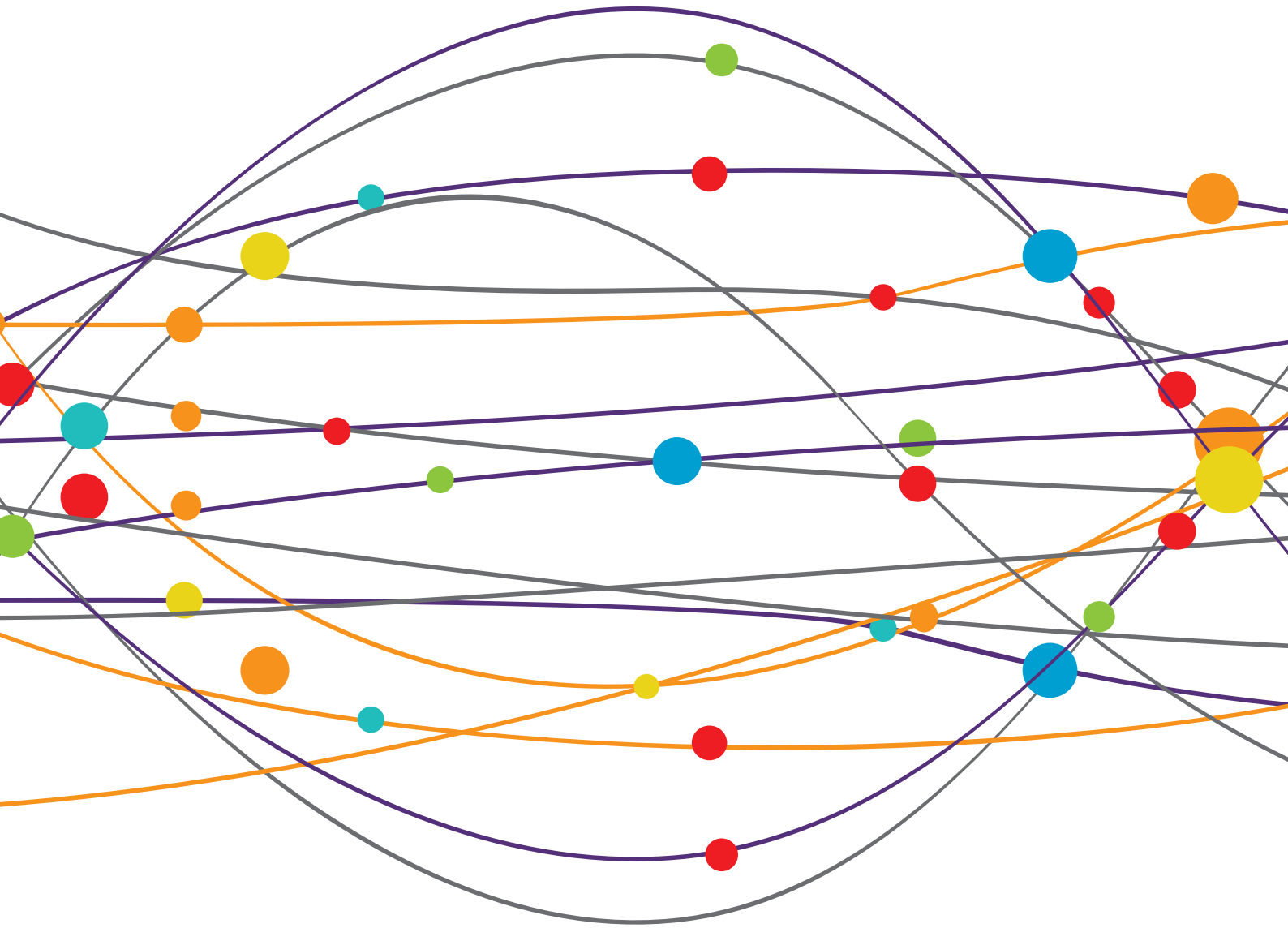

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CHALLENGES IN POSTERIOR CIRCULATION ISCHEMIC STROKE

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EDITORIAL
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Editorial: Challenges in Posterior Circulation Ischemic Stroke

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Keywords: posterior circulation stroke, basilar artery occlusion, endovascular treatment, prognosis, anatomy

Editorial on the Research Topic

Editorial: Challenges in Posterior Circulation Ischemic Stroke

Posterior circulation ischemic stroke comprises an estimated 15–20% of all ischemic strokes and differs from anterior circulation stroke in many ways. An acute occlusion of the basilar artery can trigger one of the most devastating ischemic stroke syndromes with reduced level of consciousness, loss of brainstem reflexes and tetraplegia. However, posterior circulation stroke is frequently difficult to diagnose clinically due to varying symptoms and signs like isolated vertigo and dizziness. Knowledge about specific brainstem symptoms and syndromes can aid early clinical recognition and thus, rapid initiation of appropriate diagnostic and therapeutic approaches (1). Due to the limited diagnostic accuracy of CT-based neuroimaging in the posterior circulation, magnetic resonance imaging is the preferred method for radiological confirmation of posterior circulation ischemia, however has limited availability and can be false-negative in the hyperacute setting (2). The anatomy of the posterior circulation is highly variable and stroke syndromes within have greater etiologic variability compared to the anterior circulation. Consequently, patients with acute posterior circulation ischemia seem to respond differently to acute revascularization therapies like intravenous thrombolysis (IVT) and endovascular therapy (EVT) (3). While mechanical thrombectomy has become the new gold standard in acute recanalization therapy for anterior circulation large vessel occlusions (acLVO), its efficacy and safety in acute basilar occlusion is still under debate despite recent completion of two randomized controlled trials (4–6). In parallel to acLVO where the Alberta Stroke Program Early CT Score (ASPECTS) identifies patients with benefit from EVT, imaging may play an important role to identify patients who benefit from such therapies in posterior circulation stroke and particularly basilar artery occlusion (7–11). Moreover, while perfusion imaging can facilitate patient selection for recanalization therapies in the anterior circulation, particularly in patients with unknown or late time-window, its role and relevance in posterior circulation ischemic stroke is currently less well-described (12, 13).

In the context of this clinical and scientific background, this Research Topic covers relevant aspects of posterior circulation ischemic stroke. Three main aspects are discussed.

First, the clinical diagnosis of posterior circulation ischemic stroke is frequently difficult due to varying and non-specific symptoms. The narrative review by Hoyer and Szabo summarizes important pitfalls in its diagnosis in the prehospital and emergency department setting, and provides strategies and approaches to improve speed and accuracy of its recognition and early management. Data on anatomical variants, i.e., bilateral vertebral hypoplasia as a potential risk factor for ischemic stroke, posterior fossa venous drainage and mechanisms of posterior circulation

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blood flow regulation and its implications for posterior circulation stroke are detailed in the articles by Hsu et al., De Miquel, and Tamayo and Siepmann, respectively.

Second, several articles of the collection cover novel aspects of acute treatment in patients with posterior circulation ischemic stroke and particularly basilar artery occlusion. Known data for IVT in late or unknown time window mostly focus on patients with anterior circulation ischemic stroke. It is therefore reassuring that the safety and efficacy of IVT in this scenario seem similar in patients with posterior circulation ischemic stroke, as addressed in the article by Macha et al. Their findings may inform clinicians in the usage of alteplase beyond 4.5 h from symptom onset in selected patients with posterior circulation ischemic stroke. Scientifically, however, more data on this topic is needed until a general recommendation can be made.

Given the unproven benefit of EVT on improved functional outcome in patients with basilar artery occlusion, the meta-analysis by Mbroh et al. suggests that EVT in posterior circulation large vessel occlusion (pcLVO) may be comparably sufficient in obtaining favorable functional outcome compared with acLVO. These findings parallel results of the recently published BASILAR registry, where patients who received EVT within 24 h after the estimated time of basilar artery occlusion had an improved chance to achieve a favorable functional outcome compared to patients who received best medical management only (14). In contrast, in the analysis of State-wide stroke registry data by Gruber et al., additional EVT was not superior compared to best medical management alone in patients with acute basilar artery occlusion. One must keep in mind that the results of the above mentioned analyses originate from non-randomized studies and are therefore limited in their informative value.

Patients with acute basilar artery occlusion who present with coma are unlikely to have a good clinical outcome. However, Ritvonen et al. demonstrate in their study that one fifth (21/103, 20.4%) of these patients can still achieve a favorable functional outcome. Moreover, recanalization and a lesser extent of early ischemic changes on neuroimaging [i.e., posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) > 8] were associated with favorable outcome in this study. These results confirm findings from a previous analysis of the BASICS registry data and underline the prognostic importance of imaging in patients with basilar artery occlusion (9, 15, 16).

As EVT is available in specialized stroke centers, patients with basilar artery occlusion are frequently transferred from remote hospitals in a drip-and-ship approach. The article by Alemseged and Campbell summarizes current data on tenecteplase as an alternative thrombolytic agent with greater fibrin specificity and longer half-life compared with alteplase in this scenario. As they recently demonstrated, tenecteplase achieved higher reperfusion rates in patients with large vessel occlusion including basilar artery occlusion (17, 18).

The effectiveness of EVT in acLVO has primarily been shown for patients with ICA or M1-segment occlusions, but is now also frequently performed in patients with more distal (e.g., M2-segment) occlusions. Whether EVT is safe and effective in patients with posterior cerebral artery (PCA) occlusion has been analyzed in the article by Herweh et al. as a collaboration of four major stroke centers. Their main conclusion was that EVT in isolated posterior cerebral artery occlusion appears safe and at least immediately effective, however further data from prospective or randomized studies are needed, especially on the longterm outcome activities of daily living. EVT for fetal PCA thrombectomy is another posterior circulation frontier that is also being explored in patients presenting with disabling stroke (19). Lastly, Kaiser et al. show that a regular thrombus surface (defined as smoothly straight, convex, or concave) is associated with a higher chance for successful first pass reperfusion in patients with acute basilar artery occlusion which confirms previous findings in patients with acLVO (20).

Third, as outlined above, the stroke etiology in patients with basilar artery occlusion seems more heterogenous compared to acLVO. Artery-to-artery embolism and intracranial atherosclerotic disease play an important role. Characterization of such stenoses is important for acute treatment decision making and to tailor therapy in secondary stroke prevention. By using 3T high-resolution magnetic resonance imaging in patients with recent posterior circulation stroke due to intracranial vertebrobasilar atherosclerotic disease with 70–99% stenosis, Hou et al. demonstrated that intraplaque enhancement and vertebral artery involvement were associated with artery-to-artery embolism. Questions arise whether these patients may benefit from more aggressive antiplatelet regimens.

In conclusion, this issue of *Frontiers in Neurology* provides an integrated overview of the hot topics in the field of posterior circulation ischemic stroke. Emerging from the article collection is a complex picture with focus on the anatomical, clinical and pathophysiological correlates of posterior circulation stroke, acute treatment including intravenous and endovascular therapies. The studies published in this issue emphasize the need for further research to better delineate pathophysiological aspects, clinical recognition and treatment decision making in these patients, in the wake of the BASICS and BEST basilar artery occlusion trials (4, 5, 21). Stratification of patient selection by severity of disease, imaging including multimodal CT or MRI, introduction of novel thrombolytics (i.e., tenecteplase) may play an important role in modifying the natural history of posterior circulation stroke. We look forward to learning the results of this research in the future.

AUTHOR CONTRIBUTIONS

VP drafted the manuscript. DS, TN, and SN revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Risk Factors for Long-Term Death After Medullary Infarction: A Multicenter Follow-Up Study

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Background and Purpose: We investigated the risk factors for death in patients with medullary infarction (MI) during a long-term follow-up.

Methods: We retrospectively examined 179 consecutive patients (130 men and 49 women) who had clinical and MRI findings consistent with MI between February 2012 and January 2017 at three university hospitals. Long-term outcomes were assessed by telephonic interview. The clinical and radiological features and risk factors for poor outcomes (modified Rankin scale score $\geq$ 3, all-cause death) were analyzed.

Results: Mean age of patients was 58.3 $\pm$ 12.8 years (range, 25–87); mean follow-up period after stroke onset was 42.7 $\pm$ 13.2 months (range, 24–78). Basilar artery (BA) stenosis >50% was more closely related to medial medullary infarction (MMI) than other types. There was greater frequency of ipsilateral vertebral artery hypoplasia (VAH) or V4AH and V4 occlusion in lateral MI than in other types. On rostro-caudal classification, middle (M)+dorsal (D) was most frequent, followed by the ventral (V)+M+D types. 21.2% patients showed poor long-term prognosis. Age $\geq$ 65 years, recurrent stroke, dysphagia, >50% BA stenosis, and ventral MI were risk factors for poor long-term prognosis. All-cause mortality rate was 10.6%; age $\geq$ 65 years, recurrent stroke, and dysphagia were risk factors for death in the long-term. Ventral MI and MMI+cerebellar infarction, as well as stroke mechanism of artery-to-artery embolism, were potential risk factors for death in the long-term. Pneumonia and recurrent stroke were major causes of death.

Conclusions: Long-term poor outcomes of MI and all-cause mortality were not infrequent. Older age, recurrent stroke, and dysphagia were common risk factors for poor prognosis and death.

Keywords: medullary infarction, prognosis, death, risk factors, stroke

INTRODUCTION

Medullary infarction (MI) is a rare clinical entity that can be classified into lateral and medial medullary infarction (LMI and MMI) based on the clinical and lesion patterns (1). Numerous studies have characterized the clinical manifestations of MI and their association with the anatomical site of MI (2–4). In some previous small-scale studies, most patients with MI were found to have a favorable prognosis with a low rate of mortality or clinical progression (5, 6). The lesion patterns of MI are heterogeneous owing to the unique arterial supply of medulla; therefore, there is considerable variability in the clinical manifestations of MI. Moreover, the correlation of clinical manifestations with stroke etiology, mechanism, and the prognosis of these patients is not well-characterized (7–9).

In particular, the long-term prognosis of these patients has seldom been discussed. Furthermore, there is a paucity of studies that have investigated the risk factors for survival and death in MI patients on long-term follow-up (1). Therefore, we examined the clinical and imaging features and etiopathogenesis and analyzed the risk factors for death during long-term follow-up of MI patients treated at three tertiary hospitals.

PATIENTS AND METHODS

Study Patients

We retrospectively examined 245 consecutive patients who had clinical and MRI imaging findings consistent with MI at three tertiary hospitals (People's Hospital of Zhengzhou University, the First Affiliated Hospital, and People's Hospital of Henan University of Chinese Medicine) between February 2012 and January 2017. The imaging records were retrieved from the Picture Archiving and Communication Systems (PCAS) at the three hospitals. The exclusion criteria were: patients who died in the acute phase ($n = 4$); patients who were admitted >7 days after symptom onset ($n = 9$), patients with concomitant major infarction outside the medulla including pontine, midbrain, and occipital or thalamic infarction ($n = 21$); and patients who had significant neurological sequelae attributable to previous stroke ($n = 7$). However, we included patients who showed diffusion-weighted MRI (DWI)-identified lesions (no space occupying effect) in the cerebellum ($n = 28$), because these patients may have lesions of the ispilateral vertebral artery or posterior inferior cerebellar artery in common, and there was a patient with LMI+MMI+ cerebellar infarction (C) who was classified in the LMI+MMI group. Twenty-five patients could not be followed-up because of the inability to contact them by telephone ($n = 16$) or their refusal to participate ($n = 9$). Thus, 179 patients with acute MI were included in the analysis. Data pertaining to all patients were examined by the first author, and the specific signs and symptoms recorded.

The definition of risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, atrial fibrillation, smoking, alcohol intake, and stroke history work-up protocol, at our institutes are described elsewhere (10).

Written informed consent was obtained from all participants or their legal surrogates.

Imaging Analysis

We performed DWI of acute patients and then follow-up fluid-attenuated inversion recovery/T2/T1-weighted MRI and magnetic resonance angiography (MRA) of patients with acute (<3 days after onset) stroke; in addition, some patients who had sustained focal neurological defect underwent follow-up DWI to exclude false negative results of early DWI. In patients who were admitted >3 days after stroke onset, MRI and MRA were performed only once. MRI examinations were performed using either a 1.5 Tesla or 3.0 Tesla MR imaging unit (GE Medical, Piscataway, NJ, USA). A horizontal plane at 3-mm intervals from the medulla to the midbrain was obtained. The DWI parameters were: repetition time (TR), 7,500 ms; echo time (TE), 84 ms; matrix number, 128 × 128; and two *b*-values of 0 and 1,000 s/mm. Three-dimensional (3D)-time-of-flight (TOF)-MRA and 3D-contrast-enhanced (CE)-MRA were also performed at the time of MR imaging with parameters described elsewhere (10).

Evaluation of Arterial Stenoses

The degree of arterial stenoses was categorized as mild (≤50% diameter reduction), moderate or severe (>50% diameter reduction with complete distal flow), occlusion, and aplasia [non-visualization of the entire vertebral artery (VA)]/hypoplasia [diffuse homogeneous narrowing of the entire basilar artery (BA) or VA]. We interpreted non-visualization or homogeneous narrowing of the distal VA after the origin of the posterior inferior cerebellar artery as aplasia/hypoplasia (V4AH), and irregular narrowing as atherosclerotic vascular stenosis. MRA showing double lumen, intimal flap, pearl and string sign, or improvement of vascular stenosis of the VAs or proximal BA within several days were classified as probable dissection (11). The diameter of the VA was measured at three consecutive points from the bilateral VA junction (3 mm apart) and only the maximum value was considered. VAH was presumed when VA met the following morphologic criteria on MRA: VA diameter < 2.5 mm and a concomitant diameter asymmetry ratio of <1:1.7 throughout the VA (12). BA diameter was measured at the mid-pons level on TOF source images. In the present study, vertebrobasilar dolichoectasia (VBD) was defined as BA diameter > 4.5 mm or VA diameter > 4.0 mm (10).

Assessment of Lesion Pattern and Etiology

Distribution of Infarcts Based on MRI Findings

As lesions were often invisible or vague on the initial DWI in some patients, those who had sustained a focal neurological defect underwent repeat imaging evaluation (33 patients). We used the MRI (either DWI or T2) findings obtained in the subacute stage (mean, 3.1 ± 1.2 days after stroke onset).

Abbreviations: LMI, lateral medullary infarction; MMI, medial medullary infarction; MI, medullary infarction; BMMI, bilateral medial medullary infarction; HMI, hemi-medullary infarction; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; VAH, vertebral artery hypoplasia; M, middle; D, dorsal; V, ventral; VA, vertebral artery; BA, basilar artery; LVD, large vessel disease; ABO, atheromatous branch occlusion; AAE, artery-to-artery embolism; CE, cardiogenic embolism; SVD, small vessel disease; DIS, dissection; UN, undetermined; mRS, modified Rankin scale.

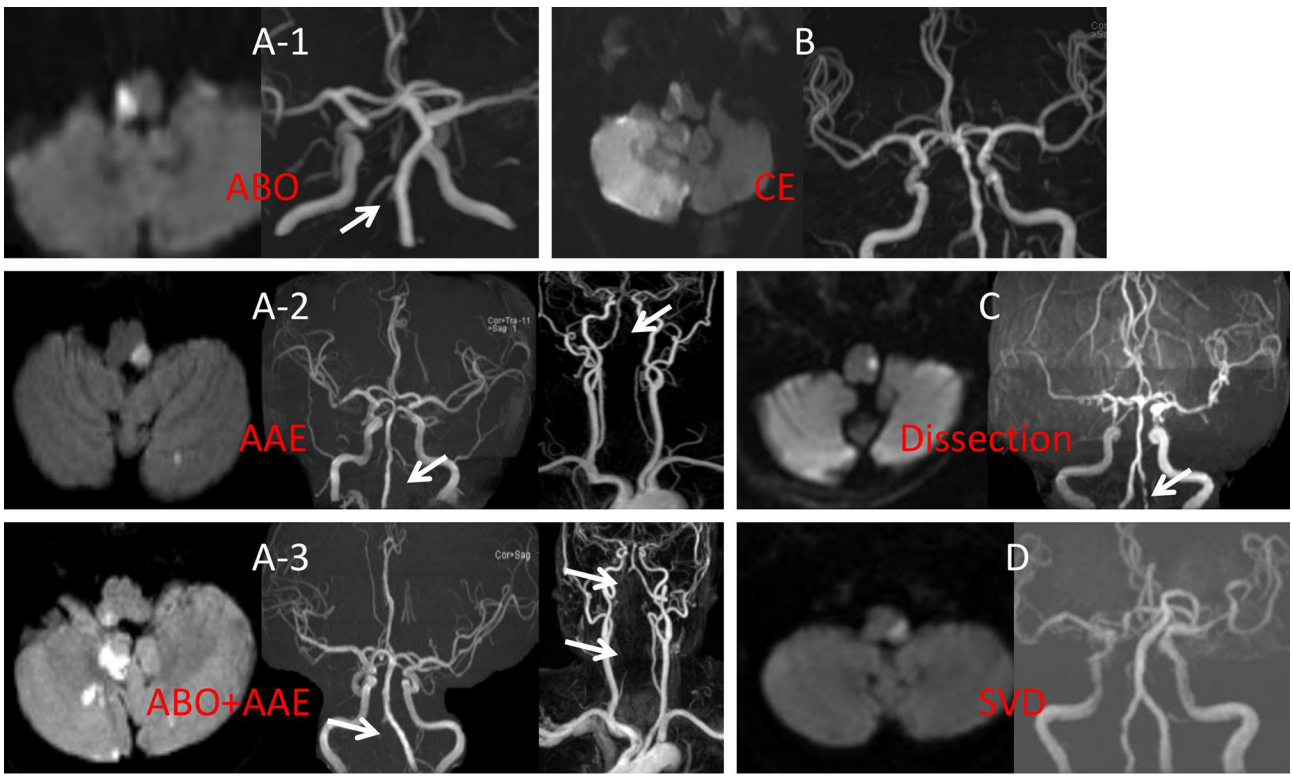

FIGURE 1 | (A-1) DWI showed right caudal medullary infarction, MRA showed right intracranial VA occlusion. **(A-2)** DWI indicated left middle medullary and cerebellar infarction, MRA showed occlusion in the proximal left VA with no distal VA disease. **(A-3)** DWI showed right rostral medullary and cerebellar multiple infarction, MRA showed in both distal and proximal right VA. **(B)** DWI showed the right rostral medullary and cerebellar multiple infarction, MRA showed bilateral VA was normal. **(C)** DWI showed caudal medullary infarction, MRA showed the pearl, and string sign of left VA. **(D)** DWI showed middle medullary infarction, MRA showed the bilateral VA were normal. ABO, atheromatous branch occlusion; AAE, artery-to-artery embolism; CE, cardiogenic embolism; SVD, small vessel disease; DWI, diffusion weighted imaging; MRA, magnetic resonance angiography; VA, vertebral artery.

Lesions were classified by two authors (YS and ZDP) who were blinded to clinical information; in case of any disagreement between the two, a topographical consensus was achieved by participation of a third neurologist. Rostro-caudally, the lesions were categorized as "rostral," "middle," and "caudal," according to criteria described previously (4). The lesions of medulla were ventro-dorsally classified according to the diagram of the rostral, middle, and caudal medulla as (4) "ventral (V)" (ventral part, presumably containing the pyramid); "middle (M)" (middle part, presumably including the medial lemniscus); and "dorsal (D)" (dorsal part, presumably including the medial longitudinal fasciculus [MLF] in a lesion extending to the dorsal surface of the medulla). According to lesions located in the whole medulla, MI patients were divided into LMI, MMI, bilateral MMI (BMMI), and hemi-medullary infarction (HMI), LMI+MMI, LMI+C, and MMI+C.

Presumed Stroke Mechanisms

The presumed mechanism of stroke was categorized by consensus among our stroke team with modification of recent guidelines and as described in a previous major study (3, 10, 13).

1. Large vessel disease (LVD). LVD was divided into three categories: (1) atheromatous branch occlusion (ABO); (2) artery-to-artery embolism (AAE); and (3) AAE+ABO. 2. Cardiogenic embolism (CE). 3. VA dissection (DIS). 4. Small vessel disease (SVD). 5. Undetermined (UN) etiology (**Figures 1A–D**).

Follow-Up Study

In patients with a follow-up period > 24 months, telephonic interviews were conducted in February 2019 by an experienced stroke research coordinator (Y.S.) who certified the modified Rankin scale (mRS) score using a structured format, exploring the general neurological outcome using a modified Rankin scale (0–5). mRS scores $\geq$ 3 were considered as poor outcome and all-cause mortality was elaborately recorded. The subjective sensory complaints of patients were assessed as described previously (3). The severity was assessed using 10-point markers on a visual numeric scale (1, slight; 10, most severe). Dysphagia was recorded by reviewing medical records at admission (these patients were screened by drinking water test in Wadi) and patients' complaints during follow-up. The cause of death and incidence of recurrent stroke were confirmed by telephonic interviews and medical records.

Statistical Analysis

We used the Chi-squared test to compare categorical variables; the Fisher exact test was used when the number of cells was small.

TABLE 1 | Clinical characteristics of 179 patients with medullary infarction.

	LMI ($n = 96$)	MMI ($n = 42$)	BMMI ($n = 9$)	LMI+MMI ($n = 1$)	HMI ($n = 3$)	LMI+C ($n = 23$)	MMI+C ($n = 5$)
Age	58.8 ± 12.5	58.9 ± 14.6	57.9 ± 10.2	72.0	53.7 ± 7.6	56.3 ± 12.7	64.6 ± 16.1
Sex(male)	67 (69.8)	31 (73.8)	6 (66.7)	1 (100.0)	3 (100.0)	21 (91.3)	2 (40.0)
Paralysis							
No	34 (35.4)	15 (35.7)	7 (77.8)	0	0	12 (52.2)	2 (40.0)
Monoplegia	8 (8.3)	5 (11.9)	1 (11.1)	0	0	2 (8.7)	0
Hemiplegia	42 (43.8)	19 (45.2)	1 (11.1)	1 (100.0)	2 (66.7)	4 (17.4)	2 (40.0)
Quadriplegia	12 (12.5)	3 (7.1)	0	0	1 (33.3)	5 (21.7)	1 (20.0)
Paresthesia							
No	10 (10.4)	2 (4.8)	4 (44.4)	0	1 (33.3)	6 (26.1)	3 (60.0)
Numb/hypalgesia	37 (38.5)	17 (40.5)	3 (33.3)	0	2 (66.7)	7 (30.4)	1 (20.0)
Others	49 (51.0)	23 (54.8)	2 (22.2)	1 (100.0)	0	10 (43.5)	1 (20.0)
Vertigo/dizziness	77 (80.2)	34 (81.0)	7 (77.8)	1 (100.0)	2 (66.7)	19 (82.6)	1 (20.0)
Dysphagia	27 (28.1)	12 (28.6)	5 (55.6)	0	2 (66.7)	9 (39.1)	1 (20.0)
Dysarthria	34 (41.5)	16 (38.1)	5 (55.6)	0	2 (66.7)	10 (43.5)	1 (20.0)
Facial paralysis	13 (13.5)	10 (23.8)	2 (22.2)	0	1 (33.3)	10 (43.5)	1 (20.0)
Nausea/vomiting	38 (39.6)	24 (57.1)	5 (55.6)	1 (100.0)	2 (66.7)	11 (47.8)	2 (40.0)
Ataxia	29 (30.2)	7 (16.7)	3 (33.3)	0	2 (66.7)	18 (78.3)	0
Nystagmus	13 (13.5)	5 (11.9)	1 (11.1)	1 (100.0)	1 (33.3)	6 (26.1)	0
Diplopia	8 (8.3)	1 (2.4)	0	1 (100.0)	0	2 (8.7)	0
Headache	21 (21.9)	14 (33.3)	3 (33.3)	0	2 (66.7)	2 (8.7)	1 (20.0)
Horner signs	5 (5.2)	3 (7.1)	2 (22.2)	1 (100.0)	1 (33.3)	2 (8.7)	0
Medical history							
Hypertension	63 (65.6)	24 (57.1)	4 (44.4)	1 (100.0)	1 (33.3)	17 (73.9)	3 (60.0)
Diabetes mellitus	37 (38.5)	14 (33.3)	2 (22.2)	0	1 (33.3)	9 (39.1)	2 (40.0)
Atrial fibrillation	1 (1.0)	2 (4.8)	0	0	0	5 (21.7)	0
Coronary heart disease	13 (13.5)	6 (14.3)	1 (11.1)	0	1 (33.3)	5 (21.7)	1 (20.0)
Hyperlipidemia	22 (22.9)	9 (21.4)	1 (11.1)	0	1 (33.3)	6 (26.1)	0
Strokes	17 (17.7)	7 (16.7)	1 (11.1)	1 (100.0)	1 (33.3)	9 (39.1)	2 (40.0)
Drinking	26 (27.1)	13 (31.0)	4 (44.4)	0	0	13 (56.5)	0
Smoking	39 (40.6)	18 (42.9)	3 (33.3)	0	0	11 (47.8)	0
Long-term follow up							
mRS ≥ 3	17 (17.7)	10 (23.8)	3 (33.3)	1 (100.0)	3 (100.0)	5 (21.7)	1 (20.0)
Death	7 (7.3)	7 (16.7)	0	0	0	3 (13.0)	2 (40.0)
Recurrent stroke	4 (4.2)	4 (9.5)	0	0	0	3 (13.0)	0

LMI, lateral medullary infarction; MMI, medial medullary infarction; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; BMMI, bilateral MMI; HMI, hemimedullary infarction; mRS, modified Rankin Scale.

The *t*-test was used to compare continuous variables. Potential risk factors ($P < 0.20$) identified on univariate analysis were included in the multivariate analysis after adjusting for age and sex. Statistical tests were performed with a 2-tailed α level of 0.05. Data were analyzed with IBM SPSS version 13.0.

RESULTS

Demographic and Clinical Features

The study population comprised of 130 men and 49 women; the mean age of the patients was 58.3 ± 12.8 years (range, 25–87). Risk factors included hypertension in 113 (63.1%) patients, diabetes mellitus in 65 (36.3%), smoking in 72 (40.2%), alcohol consumption in 56 (31.3%), hyperlipidemia in 39 (21.8%), and atrial fibrillation in 8 (4.5%) patients. Thirty-seven (20.7%) patients had a history of stroke, and 27 (15.1%) patients had a history of coronary heart disease (**Table 1**).

The most common syndromes were LMI in 96 patients (53.6%), MMI in 42 (23.5%), LMI+C in 23 (12.8%), BMMI in nine (5.0%), MMI+C in five (2.8%), HMI (infarction area > 40% of the medulla in one place) in three (1.7%), and LMI+MMI in one (0.6%) patient.

Sensory impairment was the most common symptom (154 patients); however, it could not be reliably assessed in nine patients because of severe dysarthria or confusion. Among the remaining 145 patients, sensory symptoms/signs were observed in 118 patients (81.3%). Motor dysfunction was the second most common symptom (107 patients): hemiparesis in 70,

TABLE 2 | Imaging characteristics of 179 patients with medullary infarction.

	LMI ($n = 96$)	MMI ($n = 42$)	BMMI ($n = 9$)	LMI+MMI ($n = 1$)	HMI ($n = 3$)	LMI+C ($n = 23$)	MMI+C ($n = 5$)
MRA							
BA stenosis > 50%	13 (13.5)	7 (16.7)	5 (55.6)	0	1 (33.3)	3 (13.0)	2 (40.0)
VA stenosis > 50%	32 (33.3)	16 (38.1)	2 (22.2)	0	0	9 (39.1)	3 (60.0)
V4 occlusion	12 (12.5)	5 (11.9)	0	1 (100.0)	0	4 (17.4)	0
VBD	18 (18.8)	7 (16.7)	2 (22.2)	0	0	5 (21.7)	0
BAH	2 (2.1)	4 (9.5)	3 (33.3)	0	0	0	0
VAH or V4AH	48 (50.0)	18 (42.9)	1 (11.1)	1 (100.0)	3 (100.0)	12 (52.2)	1 (20.0)
Lesions location							
Rostral	18 (18.8)	28 (66.7)	4 (44.4)	1 (100.0)	0	9 (39.1)	2 (40.0)
Middle	48 (50.0)	5 (11.9)	2 (22.2)	0	2 (66.7)	7 (30.4)	1 (20.0)
Caudal	10 (10.4)	3 (7.1)	0	0	0	2 (8.7)	0
R+M	9 (9.4)	5 (11.9)	2 (22.2)	0	1 (33.3)	3 (13.0)	2 (40.0)
M+C	11 (11.5)	2 (4.8)	1 (11.1)	0	0	1 (4.3)	0
Ventral	2 (2.1)	26 (61.9)	2 (22.2)	0	0	1 (4.3)	1 (20)
Middle	30 (31.3)	4 (9.5)	0	0	0	8 (34.8)	0
Dorsal	45 (46.9)	1 (2.4)	0	0	0	12 (52.2)	0
V+M	0	1 (2.4)	0	0	0	0	0
M+D	12 (12.5)	3 (7.1)	0	0	0	2 (8.7)	2 (40.0)
V+D	0	0	1 (11.1)	0	0	0	0
V+M+D	1 (1.0)	6 (14.3)	5 (55.6)	1 (100.0)	3 (100.0)	0	1 (20.0)
Stroke mechanisms							
ABO	27 (28.1)	12 (28.6)	1 (11.1)	0	1 (33.3)	6 (26.1)	0
AAE	24 (25.0)	8 (19.0)	2 (22.2)	0	1 (33.3)	2 (8.7)	2 (40.0)
ABO+AAE	5 (5.2)	2 (4.8)	5 (55.6)	0	1 (33.3)	5 (21.7)	1 (20.0)
SVD	13 (13.5)	4 (9.5)	0	0	0	0	0
DIS	10 (10.4)	5 (11.9)	2 (22.2)	1 (100.)	0	2 (8.7)	0
CE	1 (1.0)	2 (4.8)	0	0	0	4 (17.4)	2 (40.0)
UN	14 (14.6)	9 (21.4)	0	0	0	0	0
Initial DWI negative	17 (17.7)	15 (35.7)	0	0	0	0	1 (20.0)

ABO, atheromatous branch occlusion; AAE, artery-to-artery embolism; CE, cardiogenic embolism; SVD, small vessel disease; UN, undetermined etiology; DIS, dissection; LMI, lateral medullary infarction; MMI, medial medullary infarction; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; BMMI, bilateral MMI; HMI, hemimedullary infarction; VA, vertebral artery; BA, basilar artery; VAH, vertebral artery hypoplasia; BAH, basilar artery hypoplasia; VBD, vertebrobasilar dolichoectasia; R, rostral; M, middle; C, caudal; V, ventral; D, dorsal; DWI, diffusion weighted imaging.

quadriparesis in 20, and monoparesis in 17 patients. The motor dysfunction was severe (medical research council scale < 3 in any proximal limb) in 39 patients (36.4%). Thirty-seven patients showed mild facial paresis on the ipsilateral side (**Table 1**).

Limb ataxia was noticed in 84 patients, usually associated with mild weakness (ataxic hemiparesis). Dysarthria was present in 55 patients. Dysphagia was noted in 68 patients, 16 of whom required a nasogastric tube for feeding. The other symptoms were vertigo/dizziness ($n = 82$), headache ($n = 43$), Horner syndrome ($n = 13$), nausea/vomiting ($n = 12$), and diplopia ($n = 12$). Twenty-seven patients had nystagmus. Six patients showed internuclear ophthalmoplegia (**Table 1**).

MRI Findings and Presumed Mechanism of Stroke

Initial DWI imaging was negative in 33 (18.4%) patients. These lesions represented 35.7% of MMI, 17.7% of LMI ($\chi^2 = 7.248$, $P = 0.048$), and 20.0% of MMI+C. Of these, 42.4% were in the rostral, 26.7% were in the middle, and 30.9% were in the caudal medullary region. Risk factors and etiological mechanisms were not significantly different between patients with and without visible infarction on the initial DWI.

As shown in **Table 2**, vertebrobasliar artery lesions included BA stenosis >50% in 31 (17.3%), ipsilateral VA stenosis >50% in 62 (34.6%), ipsilateral V4 occlusion in 22 (12.3%), VBD in 32 (17.9%), basilar artery hypoplasia in nine (5.0%), and ipsilateral VAH or V4AH in 76 (42.5%) patients. Forty-seven patients had ABO (26.3%), 40 had AAE (22.3%), and 19 had ABO+AAE (10.6%). Eighteen patients were considered to have SVD (10.1%). Eight were categorized as CE (4.5%). Twenty patients had VA dissection (11.2%). The etiology was unknown in 23 (12.8%) patients. There was no significant difference with respect to stroke mechanism among LMI, MMI, BMMI, HMI, LMI+C, and MMI+C (**Table 2**).

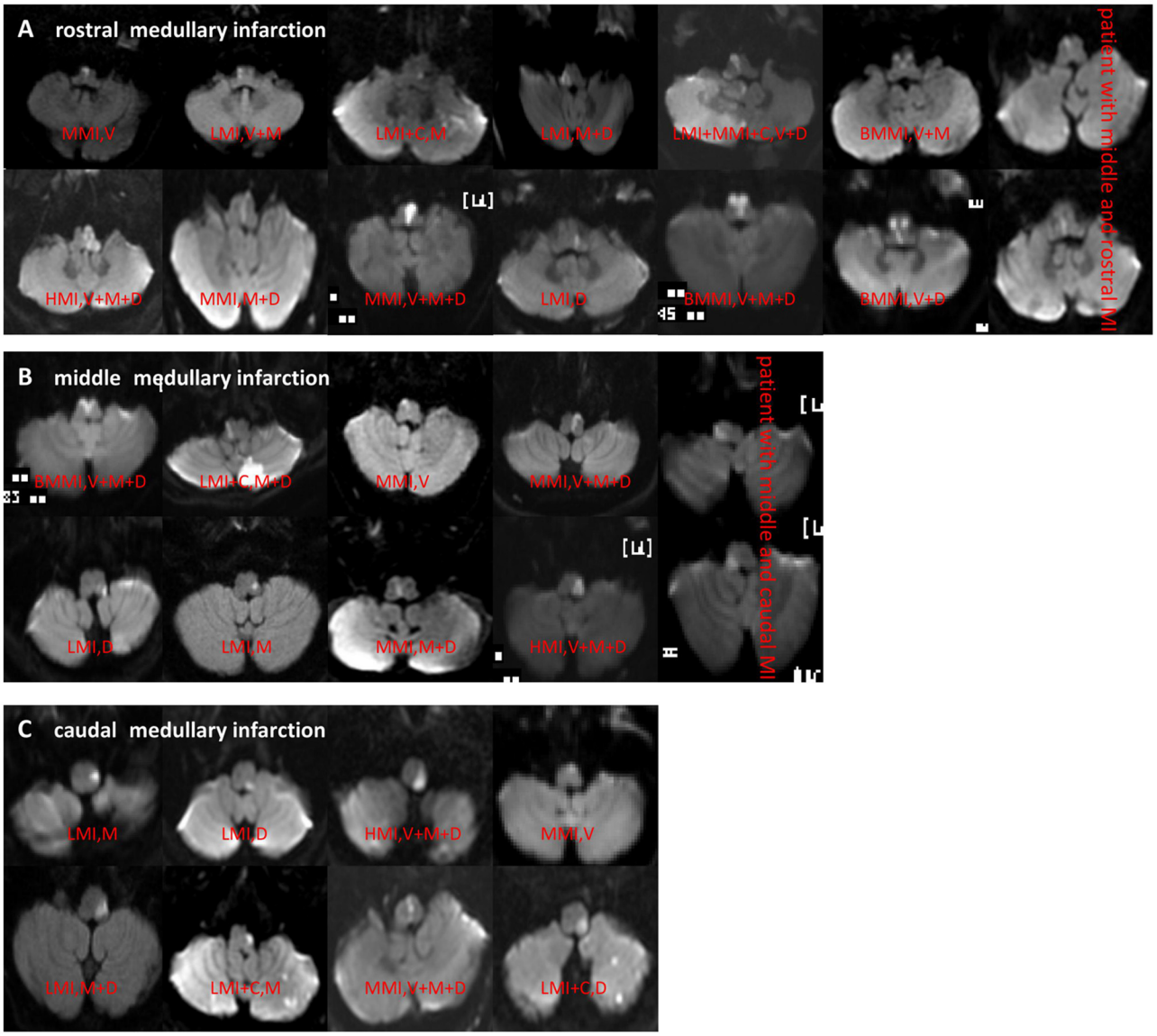

FIGURE 2 | (A–C) DWI showed different types of rostral, middle, and caudal MI. MI, medullary infarction; LMI, lateral MI; MMI, medial MI; BMMI, bilateral MMI; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; HMI, hemimedullary infarction; V, ventral; M, middle; D, dorsal.

On rostro-caudal classification, the lesions were located in the middle medulla ($n = 65$), rostral ($n = 62$), middle+rostral ($n = 22$), caudal ($n = 15$), and middle+caudal ($n = 15$). Ventro-dorsally, the lesions were located in the ventral medulla ($n = 32$), middle ($n = 42$), dorsal ($n = 58$), M+D ($n = 19$), V+M+D ($n = 17$), V+M ($n = 3$), and V+D ($n = 1$). M+D type was the most frequent, followed by the V+M+D type (**Table 2**; **Figures 2A–C**).

BA stenosis >50% was more closely related to MMI than the others ($\chi^2 = 9.749$, $P = 0.008$). LMI mostly occurred in the middle medulla, and MMI mostly occurred in the rostral medulla. The ventral medulla was the most frequently affected in MMI, while the dorsal medulla was the most frequently affected in LMI. The LMI group had a significantly greater proportion of patients with occlusion of ipsilateral VAH or V4AH ($\chi^2 = 5.989$, $P = 0.049$) and V4 ($\chi^2 = 10.595$, $P < 0.001$) than in the other groups (**Table 2**).

Risk Factors for Poor Prognosis and Death During Long-Term Follow-Up

Telephonic interviews of 179 patients were conducted 24–78 months (mean 42.7 ± 13.2 months) after stroke onset. During follow-up, 19 patients were found to have died; of these, six died of pneumonia (2, 3, 3, 4, 4, and 6 years post-stroke, respectively), four due to recurrent stroke (3, 5, 5, and 6 years post-stroke, respectively), three due

TABLE 3 | Characteristics of 19 dead patients with medullary infarction.

Patient	Age/sex	Risk factors	Stroke mechanisms	Major symptoms and signs	Lesions location of medulla	Magnetic resonance angiography	Death time	Causes of death
1	83/M	No	UN	Vertigo, headache, vomit, hemiplegia, dysphasia	MMI, rostral, ventral	V4AH	2 years	Pneumonia
2	47/M	DM, CHD, HT, stroke, hyperlipemia	ABO	Hemiplegia, dysphasia	MMI, middle-caudal, V+M+D	VA stenosis	6 years	Pneumonia
3	62/M	HT, smoking	ABO	Vertigo, hemidysesthesia, hemiplegia, dysphasia	MMI, rostral, ventral	BA and VA stenosis	4 years	Pneumonia
4	52/M	HT, DM	UN	Vertigo, vomit, diplopia, hemidysesthesia, hemiplegia, dysphasia	LMI, middle, dorsal	V4AH	3 years	Myocardial infarction
5	70/F	HT	AAE	Vertigo, hemiplegia	MMI+C, middle, M+D	VA stenosis	2 years	Lung cancer
6	70/M	HT, DM, smoking, stroke	UN	Vertigo, ataxia, dysarthria, hemidysesthesia, hemiplegia, dysphasia	LMI, caudal, middle	VBD	6 years	Myocardial infarction
7	69/M	HT, DM, CHD, stroke, hyperlipemia	AAE	Vertigo, facial paralysis, dysarthria hemidysesthesia, nystagmus, hemiplegia, dysphasia	LMI+C, R+M, dorsal	VBD	3 years	Traumatic brain hemorrhage
8	78/M	smoking, drinking	ABO+AAE	Vertigo, ataxia, nystagmus, hemidysesthesia	LMI+C, middle, dorsal	VA stenosis	5 years	Recurrent stroke
9	76/F	HT, DM	DIS	Hemidysesthesia, hemiplegia	LMI, middle, ventral	VA string	4 years	Pneumonia
10	78/M	CHD, stroke, smoking, drinking	UN	Vertigo, vomit, monoplegia, dysarthria, hemidysesthesia, nystagmus	LMI, R+M, dorsal	V4AH	3 years	Recurrent stroke
11	59/M	DM	AAE	Vertigo, hemiplegia, dysphasia	MMI, R+M, ventral	VBD, VAstenosis	6 years	Recurrent stroke
12	87/M	HT, atrial fibrillation, stroke	CE	Dysarthria, facial paralysis, quadriplegia, dysphasia	MMI+C, rostral, ventral	VA stenosis	2 years	Uncertainty
13	75/F	HT, CHD, stroke, hyperlipemia	ABO+AAE	Vertigo, vomit, dysarthria hemidysesthesia, nystagmus, dysphasia	LMI, R+M, M+D	VA stenosis	3 years	Pneumonia
14	71/F	hyperlipemia	UN	Vertigo, dysarthria, nystagmus, ataxia, dysphasia	LMI, M+C, middle	V4AH	5 years	Recurrent stroke
15	68/F	HT, CHD	AAE	Vertigo, facial paralysis, ataxia hemidysesthesia, nystagmus, hemiplegia, dysphasia	MMI, middle, ventral	VA stenosis	6 years	Brain hemorrhage
16	58/F	HT, CHD, atrial fibrillation	CE	Vertigo, facial paralysis, ataxia hemidysesthesia, nystagmus, hemiplegia	MMI, rostral, V+M+D	BA stenosis	3 years	Uncertainty
17	80/F	smoking	UN	Vertigo, vomit, headache, facial paralysis, dysphasia, hemidysesthesia, nystagmus hemiplegia	MMI, middle, M+D	VA stenosis, VAH	2 years	Myocardial infarction
18	83/M	HT, stroke	SVD	Vertigo, hemidysesthesia, hemiplegia, ataxia	LMI, rostral, dorsal	normal	2 years	Uncertainty
19	76/F	HT, DM, CHD, atrial fibrillation	CE	Vertigo, diplopia, hemiplegia, nystagmus, Horner signs, ataxia	LMI, R+M, middle	VA stenosis	4 years	Pneumonia

DM, diabetes milletus; HT, hypertension; CHD, coronary heart disease; ABO, atheromatous branch occlusion; AAE, artery-to-artery embolism; CE, cardiogenic embolism; SVD, small vessel disease; UN, undetermined etiology; DIS, dissection; LMI, lateral medullary infarction; MMI, medial medullary infarction; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; VA, vertebral artery; BA, basilar artery; VAH, vertebral artery hypoplasia; VBD, vertebrobasilar dolichoectasia; R, rostral; M, middle; C, caudal; V, ventral; D, dorsal.

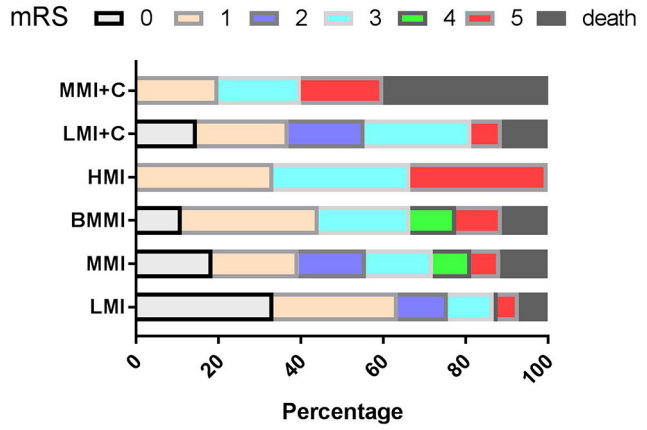

FIGURE 3 | mRS according to the types of MI during follow-up. mRS, modified Rankin Scale; LMI, lateral MI; MMI, medial MI; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction; BMMI, bilateral MI; HMI, hemimedullary infarction.

to myocardial infarction (2, 3, and 6 years post-stroke, respectively), one due to traumatic brain hemorrhage (3 years post-stroke), one due to lung cancer (2 years post-stroke), and one due to cerebral hemorrhage (6 years post-stroke). The cause of death of three patients was uncertain. Non-fatal stroke and recurrent stroke occurred in 11 patients (6.1%; **Table 3**).

During follow-up, clinical outcomes were favorable in 122 patients and poor (MRS $\geq$ 3) in 38 (21.2%) patients (**Figure 3**). On multivariate analysis of baseline date at onset, age $\geq$ 65 years (OR = 5.306, 95%CI = 2.494–9.641, $P <$ 0.001), dysphagia (OR = 3.909, 95%CI = 1.806–8.447, $P <$ 0.001), and stroke recurrence (OR = 4.826, 95%CI = 1.348–17.914, P = 0.031) were found to be risk factors for poor prognosis. Multivariate analysis of the vertebrobasilar artery status of patients showed that > 50% BA stenosis (OR = 4.348, 95%CI = 0.102–0.932, P = 0.037) was a risk factor for poor prognosis. Multivariate analysis of different infarct sites showed that ventral MI (OR = 3.850, 95%CI = 0.219–0.879, P = 0.042) was a risk factor for poor prognosis.

During follow-up, 19 patients (10.6%) had died. Multivariate analysis of baseline data at onset showed that age $\geq$ 65 years (OR = 4.394, 95%CI = 2.089–9.234, $P <$ 0.001), dysphagia (OR = 3.707, 95%CI = 1.784–7.703, $P <$ 0.001), and stroke recurrence (OR = 4.753, 95%CI = 1.202–18.804, P = 0.026) were risk factors for death (**Figure 4**). On multivariate analysis of the lesions of vertebrobasilar arteries and presumed stroke mechanism, AAE (OR = 5.235, 95%CI = 1.239–22.122, P = 0.024) was found to be a risk factor for death (**Figure 5**). Multivariate analysis of the different infarct sites showed that ventral MI (OR = 4.581, 95%CI = 1.611–26.879, P = 0.009) and MMI+C (OR = 5.163, 95%CI = 3.630–22.156, P = 0.014) were risk factors for death (**Figure 6**).

DISCUSSION

In this study, we compared the clinical symptoms, signs, and rostro-caudal and ventro-dorsal involvement in LMI, MMI, BMMI, LMI+C, and MMI+C based on a large cohort of MI patients involving a mean follow-up period of 42.7 months. This is in contrast to most previous studies that investigated the clinicotopographical correlation based on a dichotomized categorization of LMI and MMI. We also described the long-term prognosis of 179 patients with MI treated at the stroke centers of three tertiary hospitals. In the present study, 21.2% patients showed poor long-term prognosis (mRS $\geq$ 3) and 10.6% patients died. Eleven patients (6.1%) experienced recurrent stroke. In a study of long-term prognosis and mortality of all stroke patients at a Mexican hospital, 14.5% subjects died during the 4-year follow-up and the recurrence rate was 20.2% (14). The mortality and recurrence rates were higher than that in our series of medullary patients. A total of 20.9% of patients presented severe sequelae at hospital discharge, which was consistent with the present medullary case series. We further identified the risk factors for poor long-term prognosis and death using multivariate analysis.

With respect to the clinical features in our series, LMI syndrome (53.6%) was two times more common than MMI (23.5%). Interestingly, we also found three (1.7%) HMI (infarction area > 40% of the medulla in one place). Sensory impairment was the most common symptom and atheromatous branch occlusion was the most frequently presumed stroke etiology in the present study. On rostro-caudal classification, most lesions were located in the middle medulla (n = 65); on ventro-dorsal classification, most lesions were located in the ventral medulla (n = 32). These results could help us reconsider the clinical features of medullary infarction; however, this is consistent with a previous study (2).

In the present study, the most common characteristics of vertebrobasilar artery lesions were higher ipsilateral VAH or V4AH (42.5%) and ipsilateral VA stenosis >50% (34.6%), although some cases had coexisting ipsilateral V4 occlusion (12.3%) and VBD (17.9%). Hong et al. (15) assumed that unequal VA flow because of the asymmetric VAs is an important hemodynamic contributor to basilar artery curvature and development of peri-vertebrobasilar junctional infarcts. In this chronic process, VAH seemed to be the consequence of the interaction between the unequal VA flow and the basilar artery curvature, or just acted as an initial factor (16). A hypoplastic VA can also result in the ipsilateral occlusion of this vessel due to a direct decrease in blood flow and easy collapse of the vessel caused by the smaller intracranial VA caliber (17). A hypoplastic VA can cause ipsilateral posterior inferior cerebellar artery infarction by directly decreasing the blood flow in the smaller intracranial VA (18).

There is a paucity of studies on the long-term prognosis of patients with MI; in particular, there is no credible data on the prevalence of poor outcomes. In a recent study of 43 MI patients involving a median follow-up of 17 months, two patients died and two patients experienced recurrent ischemic events (19). A more recent investigation of 81 MI patients showed generally

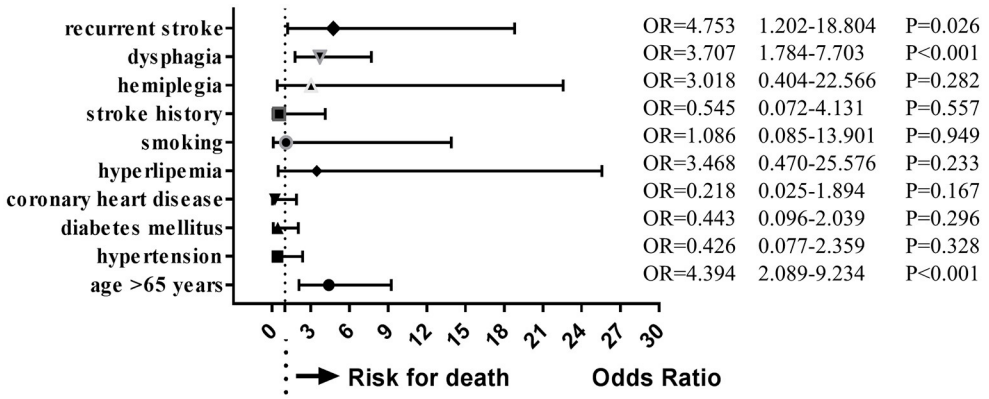

FIGURE 4 | Clincal risk factors for death. Age ≥ 65 years, dysphagia, and stroke recurrence were risk factors for death.

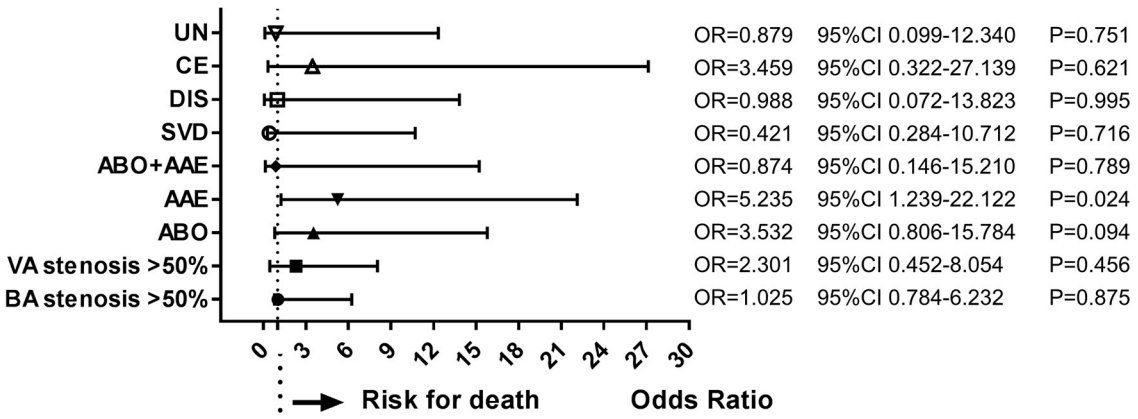

FIGURE 5 | Risk factors of stroke mechanisms for death. AAE was a risk factor for long-term death. ABO, atheromatous branch occlusion; AAE, artery-to-artery embolism; CE, cardiogenic embolism; SVD, small vessel disease; DIS, dissection; UN, undetermined.

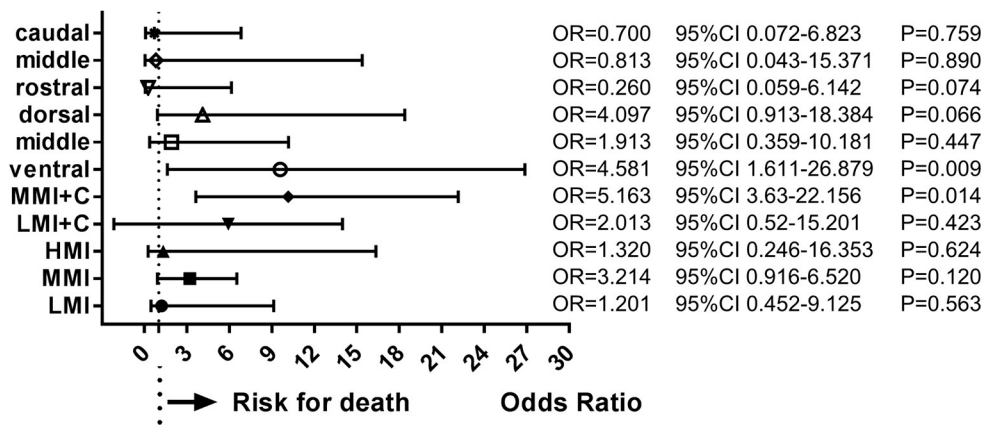

FIGURE 6 | Risk factors of infarct sites for death. Ventral MI and MMI+C were risk factors for death. LMI, lateral medullary infarction; MMI, medial medullary infarction; LMI+C, LMI+cerebellar infarction; MMI+C, MMI+cerebellar infarction.

favorable outcomes (9). Based on these reports and other small series, MI has been regarded as a benign condition. However, the outcome is not uniformly favorable, especially for MMI patients. In a follow-up study of MMI, 16.2% (11/68) patients died (3). A systematic review of 38 BMMI patients revealed poor clinical outcomes with a 23.8% in-hospital mortality (20). In

another study, 11.6% of LMI patients (5/43) died from respiratory and cardiovascular complications in the acute phase (5). In the present study, 21.2% patients showed poor long-term prognosis (mRS $\geq$ 3) and 10.6% patients died; our findings indicate the need for appropriate measures to improve the long-term outcomes of patients with MI. In a recent study of 248 LMI patients, 68 (36.1%) LMI patients showed poor functional outcome (mRS 2–6) at long-term follow-up (21); however, the authors could not determine the mortality rate.

A study by Caplan et al. revealed the poor prognosis of LMI patients more than 30 years ago (22). They reported two patients with LMI who experienced recurrent episodes of brainstem ischemia, and listed possible reasons for poor outcomes. However, the frequency and relative importance of the risk factors for long-term poor outcomes, including death, have not been fully studied in a large number of patients. Interestingly, in our study of 179 MI patients, age $\geq$ 65 years, dysphagia, and recurrent stroke were risk factors for poor prognosis and death. In a previous study of 157 LMI patients, older age, and initial dysphagia were found to be independent predictors of poor long-term prognosis (mRS $\geq$ 2) after acute LMI (23). In a study of 86 consecutive MMI patients, age and severe motor dysfunction at admission were predictors of poor prognosis (mRS $>$ 3) (3). The association of old age and dysphagia with poor prognosis is likely explained by a higher prevalence of pneumonia in elderly and dysphagic patients as compared to that in their younger counterparts and those without dysphagia. Pneumonia is a major cause of death in stroke patients. In a study of recurrent ischemic stroke in a hospital-based population in Western Norway, age was independently associated with stroke recurrence and the recurrence significantly increased the all-cause mortality (24). In a study of all types of stroke involving the use of adjusted models, the prognostic factors for early and late survival after stroke were age and in-hospital medical complications (14). High comorbidity and recurrence increased the risk of late death but not the risk of early death (14).

Stroke-related mortality varies considerably between stroke types, regions, and countries (25). However, the correlates of long-term poor prognosis and death are not well characterized in the context of medullary infarction. We showed that BA stenosis $>$50% and ventral MI are risk factors for long-term poor prognosis; more importantly, ventral MI and MMI+C were potential risk factors for death. In a recent study of 248 LMI patients, LMI accompanied by ischemic lesions at other areas was associated with poor outcomes; on multivariate analysis, age, diabetes, presence of dysphagia, and pneumonia were independently associated with poor functional outcomes (21). Our findings suggested that not only LMI but also MMI accompanied by ischemic lesions in other areas were associated with poorer prognosis and death. In a study by Kim and Han (3), severe motor dysfunction suggestive of excessive corticospinal tract damage at admission was a predictor of poor prognosis; this is consistent with our findings that ventral MI and MMI+C usually cause motor dysfunction due to involvement of the pyramidal tract. In another study of 37 MI patients, more rostral lesion locations in LMI was correlated with a poorer 90-day outcome (mRS $\geq$ 2), while more dorsal lesion locations in MMI was correlated with a poorer 90-day outcome (6). This is probably because even without hemiplegia or quadriplegia, culprit lesions with persisting dysphagia affect the activities of daily living and increase the risk of pneumonia, which is a prognostic factor for MI.

In a study of 81 consecutive patients with acute isolated MI, large artery atherosclerotic occlusive disease and dissection compared with penetrating artery disease were independently correlated with poor outcome (mRS $\geq$ 2 and/or dysphagia) in LMI. Moreover, large artery atherosclerotic occlusive disease was significantly correlated with poor outcome in MMI (9). However, in our study, artery-to-artery embolism was a predictor of all-cause death during follow-up. Hyperintense plaques and a higher prevalence of plaque surface irregularity were more frequently observed in artery-to-artery embolism group by whole-brain high-resolution magnetic resonance imaging; this suggests that artery-to-artery embolic infarction is associated distinct vulnerable plaque characteristics (26). Early detection and treatment of rupture-prone vulnerable atherosclerotic plaques is critical to reduce mortality associated with cardiovascular disease (27). These findings are noteworthy, and further research is required to elucidate the exact relation between the presumed stroke mechanism and poor outcomes. Increasingly, novel imaging techniques have been applied to evaluate poor outcomes in MI patients. In a study of 34 MI patients, 18 had a normal perfusion status, while 16 had perfusion defects in the medulla and/or inferior cerebellum; on multivariate analysis, abnormal perfusion weighted imaging and DWI patterns were independently associated with poor early and late outcomes (mRS $\geq$ 3) following MI (28).

Some limitations of our study should be considered while interpreting the findings. First, arterial lesions were determined based on MRA, which is liable to show flow-related artifacts. Second, data pertaining to clinical features were retrospectively obtained from medical records. Third, there were a small number of patients with some types of MI (such as HMI and MMI+C) owing to their rarity; this may have introduced an element of bias. Fourth, the study excluded some important cases which may limit the applicability of our findings when discussing the prognosis with the caregivers of patients. Finally, the outcomes were assessed using the mRS. In fact, mRS is not an ideal tool to assess the outcomes of LMI. Although LMI patients may be categorized as having good outcomes based on mRS score, they often have severe sensory loss, central pain, or dizziness that are not reflected with mRS. However, currently, there are no better scales for assessment of long-term outcomes of stroke patients.

CONCLUSIONS

In this study of a large cohort of MI patients, the clinical symptoms, signs, prognosis, and imaging findings of rostro-caudal and ventro-dorsal medulla were found to be different. A large proportion of patients showed poor long-term prognosis (21.2%), while the all-cause mortality rate was 10.6%. Age $\geq$ 65 years, dysphagia, recurrent stroke, and MMI+C were risk factors for poor prognosis and death.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the first affiliated hospital of Henan University of CM. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DZ and SY researched literature and conceived the study. QM, MY, HZ, and XL were involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. DZ and JZ wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.615230/full#supplementary-material

The lost to follow up data as followed (25 patients): There were 13 males and 12 females, and the mean age was 63.2 ± 11.3. There were 11 lateral medullary infarctions (LMI), eight medial medullary infarctions (MMI), five lateral medullary infarction plus cerebellum infarctions (LMI+C), and one bilateral medial medullary infarction (BMMI).

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BRIEF RESEARCH REPORT
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Bilateral Vertebral Artery Hypoplasia and Fetal-Type Variants of the Posterior Cerebral Artery in Acute Ischemic Stroke

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Aim: Unilateral vertebral artery hypoplasia is considered a risk factor for posterior circulation infarction. Despite the increasing attention on unilateral vertebral artery hypoplasia, few studies have discussed bilateral vertebral artery hypoplasia, its influence on stroke, or its collateral supply from the circle of Willis. We aimed to identify its characteristics, stroke pattern, and unique ultrasonographic and brain imaging findings.

Materials and Methods: Of the 1,301 consecutive in-patients diagnosed with acute ischemic stroke from January 2013 to December 2015, medical and laboratory data and stroke or transient ischemic attack history were recorded. We enrolled patients who underwent both brain magnetic resonance imaging and sonography examinations. Vertebral artery and posterior cerebral artery analyses were conducted in accordance with clinical criteria.

Results: Adequate imaging data were available for 467 patients. Of these, eight patients met the criteria for bilateral vertebral artery hypoplasia. The mean age was 62.9 ± 12.1 years. There were six male (75.0%) and two female patients (25.0%). A high prevalence of hypertension (7/8, 87.5%) was noted.
Sonograms displayed a very low net flow volume in the vertebral arteries, with the average net flow volume being 28.9 ± 9.7 mL/min. A high frequency (6/8; 75.0%) of the fetal variant posterior cerebral artery from the carotids was found. The infarction patterns in these patients were all bilateral, scattered, and in multiple vascular territories.

Conclusion: Patients with bilateral vertebral hypoplasia displayed a unique collateral supply, special stroke pattern, and younger stroke onset. Early recognition and stroke prevention should be considered critical in clinical practice.

Keywords: posterior circulation infarction, vertebral artery hypoplasia, posterior cerebral artery, vertebrobasilar insufficiency, ultrasonagraphy

INTRODUCTION

Posterior circulation is comprised of two vertebral arteries that join to form a single basilar artery at the level of the pons. The basilar artery divides into two posterior cerebral arteries at the level of the midbrain (1–3). Conventionally, the major hemodynamics of this area is supplied by the net flow of the vertebral arteries and partially by the collateral flow from the spinal arteries or the fetal-type posterior cerebral artery (1, 4).

Case series studies suggest that vertebral artery hypoplasia (VAH) may contribute to posterior ischemic events, especially in patients with other cerebrovascular risk factors (5, 6). The concept of regional hypoperfusion is associated with unilateral VAH and posterior circulation stroke (7). The risk of posterior ischemia is related to an increasing degree of VAH (5, 6, 8), regardless of the net flow (7). Although an increasing number of studies highlight the importance of unilateral VAH on ischemic stroke (5, 6, 8, 9), literature discussing the influence of bilateral VAH on ischemic stroke is limited (10, 11).

With regard to bilateral VAH, low flow volume in a single vertebral artery as well as inadequate net flow volume in the basilar artery ensues. Because of the chronic nature of congenital hypoplasia, the clinical symptoms and stroke patterns of this vascular disorder would differ from unilateral VAH. Chronic inadequate posterior circulation leads to the development of intracranial and extracranial collateral flow (10, 12). Recently, a case series paper correlated the fetal-type posterior circle of Willis with vertebrobasilar hypoplasia (12, 13).

In order to identify obscure clinical features, we reviewed the characteristics of patients with bilateral VAH by analyzing their clinical presentations, stroke patterns, risk factors, and the hemodynamics of collateral flow using ultrasonography and brain magnetic resonance imaging (MRI).

MATERIALS AND METHODS

Patients

This is a retrospective, observational cross-sectional study. We reviewed 1,301 consecutive in-patients diagnosed with acute ischemic stroke at the Chung Shan Medical University Hospital from January 2013 to December 2015.

Upon admission, the series examination included an MRI, sonography exam, and a stroke risk factor survey. Patients who did not receive a brain MRI or sonography exam were excluded.

Patient medical and laboratory data were recorded; this included the age, sex, presence of systemic diseases, renal function, lipid profile, drug use, electrocardiogram, and history of previous stroke or transient ischemic attacks and related clinical manifestations.

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital, Taichung, Republic of China.

MRI

The infarction lesions were identified and classified by vascular territory according to MRI and three-dimensional time of flight (3D TOF) magnetic resonance angiography (MRA) examinations. A 3-T MRI system (Siemens, Germany) with the following settings was used T2-weightedimages, TR/TE 6000/100 ms, diffusion-weighted images TR/TE 5100/60 ms, and 3D TOF TR/TE20/4 ms. The locations of ischemic stroke were categorized as proximal (medulla and posterior inferior cerebellum), middle (pons and anterior inferior cerebellum), and distal (rostral brainstem, superior cerebellum, and occipital and temporal lobes) intracranial posterior circulation territories (14, 15).

A fetal type posterior cerebral artery (PCA) was classified as complete or partial according to MRA (12, 13). A complete fetal-type PCA is considered if the P1 segment is not visualized, and a partial fetal-type PCA is considered if the P1 segment is smaller than the posterior communicating artery on brain MRI.

The basilar artery hypoplasia (BAH) was defined as a basilar artery (BA) diameter <2 mm. The BA diameter was calculated on TOF source images at the mid-pons level. Vascular dissection was diagnosed if intramural hematoma, intimal flap, the pearl-and-string, or the double lumen signs were visualized on MRI.

Brain images were reviewed by neuroradiologists and neurologists, with the former interpreting the fetal-type PCA.

Sonography

Color-coded carotid duplex and transcranial color-coded duplex examinations were reviewed for all enrolled patients. Intracranial and extracranial vessels conducted by experienced technicians using an IE-33 system (Philips Medical System, USA), equipped with a 2.0-MHz transducer. Routine measurements included thorough examinations of the bilateral neck carotid and transforaminal windows. The angle between the ultrasound beam and the direction of blood flow was adjusted manually. Blood flow examinations were targeted at the V2 and V4 segments of the vertebral artery as well as the region proximal to the distal basilar artery. The diameter and flow volume of each extracranial vertebral artery, as well as the mean velocity, and pulsatility index of the intracranial vertebrobasilar arteries were recorded and analyzed. VAH was defined according to sonographic criteria (4, 16, 17), including a $\leq$2.2 mm diameter over the V2 segment or a decreased vertebral flow volume of $\leq$30 mm/s. Bilateral VAH was defined as both vertebral arteries meeting the sonographic criteria of VAH and there was no evidence of dissection findings on MRI.

Statistics

All statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). Continuous data is expressed as mean$\pm$SD.

RESULTS

Of the 1,301 patients diagnosed with acute ischemic stroke, 467 (149 pateints with posterior circulation infarction) underwent both MRI and sonographic examinations and were enrolled in the present study. In patients with posterior circulation, 80 of them met the criteria of unilateral VAH. Eight of the enrolled patients met the diagnostic criteria for bilateral VAH. The mean BA diameter was 2.68 $\pm$ 0.20 mm (range from 2.29 to 3.08 mm).

In our study, the frequency of bilateral VAH was 1.7% (8/467), which is similar to that found in previous studies (11, 18). The characteristics of patients with bilateral VAH are listed in **Table 1**.

TABLE 1 | Demographic and clinical characteristics of eight patients with bilateral vertebral artery hypoplasia.

	Bilateral hypoplasia ($n = 8$)	Range
Age on stroke, years, mean ±SD	62.9 ± 12.1	46–87
Gender(male), n (%)	6 (75%)	
Hypertension, n (%)	7 (87.5%)	
Diabetes, n (%)	2 (25%)	
Hyperlipidemia, n (%)	1 (12.5%)	
Smoking, n (%)	2 (25%)	
Alcohol, n (%)	2 (25%)	
Renal function, eGFR(mg/dL)	77.3 ± 25.8	29–119
Atrial fibrillation or heart disease, n (%)	0 (0%)	

SD, standard deviation; Egfr, estimated glomerular filtration rate.

TABLE 2 | Total VA flow volume, onset age and stroke location analysis in bilateral, unilateral, or non-vertebral artery hypoplasia groups.

	Non-VAH (61 cases)	Unilateral-VAH (80 cases)	Bilateral-VAH (8 cases)
Total VA flow volume	132.9 ± 31.8 mL/min	71.4 ± 21.1 mL/min	28.9 ± 9.7 mL/min
Stroke onset age	66.6 ± 11.5	72.4 ± 10.2	62.9 ± 12.9
Multiple vascular territory infarctions	9/61 (14.7%)	17/80 (21.2%)	5/8 (62.5%)

VAH, vertebral artery hypoplasia; VA, vertebral artery.

There were six male (75.0%) and two female patients (25.0%). The average age was 62.9 years (range, 46–87). None of these patients had atrial fibrillation or heart disease. A high prevalence of hypertension (7/8, 87.5%) was noted. The prevalence of other stroke risk factors, including diabetes mellitus, dyslipidemia, smoking, and alcohol consumption ranged from 12.5 to 25.0%. We compared net flow volume, onset age, and stroke location analysis in bilateral VAH, unilateral VAH, and non-VAH groups, listed in **Table 2**. The mean net flow volume was 28.9 ± 9.7 mL/min, which is below the criteria of vertebrobasilar insufficiency (<100 mL/min) (7), and the defined value of unilateral VAH (30 mL/min) (16). In the bilateral VAH group, we found their onset age was younger and with more multiple vascular territory lesions.

The distribution of stroke and individual PCA types is listed in **Table 3**. Most of the infarctions were bilateral and multiple (5/8, 62.5%). A fetal-type PCA was recognized in six patients (6/8, 75.0 %), two with a complete bilateral, two with a partial bilateral, and two with a complete unilateral fetal-type PCA.

DISCUSSION

The prevalence of VAH ranges from 4 to 7% in the normal population (6, 7, 17). In posterior circulation stroke, the prevalence is increased to more than 40% according to different clinical studies (5, 18). Bilateral VAH is recognized in 1.6 to 3.4 % of patients with ischemic stroke (9, 18).

In our previous study, compared to anterior circulation infarction, there was a significantly higher frequency of VAH in posterior circulation infarction (22.38 vs. 44.75%, $p < 0.0001$) (7). Literature has demonstrated that VAH plays an important role in posterior circulation stroke (5–7, 9).

TABLE 3 | Infarction region and clinical manifestation of stroke in patient population.

Age	Gender	Infarction territory	Brain territory locations	PCA type	Initial manifestation at stroke
41–50	Male (Patient 1)	Pons, midbrain and bilateral cerebellum hemisphere	*P+M+D	Bilateral fetal type	Dizziness and unsteady gait
	Male (Patient 2)	Left PICA territory (lateral medulla)	P	Bilateral partial fetal type	Right limb paresthesia
51–60	Male (Patient 3)	Right medulla, pons, and cerebellum	P+M	Right fetal type	Dizziness, diplopia and left facial paresthesia
	Female (Patient 4)	Left pons and bilateral cerebellum hemisphere	P+M+D	Bilateral partial fetal type	Dizziness and unsteady gait
61–70	Male (Patient 5)	Left pons and left anterior medulla and right vermis	P+M+D	Non-fetal type	Right hemiparesis and unsteady gait, lethargy
	Male (Patient 6)	Left thalamus and left occipital lobe	D	Right fetal type	Blurred vision and right hemiparesis and right paresthesia
71–80	Male (Patient 7)	Bilateral pons (right>left), midbrain, and bilateral cerebellar hemisphere	P+M+D	Non-fetal type	Severe dysarthria and left hemiplegia
81–90	Female (Patient 8)	Bilateral pons and cerebellar hemisphere	M+D	Bilateral fetal type	Dysarthria, dysphagia, and unsteady gait

**P, proximal; M, middle; D, distal posterior circulation territory.*

In this study, we found that patients with bilateral VAH developed stroke at a younger age (six patients <66 years) than the mean age of ischemic stroke, which ranges from 66 to 70 years (19), and other groups with posterior circulation infarctions (**Table 2**). The prevalence of hypertension in this group was significantly higher than the general stroke population (20). Cerebral autoregulation for chronic vertebrobasilar insufficiency may explain the blood pressure response (21).

Table 3 displays the initial manifestation of the patient population, which included dizziness, severe dysarthria, hemiplegia, and ataxia. In unilateral VAH-related stroke, the location of the infarct is usually limited to the territory of the ipsilateral artery, particularly in lateral medullar infarction and posterior inferior cerebellar artery infarction (2, 22, 23). In bilateral VAH, the infarction territory was mostly bilateral, involving multiple vascular territories, despite receiving collateral blood supply from the fetal-type PCA (**Table 3** and **Figure 1**). The clinical presentation of these patients illustrates the high variability and burden of posterior circulation infarction. Most cases of multiple infarctions resulted in severe handicap or coma; therefore, it is important to detect at-risk patients.

Scattered brain infarction is usually related to cardioembolic stroke or artery-to- artery embolism (24); however, no patients in our population had atrial fibrillation, other heart disease, or significant atherosclerosis across the major arteries, suggesting the effect of hypoperfusion in bilateral VAH-related stroke. Several studies reported unilateral VAH to be associated with relative hypoperfusion in the dependent vascular territory (5, 7). According to the extracranial ultrasonography of our patient group, the mean (±SD) of the total vertebral flow volume was low(28.9 ± 9.7 mL/min, **Table 2**), compared with the non-VAH or unilateral VAH group (**Table 2**), which suggest severe hypoperfusion of the vertebrobasilar system, and as a consequence, development of an earlier and more severe posterior circulation infarction (**Table 2**).

In this study, bilateral VAH evolving into a smaller basilar artery (mean BA diameter 2.68 ± 0.20 mm, range from 2.29 to 3.08 mm) was recognized. Artery to artery embolism from vertebrobasilar hypoplasia would also contribute to scattered infarctions. Literature has demonstrated (25) BAH was associated with pontine infarction and VAH was associated with the medulla and inferior cerebellum. Emboli were known to preferentially reach the distal posterior circulation arteries (14). However, it is difficult to recognize the true origin of embolism since the artery to artery embolism and large artery hemodynamic should be one of concern.

For the treatment of bilateral VAH, early preventive drugs for ischemic insults, including antiplatelet or anticoagulant drugs, could be considered in symptomatic patients. Reconstruction of the blood supply, such as bypass surgery, would be another option (26).

Conventionally, a fetal-type PCA was thought to be a normal variant and common in the general population; however, in some reports this vascular type was associated with a higher risk for ischemic stroke, both in the anterior and posterior circulation (3, 4, 27, 28). Until now, its significance has been under debate.

In the literature, the incidence of a unilateral and bilateral fetal-type PCA ranged from 4 to 26% and 2 to 4%, respectively (13, 27, 28). Studies state commonly reported symptoms in patients with a fetal-type PCA to be dizziness, headache, and focal neurological deficits (3, 28). In our population, 75% of patients with bilateral VAH also displayed a fetal-type PCA, illustrating a sizable co-existence (75%) of bilateral VAH and a unilateral or bilateral fetal-type PCA. This finding corresponds to findings from previous studies that suggest the simultaneous occurrence of a hypoplastic vertebrobasilar system and fetal-type circle of Willis, and the increased development of ischemic events in the posterior circulation (3, 12).

From an embryological perspective, due to the delayed development of the P1 segment, the PCAs are supplied by the internal carotid arteries via the posterior communicating arteries temporally.

Typically, an adult PCA is complete at 6–7 weeks of embryological development (29). Inadequate flow of the basilar PCA system may interrupt the normal development of the PCA. Nevertheless, it is not clear how a fetal-type circle of Willis responds to unilateral VAH (30) or significantly inadequate basilar flow (in this study), or how it evolves to the adult configuration, which leads to a higher risk for both anterior and post-ischemic strokes (12, 27). However, the significance and pathophysiology of a fetal-type PCA in stroke remains unclear. Further comprehensive research is necessary.

In this study, most patients with bilateral VAH displayed a fetal variant of the PCA, supplied from the anterior circulation via the posterior communicating artery segment. However, with such hemodynamic compensation, supplementation via the fetal-type PCA still failed to support the vertebrobasilar system, resulting in a multifocal scattered infarction in the posterior circulation.

There were several limitations in this study. First, the case number of bilateral VAH is small, and we enrolled our samples from in-patients and not in healthy subjects. Overestimated frequencies and symptoms of bilateral VAH would be suspected. Because we applied the duplex ultrasonographic criteria of VAH, stenosis over the VA orifice or decreased VA flow volume due to atherosclerosis stenosis is a possible trap as applying the sonographic criteria of VAH diagnosis. Compared evaluation of the contrast-enhanced MRA images at the same time would result in a more reliable diagnosis.

CONCLUSION

We evaluated the clinical and vascular characteristics of patients with stroke and bilateral VAH. We found a younger age at stroke onset, obvious hypertension, bilateral and multiple vertebrobasilar infarcts, and a high prevalence of the fetal PCA in our enrolled patients.

Clinically, bilateral VAH may pose a significant risk to the posterior circulation; therefore, early detection and prevention are crucial in this patient group.

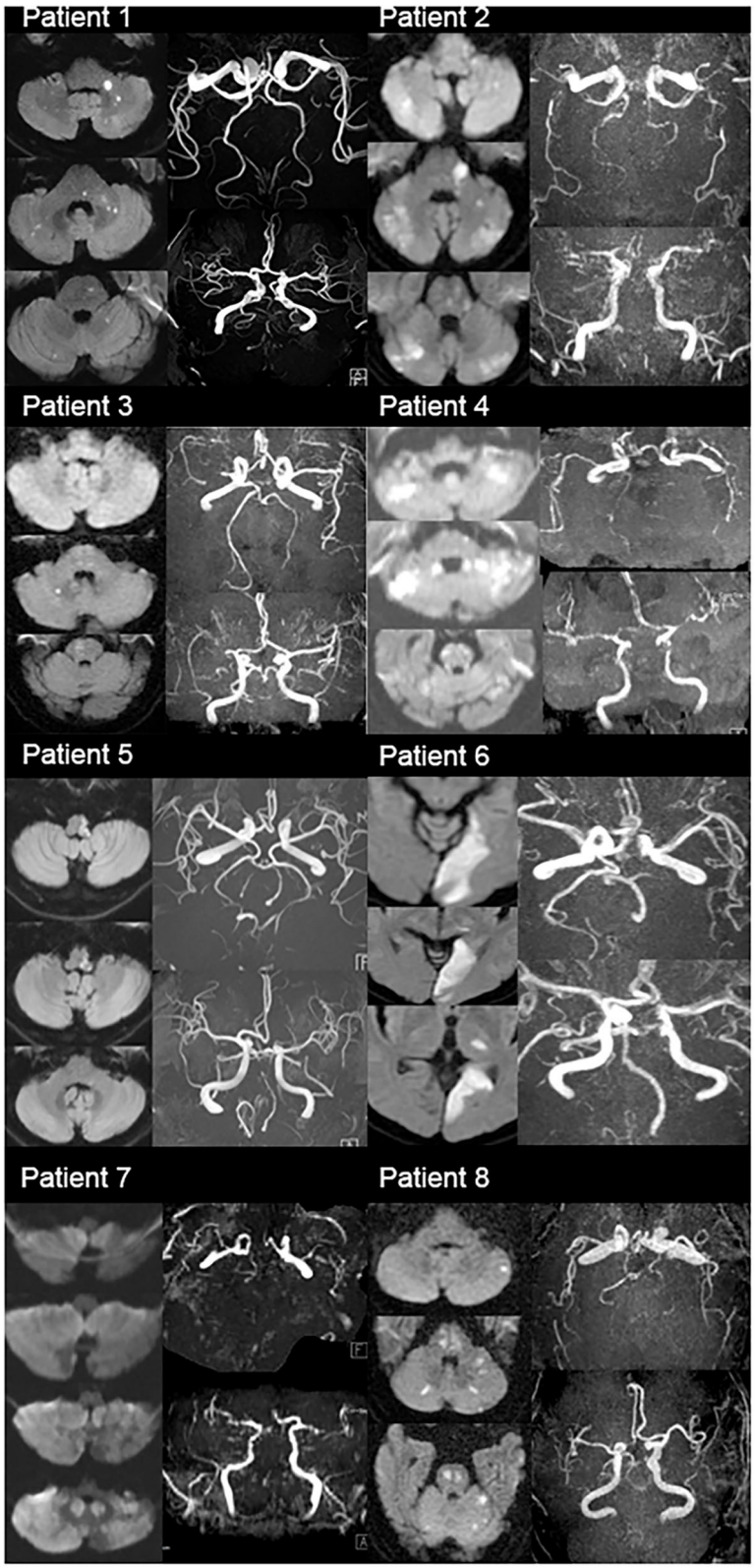

FIGURE 1 | MRI diffusion-weighted images (DMI) and MRA images of total eight patients (MRI DWI showed multiple infarctions in these patients; MRA showed fetal type PCA, vertebral hypoplasia, small caliber of basilar artery, or invisible vertebrobasilar arteries).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Chung Shan Medial University Hospital, Taichung, Republic of China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

H-YC designed the study. C-FH, K-WC, C-HS, and C-YS collected and organized data. C-FH and H-YC analyzed and interpreted the data. All authors read and approved the final manuscript.

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Comatose With Basilar Artery Occlusion: Still Odds of Favorable Outcome With Recanalization Therapy

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Background: Around 30–60% of patients with basilar artery occlusion (BAO) present with coma, which is often considered as a hallmark of poor prognosis.

Aim: To examine factors that will help predict outcomes in patients with BAO comatose on admission.

Methods: A total of 312 patients with angiography-proven BAO were analyzed. Comas were assessed as Glasgow Coma Scale (GCS) of ≤8 or impaired level of consciousness ascertained in the medical records. Outcomes were evaluated with the modified Rankin Scale (mRS) over a phone call at 3 months. In our study, 53 patients were excluded due to inadequate data on the level of consciousness.

Results: In total, 103/259 (39.8%) of BAO patients were comatose on admission. Factors associated with acute coma were higher age, coronary artery disease, convulsions, extent of early ischemia by posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) < 8, absence of patent posterior collateral vasculature, and occlusion over multiple segments of BA. A total of 21/103 (20.4%) of comatose patients had a favorable outcome (mRS 0–3), and 12/103 (11.7%) had a good outcome (mRS 0–2). Factors associated with a favorable outcome in comatose BAO patients were younger age ($p = 0.010$), less extensive baseline ischemia ($p = 0.027$), recanalization ($p = 0.013$), and avoiding symptomatic intracranial hemorrhage (sICH) ($p = 0.038$). Factors associated with the poorest outcome or death (mRS 5–6) were older age ($p = 0.001$), diabetes ($p = 0.022$), atrial fibrillation ($p = 0.016$), lower median GCS [4 (IQR 3.6) vs. 6 (5–8); $p = 0.006$], pc-ASPECTS < 8 ($p = 0.003$), unsuccessful recanalization ($p = 0.006$), and sICH ($p = 0.010$). Futile recanalization (mRS 4–6) was significantly more common in comatose patients (49.4 vs. 18.5%, $p < 0.001$).

Conclusions: One in five BAO patients with acute coma had a favorable outcome. Older patients with cardiovascular comorbidities and already existing ischemic lesions before reperfusion therapies tended to have a poor prognosis, especially if no recanalization is achieved and sICH occurred.

Keywords: basilar artery, outcome, coma, stroke, recanalization therapy

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INTRODUCTION

Basilar artery occlusion (BAO) accounts for 1% of all ischemic strokes but is still often considered the most appalling form of stroke (1, 2). The clinical picture of BAO varies greatly, and roughly 30–60% of patients present with the most shocking state, being comatose on admission (3–10). This initial coma or imminent locked-in state results typically from dense pontine ischemia, which anatomically encompasses essential areas forming the reticular activating system responsible for sustaining consciousness and motor pyramidal tracts (1, 11).

Indeed, in the face of the poor outcome reported to be associated with progressing pontine ischemia and depressed consciousness, acute coma in BAO, a discrete clinical entity, is one of the most challenging emergencies to be coped with by the emergency department (ED) attending neurologists and other acutologists (6, 12). However, it has also been reported that, with successful recanalization therapy, up to 15–26% of these patients presenting comatose on admission will eventually have a favorable outcome [modified Rankin Scale (mRS) 0–3] (6, 13, 14).

Which clinical signs, imaging characteristics and presumptive biomarkers could be used to assist in early risk stratification supporting initial management decisions, i.e., aggressive or de-escalated supportive therapy, and guide pressing interactions with the close ones? Mortality among intubated and mechanically ventilated stroke patients is high, yet the treatment decisions are not simple. It is one of the greatest challenges in the acute setting to estimate the prognostic potential to life "worth living" and the extent of treatments worth giving (15). Coma on presentation has been one negative prognostic marker to influence such decisions, especially regarding invasive therapies (4). Neurologists managing these patients often lack urgent directions in making these fundamental care decisions, for which this analysis was performed.

BAO carries high mortality of up to 95% if recanalization does not occur (1, 2, 7). Pallesen et al. (6) reported brainstem ischemia to be an important factor in predicting mortality in comatose BAO patients, which underlines the need for the early reversal of BAO with intravenous thrombolysis (IVT) or endovascular treatment (EVT). However, according to our knowledge, the baseline characteristics potentially predicting the outcome after BAO patients presenting with coma have never been systemically examined. This led us to carry out the present investigation in our sizable consecutive cohort of BAO patients treated with IVT and/or EVT.

AIM OF THE STUDY

We set out to examine factors that would help in predicting the outcome in BAO patients presenting with acute coma on admission.

METHODS

Patients

A total of 312 consecutive patients with angiography-proven BAO, treated between June 1995 and September 2019 in the Department of Neurology, Helsinki University Hospital, were analyzed. Coma was assessed as Glasgow Coma Scale (GCS) of $\leq$8 either in emergency medical service (EMS) records or at ED (whichever is lowest) before initiation of recanalization therapy. In subjects where GCS was not routinely reported, the level of consciousness was ascertained from the medical records describing the detailed responsiveness of the patient. In essence, the patient was defined as "comatose" if the level of consciousness was documented to be clearly impaired or if there was a need for intubation due to a low level of consciousness. We do performed endovascular intervention in the majority of the cases under conscious sedation, and if a patient was intubated only to perform neurointerventional therapy or neuroimaging, and not because of the low level of consciousness, the patient was not defined as "comatose." As the level of consciousness on presentation could not be ascertained reliably due to insufficient EMS records and/or patient medical records, 53 patients were excluded.

Patient data, including also the 3-month follow-up assessment, were collected as a part of routine hospital care, and approval from an ethics committee or informed consent were thus not required to collect and reconcile retrospective clinical data in our institution. National Institutes of Health Stroke Scale (NIHSS) score is obtained for all acute recanalization patients on admission but since its determination may be interfered with by a low level of consciousness and possible anesthetic sedation, we excluded it from the analyses. The BAO "phenotype" was defined as a sudden or progressive onset of symptoms, as previously described (1).

Imaging

Imaging was performed on admission for all patients with either computed tomography (CT) or magnetic resonance imaging (MRI) accompanied by CT angiography (CTA), MR angiography (MRA), or digital subtraction angiography (DSA). Control imaging was obtained ∼24 h after treatment and whenever clinical deterioration occurred. The extent of baseline ischemia was evaluated with the posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS) (16) (**Figure 1**).

Occlusion length was dichotomized to either "long," consisting of two or more basilar artery segments (proximal, middle, and distal), or "short," consisting of one segment. Whether occlusion extended to the vertebral artery (VA) was also analyzed. Recanalization was assessed from controlled angiography images and dichotomized as partial to complete [thrombolysis in myocardial infarction (TIMI) score 2–3] or nil to minimal (TIMI 0–1) (17). Futile recanalization was defined as successful recanalization with no clinical benefit demonstrated as an mRS score 4–6 at 3 months (18).

Collateral vasculature was assessed from baseline angiography images by identifying the presence and number of posterior communicating arteries (PCom) and the presence of at least one superior cerebellar artery (SCA) and posterior cerebral artery (PCA). Symptomatic intracranial hemorrhage (sICH) was defined according to European Cooperative Acute Stroke Study II (ECASS II) criteria (19). Radiological data were analyzed by an experienced neuroradiologist (HS/PV/OS).

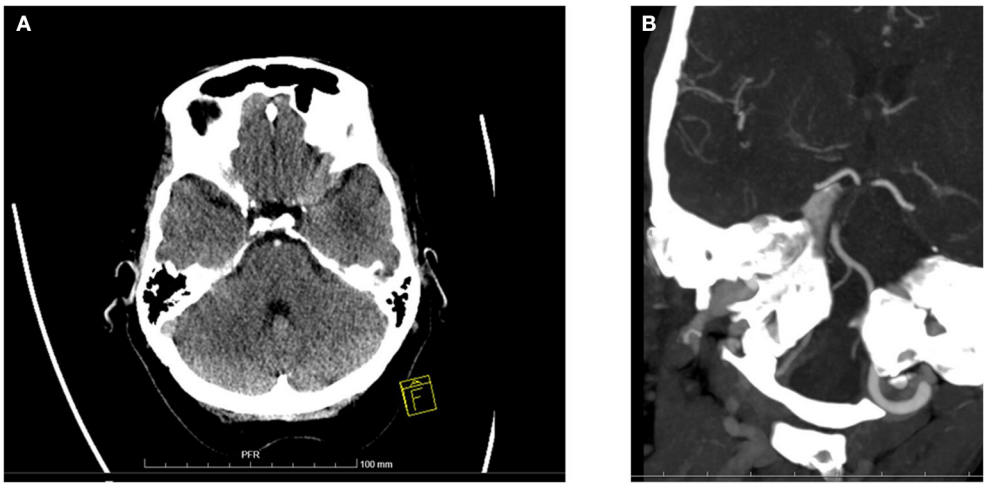

FIGURE 1 | Baseline ischemic changes and basilar artery occlusion in computer tomography. **(A)** A 69-year-old woman was comatose on admission (GCS 4) and diagnosed with basilar artery occlusion. This baseline CT scan shows extensive ischemic changes in both cerebellar hemispheres and bilaterally in pons. Overall pc-ASPECTS was 5. A dense basilar artery is also seen. Patient received IVT but died on day 3 of hospitalization. **(B)** A 65-year-old woman was comatose on admission (GCS 6). Baseline CTA shows long BAO over mid- and caudal BA. IVT was administered and subsequent mechanical thrombectomy was performed with successful recanalization. Patient recovered with a 3-month mRS of 1.

Outcome

The outcome was measured with an mRS obtained at 3 months by a certified neurologist. It was then dichotomized as favorable (mRS 0–3) vs. poor (mRS 4–6). An mRS score of 3 was considered still favorable due to the abysmal natural course of BAO, and this is unlike anterior circulation, where an mRS 0–2 is most often regarded as a favorable outcome. Secondary outcome measures were a good outcome (mRS 0–2) and being bedridden or dead (mRS 5–6) at 3 months. Mortality was also analyzed.

Statistical Analyses

Dichotomous variables were analyzed with Pearson's chi-square test or Fisher's exact test when appropriate. The distribution of continuous variables was tested for normality and analyses were performed with *t*-test for normally distributed or with Mann-Whitney U-test for non-normally distributed variables. Multivariable analysis of factors associated with coma was made with a stepwise backward logistic regression model, and variables with probability (p) value < 0.1 in univariate model were included in order to avoid selection bias and overfitting. For factors associated with favorable outcomes in comatose patients, no multivariable model was possible to construct due to the small number of subjects. Therefore, only the univariate model was built. SPSS 25 (IBM, Armonk, NY, USA) was used in all statistical analyses.

RESULTS

Among the cohort of 259 BAO patients, 103 (39.8%) presented comatose (GCS ≤ 8) on admission. 85/103 (82.5%) of comatose patients were intubated. For all of them, the reason for intubation was a poor clinical condition or securing the airway because of impaired consciousness. In total, 35 patients (13.5%) had baseline imaging with MRI, and the remaining majority underwent CT scans. Patient characteristics are shown in **Table 1**. Comatose patients tended to be older, had more frequent histories of coronary artery disease and myocardial infarctions, and were more likely to present with convulsions. Regarding brain imaging findings of the posterior circulation area, patients with initial coma had more often extensive baseline ischemic lesions as evaluated with pc-ASPECTS < 8 (29.1 vs. 11.6%, $p < 0.001$) and more often radiological signs of bilateral ischemia (35.3 vs. 14.5%, $p < 0.001$).

In vascular imaging of the posterior circulation, collateral circulation was less complete in comatose patients as compared to non-comatose patients with absence of patent PComs of the circle of Willis in 29.0 vs. 13.6% ($p = 0.003$) and absence of SCAs in 42.0 vs. 22.4% ($p = 0.001$), respectively. Comatose patients also had multiple segments (≥ 2) of BA occluded and a higher incidence of occlusions extending to the vertebral artery (VA) (**Table 1**).

There was no difference in the rate of EVT or IVT between comatose and non-comatose patients, and the vast majority underwent IVT (90.3%). There were only three patients not treated with recanalization therapy. In detail, there was one patient with spontaneous recanalization in DSA and 3-month mRS 3, one patient with EVT attempt but no successful thrombectomy due to difficult stenosis and no access with thrombectomy device (mRS 6), and another with only IVT bolus administered but discontinued infusion due to a history of malignancy (mRS 4). Treatment delays did not differ between comatose and non-comatose BAO patients (**Table 1**).

In multivariable analysis (**Table 2**) factors independently associated with acute coma in BAO, patients were of older age, had a history of coronary artery disease, convulsions, presence

TABLE 1 | Characteristics of comatose vs. non-comatose patients at presentation.

n (%)/median (IQR)	All ($n = 259$)	Non-comatose ($n = 156$, 60.2%)	Comatose ($n = 103$, 39.8%)	*p*
Demographic and clinical characteristics				
Male sex	169 (65.3%)	106 (67.9%)	63 (61.2%)	0.262
Age (years)	68 (59–77)	64 (58–75)	73 (63–79)	**<0.001**
Diabetes	42 (16.2%)	24 (15.4%)	18 (17.5%)	0.655
Atrial fibrillation	60 (23.2%)	31 (19.9%)	29 (28.2%)	0.122
Hypertension	149 (57.5%)	85 (54.5%)	64 (62.1%)	0.223
Dyslipidemia	106 (40.9%)	64 (41.0%)	42 (40.8%)	0.968
Chronic heart failure	22 (8.5%)	10 (6.4%)	12 (11.7%)	0.139
Coronary artery disease	46 (17.8%)	21 (13.5%)	25 (24.3%)	**0.026**
History of myocardial infarction	26 (10.0%)	11 (7.1%)	15 (14.6%)	**0.049**
Previous stroke	63 (24.3%)	38 (24.4%)	25 (24.3%)	0.987
Sudden onset phenotype	214 (82.6%)	125 (80.1%)	89 (86.4%)	0.192
Prodromal symptoms	56 (21.6%)	37 (23.7%)	19 (18.4%)	0.313
Convulsions	37 (14.3%)	12 (7.7%)	25 (24.3%)	**<0.001**
Radiological parameters				
pc-ASPECTS < 8	48 (18.6%)	18 (11.6%)	30 (29.1%)	**<0.001**
Bilateral ischemia	58 (22.8%)	22 (14.5%)	36 (35.3%)	**<0.001**
Brainstem ischemia	48 (18.9%)	24 (15.8%)	24 (23.5%)	**0.122**
No patent PComs	49 (19.8%)	20 (13.6%)	29 (29.0%)	**0.003**
2 PComs	132 (53.4%)	89 (60.5%)	43 (43.0%)	**0.007**
At least one patent PCA	233 (94.3%)	138 (93.9%)	95 (95.0%)	0.708
At least one patent SCA	172 (69.6%)	114 (77.6%)	58 (58.0%)	**0.001**
Long BAO (≥2 segments)	100 (40.0%)	47 (31.5%)	53 (52.5%)	**0.001**
BAO exceeding to VA	59 (23.7%)	27 (18.1%)	32 (32.0%)	**0.012**
Treatments				
IVT	234 (90.3%)	141 (90.4%)	93 (90.3%)	0.980
EVT	75 (29.0%)	45 (28.8%)	30 (29.1%)	0.961
IVT + EVT	53 (20.5%)	32 (20.5%)	21 (20.4%)	0.981
Time delays (min)				
OTT	252 (138–720)	238 (125–780)	282 (158–640)	0.334
SDT	155 (78–451)	152 (75–474)	158 (85–371)	0.659
DTN	51 (25–195)	85 (38–180)	65 (30–185)	0.060

Data available in >95% for all parameters. IQR, interquartile range; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PCom, posterior communicating artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; BAO, basilar artery occlusion; VA, vertebral artery; IVT, intravenous thrombolysis; EVT, endovascular treatment; OTT, Onset-to-treatment time, SDT, symptom-to-door time; DTN, Door-to-needle time.
Statistically significant p-values (<0.05) are bolded.

of extensive baseline ischemia, absence of PComs and SCAs, and long BA occlusion.

Initial coma was associated with poor outcome, and 79.6% of comatose patients had an mRS 4–6 at 3 months compared to 38.4% among non-comatose patients ($p < 0.001$). Overall, 59.2% of comatose patients died within 3 months (**Table 3**), and 72.8% of patients with initial coma were either bedridden or died (mRS 5–6) at 3 months, which compared to the 28.5% of non-comatose patients ($p < 0.001$). Of the comatose patients, 13.6% had an mRS of 5 at 3 months. However, up to 20.4% of comatose patients still had a favorable outcome (mRS 0–3), and 11.7% had a good outcome of mRS 0–2 at 3 months. There was no significant difference in rates of recanalization between comatose and non-comatose patients, but futile recanalization (mRS 4–6) was significantly more common in comatose patients (49.4 vs. 18.5%, $p < 0.001$). There was a trend toward a higher rate of post-treatment sICH in comatose patients (13.9 vs. 7.8%), but this was not statistically significant ($p = 0.117$).

An exact GCS score was available for 83/103 of comatose patients. A total of 19 patients had GCSs scores of three. The GCS was four in 18 patients, five in 15 patients, six in 11 patients, and seven in 14 patients. Only six patients had GCS score of eight. In total, 3/19 (15.8%) of patients with a GCS score of three had an mRS 0–3 at 3 months. The rest of these patients (16/19, 84.2%) had the poorest outcome of an mRS of 5–6, and 13 of them (68.4%) were dead at 3 months. Half of the patients with GCS score of eight had an mRS 0–3 at 3 months, one died, and two had the poorest outcome (mRS 5–6).

Characteristics associated with favorable outcomes in patients with initial coma are shown in **Table 4**. Patients with favorable

3-month outcome were younger [median age 65 (IQR 57–74) vs. 74 (66–80) years, $p = 0.010$] and displayed less frequent extensive baseline ischemic lesions (pc-ASPECTS < 8 in 9.5 vs. 34.1%, $p = 0.027$) compared with patients with an outcome mRS of 4–6. Other demographic or clinical characteristics did not differ between the outcomes of comatose patients, nor did the radiological surrogates of vascular collateralization. Recanalization was a necessary requirement for a favorable outcome (i.e., mRS 0–3) in all but two patients (in 19/21). None of the patients that achieved a favorable outcome had sICH (**Table 4**).

Factors predicting the worst possible outcome, projected being bedridden or dead, in a univariate model are shown in **Table 5**. Patients with a 3-month mRS 5–6 were older, presented with diabetes and atrial fibrillation more frequently, presented with lower median GCS score [median 4 (IQR 3–6) vs. 6 (5–7), $p = 0.026$], and had more often extensive baseline ischemic changes and bilateral ischemia in baseline imaging. All patients with acute coma and post-treatment sICH had an mRS 5–6 at 3 months (11 dead and 3 with an mRS of 5). The rate of recanalization was lower in patients with the worst outcome (64.0 vs. 88.9%, $p = 0.006$). Extensive baseline ischemic changes were a major factor predicting the poorest outcome (mRS 5–6). In total, 30/103 (29.1%) of the acutely comatose patients had pc-ASPECTS < 8, and only two of them achieved favorable outcomes (mRS 0–3). In terms of patients with acute coma and pc-ASPECTS < 8, 93.3% (28/30) were bedridden or dead (mRS 5–6) after 3 months (**Table 5**). When patients with pc-APECTS < 8 were excluded from analysis, 26.0% (19/73) of patients with initial coma achieved favorable outcome, and 64.4% (47/73) had an mRS 5–6.

TABLE 2 | Factors associated with acute coma in BAO patients.

	OR	95% C.I.	*p*
Age (per year)	1.04	1.01–1.06	0.004
CAD	2.18	1.01–4.74	0.049
Convulsions	4.96	2.12–11.61	<0.001
pc-ASPECTS < 8	3.64	1.74–7.62	0.001
Absence of patent PComs	2.44	1.17–5.09	0.018
At least one patent SCA	0.40	0.21–0.75	0.004
Long BAO (≥2 segments)	2.55	1.39–4.67	0.002

CAD, coronary artery disease; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PCom, posterior communicating artery; SCA, superior cerebellar artery; BAO, basilar artery occlusion.

*Factors with probability value (p) < 0.1 in a univariate model (**Table 1**) were included in a backward stepwise logistic regression model.*

DISCUSSION

Approximately 40% of BAO patients were initially comatose, which is in line with rates of 30–60% reported in previous studies (3–10). The main observation of this study was that, despite the dismal presentation on admission, still 2/10 comatose BAO patients treated with recanalization therapy reached functionally meaningful survival. Coma vs. no coma on presentation was not associated with differences in receiving either IVT or EVT treatment, nor with the differences in onset to treatment or symptom to door times. Our data consists of a large cohort of BAO patients treated in our institution between 1995 and 2019. In view of data from RCTs published in 2015 (20) demonstrating the efficacy of EVT in large vessel occlusions in anterior circulation, EVT was adopted in more routine use only after this in 2015. As previously reported by us (21), our IVT-treated cohort had comparable outcome rates with many EVT cohorts, and therefore no evidence-based amendment toward EVT-based treatment strategy has been made in our written in-house stroke management guidelines (**Figure 2**), although the rates of EVT have increased in recent years.

In our present cohort, older age, a history of coronary artery disease as a manifestation of atherosclerosis, convulsions at onset, extensive early ischemia in the vertebrobasilar region, and a lack of patent collateral vasculature of either circle of

TABLE 3 | Outcome measures between comatose vs. non-comatose patients.

Outcome, *n* (%)	All (*n* = 259)	Non-comatose (*n* = 156, 60.2%)	Comatose (*n* = 103, 39.8%)	*p*
90-day mRS				
mRS 0–2	88 (34.6%)	76 (50.3%)	12 (11.7%)	**<0.001**
mRS 0–3	114 (44.9%)	93 (61.6%)	21 (20.4%)	**<0.001**
mRS 5–6	118 (46.5%)	43 (28.5%)	75 (72.8%)	**<0.001**
Dead at 3 months	98 (38.3%)	37 (24.2%)	61 (59.2%)	**<0.001**
Recanalization (TIMI 2–3)†	155 (75.6%)	98 (76.6%)	57 (74.0%)	0.682
Futile recanalization‡	61 (30.3%)	23 (18.5%)	38 (49.4%)	**<0.001**
sICH	26 (10.2%)	12 (7.8%)	14 (13.9%)	0.117

†*Data available in 79%.*

‡*Data available in 78%.*

mRS, modified Rankin Scale; TIMI, Thrombolysis in Myocardial Infarction; sICH, symptomatic intracerebral hemorrhage.

The outcome was assessed at 3 months. Futile recanalization was determined as successful recanalization but ending up with a poor outcome (modified Rankin Scale 4–6). Symptomatic intracranial hemorrhage (sICH) was defined according to European Cooperative Acute Stroke Study II (ECASS II) criteria.

Statistically significant p-values (<0.05) are bolded.

TABLE 4 | Characteristics associated with favorable outcome in comatose BAO patients.

n (%)/median (IQR)	All (*n* = 103)	mRS 0–3 (*n* = 21, 20.4%)	mRS 4–6 (*n* = 82, 79.6%)	*p*
Characteristics				
Male sex	63 (61.2%)	14 (66.7%)	49 (59.8%)	0.562
Age	73 (63–79)	65 (57–74)	74 (66–80)	**0.010**
Diabetes	18 (17.5%)	1 (4.8%)	17 (20.7%)	0.112
Atrial fibrillation	29 (28.2%)	3 (14.3%)	26 (31.7%)	0.113
Hypertension	64 (62.1%)	13 (61.9%)	51 (62.2%)	0.980
Dyslipidemia	42 (40.8%)	6 (28.6%)	36 (43.9%)	0.202
Chronic heart failure	12 (11.7%)	4 (19.0%)	8 (9.8%)	0.259
Coronary artery disease	25 (24.3%)	5 (23.8%)	20 (24.4%)	0.956
Previous myocardial infarction	15 (14.6%)	3 (14.3%)	12 (14.6%)	1.000
Previous stroke	25 (24.3%)	4 (19.0%)	21 (25.6%)	0.531
Sudden onset phenotype	89 (86.4%)	18 (85.7%)	71 (86.6%)	1.000
Prodromes	19 (18.4%)	3 (14.3%)	16 (19.5%)	0.757
Convulsions	25 (24.3%)	5 (23.8%)	20 (24.4%)	0.956
Lowest GCS on admission†	5 (4–6)	6 (4–7)	5 (4–6)	0.212
Radiological parameters				
pc-ASPECTS < 8	30 (29.1%)	2 (9.5%)	28 (34.1%)	**0.027**
Bilateral ischemia	36 (35.3%)	5 (23.8%)	31 (38.3%)	0.217
Brainstem ischemia	24 (23.5%)	3 (14.3%)	21 (25.9%)	0.388
No patent PComs	29 (29.0%)	6 (30.0%)	23 (28.8%)	0.912
2 PComs	43 (43.0%)	10 (50.0%)	33 (41.3%)	0.480
At least one patent PCA	95 (95.0%)	19 (95.0%)	76 (95.0%)	1.000
At least one patent SCA	58 (58.0%)	11 (55.0%)	47 (58.8%)	0.761
Long BAO (≥2 segments)	53 (52.5%)	11 (55.0%)	42 (51.9%)	0.801
BAO exceeding to VA	32 (32.0%)	4 (20.0%)	28 (35.0%)	0.198
Recanalization (TIMI 2–3)‡	57 (74.0%)	19(95.0%)	38 (66.7%)	**0.013**
sICH (ECASS II)	14 (13.9%)	0 (0.0%)	14 (17.5%)	**0.038**
Treatments				
IVT	93 (90.3%)	19 (90.5%)	74 (90.2%)	0.974
EVT	30 (29.1%)	5 (23.8%)	25 (30.5%)	0.548
IVT + EVT	21 (20.4%)	3 (14.3%)	18 (22.0%)	0.554
Time delays (min)				
OTT	282 (158–640)	247 (165–415)	305 (158–640)	0.595
SDT	158 (85–371)	170 (106–371)	156 (82–371)	0.964
DTN	85 (38–180)	89 (51–165)	85 (38–189)	0.902

†*Data available in 81%.*

‡*Data available in 75%.*

mRS, modified Rankin Scale; IQR, interquartile range; GCS, Glasgow Coma Scale; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PCom, posterior communicating artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; BAO, basilar artery occlusion; VA, vertebral artery; TIMI, thrombolysis in myocardial infarction; IVT, intravenous thrombolysis; EVT, endovascular treatment; OTT, Onset-to-treatment time; SDT, symptom-to-door time; DTN, Door-to-needle time.

Univariate model; a multivariable regression model was not constructed due to the small sample size.

Statistically significant p-values (<0.05) are bolded.

Willis or cerebellum, besides long occlusions, were independently associated with acute coma in BAO patients. All of these have a logical neuroanatomical and neurophysiological explanation. Anatomically, the area vital to upholding consciousness is the pontine tegmentum, containing the ascending reticular activating system with a complex network of neurons (1, 11, 22, 23). Cerebrovascular atherosclerosis often leads to occlusions of the proximal and middle segments of the BA resulting in pontine ischemia and affecting areas upholding consciousness (1). Convulsive-like movements and extension rigidity arise from pontine pyramidal tracts and are therefore suggestive of brainstem ischemia often involving also areas of reticular activating circuitry (1, 2). Posterior circulation (Pc) ASPECTS below 8 correlates well with the brainstem ischemia since 64.6% of patients with pc-ASPECTS < 8 had brainstem ischemia either alone or combined with other VB-areas.

The observation that multisegmental occlusions of BA associated with initial coma are consistent with the probability

TABLE 5 | Factors associated with poorest outcome (mRS 5–6) in comatose BAO patients.

n (%)/mean (SD)/median (IQR)	All (*n* = 103)	mRS 0–4 (*n* = 28, 27.2%)	mRS 5–6 (*n* = 75, 72.8%)	*p*
Characteristics				
Male sex	63 (61.2%)	19 (67.9%)	44 (58.7%)	0.395
Age	71 (12)	65 (14)	73 (10)	**0.001**
Diabetes *n*	18 (17.5%)	1 (3.6%)	17 (22.7%)	**0.022**
Atrial fibrillation	29 (28.2%)	3 (10.7%)	26 (34.7%)	**0.016**
Hypertension	64 (62.1%)	18 (64.3%)	46 (61.3%)	0.783
Dyslipidemia	42 (40.8%)	9 (32.1%)	33 (44.0%)	0.276
Chronic heart failure	12 (11.7%)	4 (14.3%)	8 (10.7%)	0.731
Coronary artery disease	25 (24.3%)	7 (25.0%)	18 (24.0%)	0.916
Previous myocardial infarction	15 (14.6%)	3 (10.7%)	12 (16.0%)	0.754
Previous stroke	25 (24.3%)	6 (21.4%)	19 (25.3%)	0.681
Sudden onset phenotype	89 (86.4%)	25 (89.3%)	64 (85.3%)	0.753
Prodromes	19 (18.4%)	4 (14.3%)	15 (20.0%)	0.506
Convulsions	25 (24.3%)	7 (25.0%)	18 (24.0%)	0.916
Lowest GCS on admission†	5 (4–6)	6 (5–7)	4 (3–6)	**0.026**
Radiological parameters				
pc-ASPECTS < 8	30 (29.1%)	2 (7.1%)	28 (37.3%)	**0.003**
Bilateral ischemia	36 (35.3%)	5 (17.9%)	31 (41.9%)	**0.023**
Brainstem ischemia	24 (23.5%)	3 (10.7%)	21 (28.4%)	0.061
No patent PComs	29 (29.0%)	9 (33.3%)	20 (27.4%)	0.561
2 PComs	43 (43.0%)	13 (48.1%)	30 (41.1%)	0.527
At least one patent PCA	95 (95.0%)	25 (92.6%)	70 (95.9%)	0.610
At least one patent SCA	58 (58.0%)	14 (51.9%)	44 (60.3%)	0.449
Long BAO (≥2 segments)	53 (52.5%)	14 (51.9%)	39 (52.7%)	0.940
BAO exceeding to VA	32 (32.0%)	6 (22.2%)	26 (35.6%)	0.202
Recanalization (TIMI 2–3)‡	57 (74.0%)	25 (92.6%)	32 (64.0%)	**0.006**
sICH (ECASS II)	14 (13.9%)	0 (0.0%)	14 (19.2%)	**0.010**
Treatments				
IVT	93 (90.3%)	26 (92.9%)	67 (89.3%)	0.724
EVT	30 (29.1%)	8 (28.6%)	22 (29.3%)	0.940
IVT + EVT	21 (20.4%)	6 (21.4%)	15 (20.0%)	0.873
Time delays (min)				
OTT	282 (158–640)	235 (162–379)	315 (158–642)	0.237
SDT	158 (85–371)	159 (98–368)	158 (82–451)	0.961
DTN	85 (38–180)	69 (38–127)	89 (38–214)	0.216

†*Data available in 81%.*

‡*Data available in 75%.*

mRS, modified Rankin Scale; SD, Standard deviation; IQR, interquartile range; GCS, Glasgow Coma Scale; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; PCom, posterior communicating artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; BAO, basilar artery occlusion; VA, vertebral artery; TIMI, thrombolysis in myocardial infarction; IVT, intravenous thrombolysis; EVT, endovascular treatment; OTT, Onset-to-treatment time; SDT, symptom-to-door time; DTN, Door-to-needle time.

Univariate model; a multivariable regression model was not possible to construct due to the small sample size.

Statistically significant p-values (<0.05) are bolded.

of a greater number of perforating pontine arteries lacks patency on presentation. In line with these findings, both Ferbert et al. (3) and Cross et al. (24) reported a clot location most often in either proximal or middle segment of BA in comatose BAO patients. The finding that collateral status associated with coma on presentation is consistent with the concept of reverse "backflow" from the PComs and SCAs supplying circulation in the arterial branches distal to BAO maintaining brainstem vitality for longer periods of time (25). Greater collateral status has been reported to be associated with a better prognosis (26, 27).

The rates of 35 and 45% of good (mRS 0–2) and favorable outcomes (mRS 0–3), respectively, among the whole BAO cohort (**Table 3**) are in line with or slightly better than in previous cohorts (10, 12, 14, 18, 27–30). Poorer outcomes were significantly more frequent in comatose patients (**Table 3**). Multiple previous studies report unconsciousness as a predictor of poor outcome (6, 12, 14, 31–33), while others have failed to demonstrate such correlation reaching statistical significance (4, 5, 9, 10, 24). This might be in part explained by the small number of study subjects and varying patient selection. When ischemic

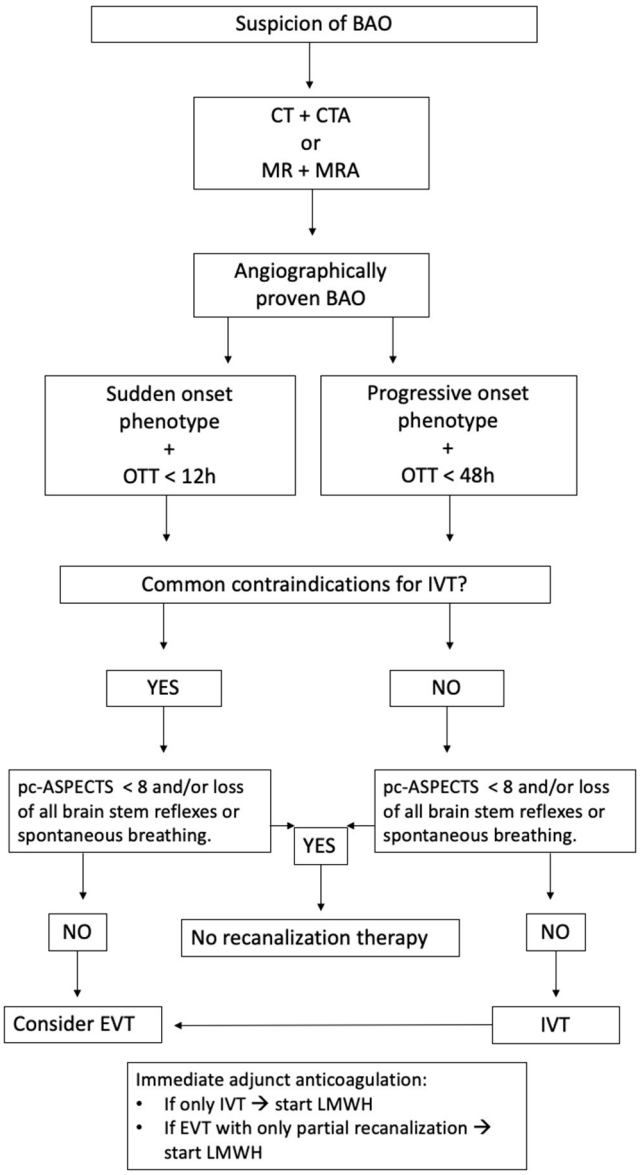

FIGURE 2 | Simplified flow chart on BAO treatment. BAO, Basilar artery occlusion; OTT, Onset-to-teatment time; IVT, Intravenous thrombolysis; pc-ASPECTS, posterior circulation Acute Stroke Prognosis Early CT Score; EVT, Endovascular treatment; LMWH, Low-molecular-weight heparin.

stroke patients requiring ventilation support were analyzed, GCS < 10 on admission was an independent predictor of both early and late mortality (34). However, in the present study favorable outcome (3-month mRS 0–3) was achieved in one-fifth of BAO patients with initial coma. Similar results have been previously reported in the BASICS registry with a rate of good outcome of 17% in intraarterial thrombolysis (IAT) and 26% in IVT treated BAO patients with coma, tetraplegia, or locked-in state on presentation (13). In our previous smaller study, we found a favorable outcome (mRS 0–3) in 22.5% of BAO patients needing intubation and mechanical ventilation (14). These rates are slightly higher than those reported by Pallesen et al. (6) with 15.4% of comatose BAO patients achieving a favorable outcome (mRS 0–3). This might be partly explained with a relatively high number of patients with no recanalization therapy in their study since 33% of comatose patients did not receive any recanalization therapy, 38% underwent IAT, 4% were treated with IVT, and 24% were treated with IVT + IAT.

Since reduced consciousness in the case of BAO arises from brainstem ischemia that might be reversed with rapid recanalization therapy, it is conceivable that even a patient with acute coma can be recovered if permanent brainstem tissue damage remains limited. Indeed, Chandra and coworkers (4) reported that low GCS scores did not correlate with poor neurologic outcomes in patients with acute BAO managed with intraarterial therapy (4). Furthermore, Nagel et al. (9) reported that lower GCS was associated with less favorable outcome but when the multivariable model was construed, only pc-ASPECTS remained as an independent predictor of outcome (9). Similarly, 96% of patients with pc-ASPECTS < 8 at baseline had poor outcomes (3-month mRS 3–6) in our previous study (35). In the present study, 93% of patients with acute coma and pc-ASPECTS < 8 ended up dead or bedridden at 3 months. With further simulation of the current cohort, it was observed that, when BAO patients with low pc-ASPECTS were excluded from the analysis, the rate of favorable outcome raised to 26% within comatose patients, and the rate of the most devastating outcome of mRS 5–6 reduced to 64% (vs. 72.8%). This supports our present in-house treatment guideline in which extensive brainstem ischemia is a contraindication for BAO recanalization treatment but not coma as such (**Figure 2**). Since the cohort includes patients also from a period prior to the European label for IVT use in acute stroke, the experience and adherence to in-house protocol for BAO treatment has improved over the years (21).

Besides the absence of ischemic changes, factors associated with favorable outcomes in comatose BAO patients included younger age, successful recanalization, and avoiding post-treatment sICH, the latter two of which are treatment-related efficacy and safety goals worth further honing. On the other hand, additional factors associated with the poorest outcome (mRS 5–6) were older age, a burden of cardiovascular comorbidities (i.e., diabetes and atrial fibrillation), being deeply comatose, and imaging showing extensive ischemic changes. Although several of these factors have previously been shown to predict outcome after BAO (12, 14, 28–30, 36, 37), the relative predictive value of these factors projecting poor and favorable outcomes of initially comatose patients has not been described in detail due to relatively small study populations and cohort sizes of BAO. We remain with the clinical challenge of weighing each of these in decision making, taking all of them into consideration in each BAO patient.

An acutely comatose BAO patient is one of the most challenging emergencies in neurological ED evaluation. After the correct diagnosis has been reached, physicians need to conduct risk stratification to support decision making about the aggressiveness of the immediate therapy. The prognosis of BAO without recanalization is abysmal (1, 2), but the rate of futile recanalization is also high; roughly 50% of comatose patients in the present study did not avoid institutionalized living

conditions or death despite success in recanalization. Mortality among mechanically ventilated stroke patients is known to be high, yet some of these patients do survive, occasionally even with no or only slight disability (15). It is known that physicians tend to be overly pessimistic in predicting survival and quality of life in patients with severe stroke or other critical illness and that many physicians' personal mindsets also affect their treatment decisions (15). This should be acknowledged in order to avoid a self-fulfilling prophecy. On the other hand, novel endovascular recanalization procedures and life-sustaining therapies in intensive care and stroke units are considerably expensive when given futilely to reach excellent vascular patency in patients projected toward a desperate prognosis. Avoiding sheer mortality should not be the steadfast main goal, and the probability of meaningful recovery with an acceptable quality of life should always be kept in mind when making treatment decisions. Therefore, every evidence-based assistance available is invaluable for physicians treating these infrequent BAO patients. This underlines the importance of our present evaluation of factors that might facilitate the challenging risk stratification and decision making in the acute setting.

Limitations of the present study are the relatively restricted number of subjects and the incomplete availability of radiological recanalization data for all patients, especially the ones with early clinical deterioration or death within 24 h. Due to the small number of comatose patients, no multivariable regression models regarding their outcome were possible to construe. However, we report data from a previously well-established single-center cohort of an experienced stroke unit with a long-honed recanalization therapy protocol for BAO (5, 7, 14, 21, 30, 35, 38).

In conclusion, one-fifth of BAO patients presenting with initial coma achieved a favorable outcome within 3 months. These patients were younger and lacking extensive baseline ischemic lesions of the vertebrobasilar region on baseline brain imaging. Therefore, unconsciousness *per se* and seemingly bleak clinical conditions upon presentation should not as such exclude BAO patients from receiving aggressive recanalization therapy. Rather, initial and post-treatment decisions during subsequent days should be made individually, considering prognostic key baseline characteristics, where the volume and location of infarction should be dominant in assisting maintenance or de-escalation of intensive care (9, 39). These characteristics can be brought up in discussions with the closest ones and when making decisions regarding the prolongation of intensive care unit treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JR, TS, PL, and DS contributed to the design of the study and the writing process of the manuscript. HS, OS, and PV collected the radiological data. JR performed statistical analyses. All authors contributed to manuscript revision, read, and approved the submitted version.

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Evaluation of Endovascular Treatment for Acute Basilar Occlusion in a State-Wide Prospective Stroke Registry

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Context: Despite overwhelming evidence for endovascular therapy in anterior circulation ischemic stroke due to large-vessel occlusion, data regarding the treatment of acute basilar artery occlusion (BAO) are still equivocal. The BASICS trial failed to show an advantage of endovascular therapy (EVT) over best medical treatment (BMT). In contrast, data from the recently published BASILAR registry showed a better outcome in patients receiving EVT.

Objective: The aim of the study was to investigate the safety and efficacy of EVT plus BMT vs. BMT alone in acute BAO.

Methods: We analyzed the clinical course and short-term outcomes of patients with radiologically confirmed BAO dichotomized by BMT plus EVT or BMT only as documented in a state-wide prospective registry of consecutive patients hospitalized due to acute stroke. The primary endpoint was a favorable functional outcome (mRS 0–3) at hospital discharge assessed as common odds ratio using binary logistic regression. Secondary subgroup analyses and propensity score matching were added. Safety outcomes included mortality, the rate of intracerebral hemorrhages, and complications during hospitalization.

Results: We included 403 patients with acute BAO (2017–2019). A total of 270 patients (67%) were treated with BMT plus EVT and 133 patients (33%) were treated with BMT only. A favorable outcome (mRS 0–3) was observed in 33.8% of the BMT and 26.7% of the BMT plus EVT group [OR.770, CI (0.50–1.2)]. Subgroup analyses for patients with a NIHSS score > 10 at admission to the hospital revealed a benefit from EVT [OR 3.05, CI (1.03–9.01)].

Conclusions: In this prospective, quasi population-based registry of patients hospitalized with acute BAO, BMT plus EVT was not superior to BMT alone. Nevertheless, our results suggest that severely affected BAO patients are more likely to benefit from EVT.

Keywords: thrombectomy, best medical treatment, posterior circulation, thrombolysis, endovascular treatment, basilar artery occlusion (BAO)

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INTRODUCTION

Arterial occlusions of the posterior intracranial circulation account for about 20% of all ischemic strokes, and of these, an estimated 15% are due to basilar artery occlusion (BAO) (1). The spontaneous course of BAO is associated with high mortality and morbidity mostly leading to poor patient outcome. Evidence for effective therapies is scarce (2). Whereas the benefit of endovascular therapy (EVT) in anterior circulation ischemic strokes due to large-vessel occlusion has been proven by several randomized trials, (3–7) the efficacy of EVT over standard medical care has not yet been unequivocally shown in BAO patients. Recently, two randomized-controlled trials failed to prove additional benefit of EVT in patients with acute BAO (8, 9). By contrast, a consecutive registry of patients with angiographically proven BAO showed that patients receiving EVT tend to benefit in terms of functional recovery after 90 days, whereas the differences in thrombolytic treatment and process times should be noted (10).

We aimed to investigate the safety and efficacy of EVT plus best medical treatment (BMT) vs. BMT alone in acute BAO using consecutive, quasi population-based, real-life data from our mandatory state-wide quality assurance registry.

MATERIALS AND METHODS

We retrieved data from a mandatory prospective stroke inpatient quality assurance registry covering the entire federal state of Hessen in Germany (6,285,000 inhabitants). The register represents the complete hospital landscape of the state of Hesse, i.e., a total of 119 hospitals. Data entry is compulsory by a federal contract and the registry achieves a nearly 100% completion, verified by administrative hospital data. Due to the anonymized data collection in the context of quality assurance measures, individual consent and ethical votes were not required.

We included patients fulfilling the following criteria: (1) discharge diagnosis of ischemic stroke (ICD-10: I63), (2) age 18 years or older, and (3) BAO confirmed by computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography. Estimated BAO time was recorded from symptom onset to the arrival time at the hospital. In case the symptom onset was not known, the time of last seen well was assumed instead. If no last seen well could be determined, the duration of symptom onset to admission was noted as unknown.

We collected information on baseline characteristics, stroke risk factors, stroke severity, and neurological deficits at presentation, pre- and post-treatment angiographic findings, process times, type of treatment, and functional outcomes at discharge for three subsequent years (2017–2019).

We distinguished between patients who received BMT (e.g., intravenous thrombolysis, coagulation management, and blood pressure management) and patients who additionally underwent endovascular thrombectomy (BMT + EVT). The primary clinical efficacy outcome was a favorable outcome defined as modified Rankin scale (mRS) from 0 to 3 points at discharge from hospital. The mRS is a seven-level scale [range, 0 (no symptoms) to 6 (death)] for the assessment of neurologic functional disability (11). Common odds ratio for a shift in scores on the mRS was calculated by ordinal logistic regression.

The main secondary clinical efficacy outcome was good or excellent functional outcome at discharge from hospital (mRS 0–2/0–1). As safety outcomes mortality and complications during hospital stay were recorded.

Statistical Analysis

We compared baseline characteristics, treatment metrics, outcomes, and severe adverse events between the BMT-alone and BMT plus EVT group. Data are presented as means [standard deviation (SD)] if normal distributed or medians [interquartile ranges (IQRs)] or numbers with percentages, unless otherwise indicated.

Univariate analysis was performed using the Mann–Whitney U test, χ^2 test, as appropriate. The primary outcome variable was the adjusted common odds ratio for a favorable outcome on the mRS score (0–3 points); this ratio was estimated with binary logistic regression. The adjusted common odds ratios are reported with 95% CIs to indicate statistical precision.

Adjusted estimates of outcome (common odds ratio, odds ratio, and β) were calculated by taking the following variables into account: age, baseline NIHSS, sex, and intravenous thrombolysis (IVT).

For propensity score matching analysis, we performed a 1:1 matching based on the nearest-neighbor matching algorithm with a caliper width of 0.2 of the propensity score with age, care situation prior admission (independent at home, care at home, and care in institution), mRS at admission, baseline NIHSS, and medical history, such as diabetes mellitus, arterial hypertension, and prior stroke. In line with randomized trials of acute stroke therapies, only patients with an independent lifestyle and time from onset to admission <24 h were included for propensity score matching to exclude comorbidities as potential influence factors.

The significance level was set to $P < 0.05$, and all tests of hypotheses were two-sided. Data were analyzed with SPSS 26 (IBM; Armonk, BY, USA) and GraphPad 9 (GraphPad Software, USA).

RESULTS

Baseline Characteristics

In total, 403 patients with acute BAO were included. A total of 270 patients (67%) were treated with BMT plus EVT and 133 patients (33%) were treated with BMT alone (**Table 1**). Patients from the BMT group were slightly older (73.4 ± 13.1 years, $p = 0.06$) than those in the BMT plus EVT group (71.1 ± 12.9 years, $p = 0.06$) and fewer patients in this group were functionally independent before the stroke (75.2 vs. 84.1%, $p = 0.008$). The burden of vascular risk factors (diabetes and hypertension) and previous stroke was numerically but non-significantly higher in the BMT-only group. The median NIHSS at admission was significantly higher in the BMT plus EVT

TABLE 1 | Baseline characteristics upon hospital admission and process measures.

	Overall			Propensity Score Matched		
	BMT ***n* = 133**	**BMT + EVT** ***n* = 270**	***p***	**BMT** ***n* = 73**	**BMT + EVT** ***n* = 73**	***p***
Age (years, mean, SD)	73.4 ± 13.1	71.1 ± 12.9	0.06	69.86 (±13.2)	68.3 (±13.3)	0.485
Female	68 (51.1)	114 (42.2)	0.347	33 (45.2)	31 (42.5)	0.868
NIHSS (median, IQR)	8 (3–20)	14 (7–22)	<0.001	6 (3–17)	8 (4–18)	0.255
NIHSS < 10	72 (54.1)	94 (34.8)	<0.001	45 (61.6)	37 (50.7)	0.243
NIHSS ≥ 10	61 (45.9)	176 (65.2)	<0.001	28. (38.4)	36 (49.3)	0.243
Need for care prior stroke			0.008			
- independent	100 (75.2)	227 (84.1)		100 (100)	100 (100)	–
- care at home	11 (8.3)	25 (9.3)		–	–	
- institutional care	22 (16.5)	18 (6.7)		–		
Admission to hospital			0.218			0.776
- self-initiated	3 (2.3)	2 (0.7)		3 (4.1)	0 (0)	
- *via* family physician	4 (3.0)	5 (1.9)		1 (1.4)	1 (1.4)	
- *via* emergency service	95 (71.4)	180 (66.7)		50 (68.5)	51 (69.9)	
- secondary transfer	31 (23.3)	83 (30.7)		19 (26.0)	21 (28.8)	
OAT prior admission			0.364			0.748
- no OAT	118 (88.7)	220 (81.5)		65 (89.0)	62 (84.9)	
- Vitamin K Antagonist	5 (3.8)	18 (6.7)		4 (5.5)	6 (8.2)	
- NOAC	10 (7.5)	32 (11.9)		4 (5.5)	5 (6.8)	
Risk factors						
Previous stroke	33 (24.8)	60 (22.2)	0.348	17 (23.3)	14 (19.2)	0.851
Hypertension	106 (79.7)	202 (74.8)	0.241	58 (79.5)	60 (82.2)	0.834
Diabetes	38 (28.6)	65 (24.1)	0.441	19 (26.0)	21 (28.8)	0.853
Stroke symptoms						
Aphasia	31 (23.3)	71 (26.3)	0.221	13 (17.8)	13 (17.8)	1.0
Dysarthria	72 (54.1)	149 (55.2)	0.050	37 (50.7)	40 (54.8)	0.740
Dysphagia	51 (38.3)	128 (47.4)	0.002	23 (31.5)	34 (46.6)	0.089
Paresis	77 (57.9)	154 (57.0)	0.336	39 (53.4)	28 (38.4)	0.331
Onset to admission						
0–6 h	66 (49.6)	177 (65.6)	0.472	44 (60.3)	43 (58.9)	0.99
6–24 h	30 (22.6)	46 (17.0)	0.223	29 (39.7)	30 (41.1)	0.99
>24 h	16 (12.0)	10 (3.7)	0.002	–	–	–
unknown	21 (15.8)	37 (13.7)	0.549	–		–
Treatment						
Thrombolysis	44 (33.1)	45 (16.6)	0.001	30 (41.1)	37 (50.7)	0.319
Endovascular treatment	–	270 (100)	–	–	100 (100)	–
– TICI IIB/III		200 (74.1)		–	55 (75.3)	
Door-to-needle (mean, SD)	21.0 ± 24.1	23.9 ± 21.5	0.274	18.0 ± 17.3	23.9 ± 24.9	0.360
Door-to-imaging (mean, SD)	25.7 ± 38.2	20.1 ± 26.8	0.842	19.4 ± 27.7	25.2 ± 33.7	0.371
Door-to-groin (mean, SD)	–	69.9 ± 87.3	–	–	76.2 ± 90.0	–
Length of hospitalization (day, mean, SD)	10.8 ± 12.5	12.1 ± 13.2	0.337	12.9 ± 15.1	12.3 ± 8.8	0.773

BMT, best medical treatment; EVT, endovascular thrombectomy; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified rankin scale; OAT, oral anticoagulation treatment; NOAC, novel oral anticoagulant; TICI, thrombolysis in cerebral infarction scale, unless otherwise declared n (%).

group (14 points vs. 8 points, $p < 0.001$) and more patients showed dysarthria ($p = 0.05$) and dysphagia ($p = 0.002$). Overall, 33.1% of patients in the BMT and 16.6% in the BMT plus EVT group received IVT with a mean door-to-needle time of 21.0 min (±24.1, BMT) and 23.9 min (±21.5, $p = 0.27$) and a mean door-to-groin time of 69.9 min (±87.3, BMT plus EVT).

Primary and Secondary Efficacy Outcomes

Of the patients in the BMT group and the BMT plus EVT group, 33.8 and 26.7%, respectively, reached favorable outcome (mRS 0–3) [OR 0.770, CI (0.50–1.20)]. The median short-term mRS at discharge after a median length of stay of 9 days (IQR 4–16 days) was 5 and did not differ between BMT and BMT plus EVT ($p = 0.28$, **Table 2**). Common odds ratio for a shift in scores on the

TABLE 2 | Primary and secondary efficacy outcomes and safety outcomes.

	Overall			Propensity Score Matched		
	BMT	**BMT + EVT**		**BMT**	**BMT + EVT**	
	***n* = 133**	***n* = 270**	***p***	***n* = 73**	***n* = 73**	***p***
Primary Outcome (*n*, %)						
mRS 0–3	45 (33.8)	87 (26.7)	0.248	29 (41.4)	31 (43.1)	0.844
Secondary Outcome (*n*, %)						
mRS 0–2	33 (24.8)	51 (18.9)	0.323	23 (32.9)	19 (26.4)	0.398
mRS 0–1	18 (13.5)	26 (9.6)	0.506	14 (20.0)	9 (12.5)	0.225
mRS (median, IQR)	5 (2–6)	5 (3–6)	0.284	4 (2–6)	4 (2–5)	0.962
mRS (median, IQR)						
0–6 h onset to admission	5 (3–6)	5 (3–6)	0.952	4 (2–6)	4 (2–5)	0.467
6–24 h onset to admission	4 (2–5)	5 (4–6)	0.496	4 (2–5)	4 (3–6)	0.330
>24 h onset to admission	3 (2–6)	4.5 (2–6)	0.517	–	–	–
unknown onset	6 (4–6)	5 (4–6)	0.479			
mRS (median, IQR)						
<10 NIHSS on admission	3 (1.75–5)	3 (2–5)	0.351	3 (1–5)	3 (1–5)	0.940
≥10 NIHSS on admission	6 (5–6)	5 (4–6)	0.037	5 (5–6)	5 (4–6)	0.207
mRS (median, IQR)						
<70 years	4 (2–6)	5 (2–6)	0.502	4 (2–5)	4 (2–5)	0.677
≥70 years	5 (4–6)	5 (4–6)	0.358	4.5 (2–6)	4 (3–6)	0.685
Safety outcome (*n*, %)						
Mortality	44 (33.8)	94 (36.2)	0.730	18 (24.7)	14 (19.1)	0.549
Surgical decompression	3 (2.3)	11 (4.1)	0.336	3 (4.1)	2 (2.7)	0.999
Pneumonia	109 (82.0)	73 (27.0)	0.047	15 (20.5)	17 (23.3)	0.842
Brain edema	7 (5.3)	24 (8.9)	0.199	5 (6.8)	5 (6.8)	1
Intracerebral bleeding	1 (0.8)	4 (1.5)	0.534	0 (0)	2 (2.7)	0.497
Cerebral arterial embolism	4 (3.0)	13 (4.8)	0.396	2 (2.7)	4 (5.5)	0.681

BMT, best medical treatment; EVT, endovascular thrombectomy; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified rankin scale.

mRS was not significant comparing BMT vs. BMT plus EVT [OR 0.81 (0.56–1.19), **Figure 1A**].

Good functional outcome, defined as mRS 0–2 at discharge, was reached by 24.8% of the BMT and 18.9% of the BMT plus EVT group ($p = 0.32$). In patients with a severe stroke (NIHSS ≥ 10), median mRS at discharge was 6 in patients of the BMT and 5 in patients of the BMT plus EVT group ($p = 0.04$). Results of the subgroup analysis are presented in **Table 2**. Regarding the best treatment option for patients with a severe stroke, there was a significant signal for a benefit from additional EVT [OR 3.05, CI (1.03–9.01), **Figure 2**]. A further subgroup analysis showed that patients with an onset to hospital admission time from 6 to 24 h achieved a significantly better outcome by BMT alone compared to BMT plus EVT [OR 0.33 (0.12–0.92)].

Propensity Score Matched

After propensity score matching, the baseline characteristics of the BMT and BMT plus EVT group were well-balanced (**Table 1**). There was no significant difference in either the primary or secondary endpoints (**Table 2**). Common odds ratio for a shift in scores on the mRS was not significant comparing BMT vs. BMT plus EVT [OR 0.98 (0.60–1.61), **Figure 1B**]. Favorable outcome (mRS 0–3) was reached in 42% within the BMT and in 41% within the BMT plus EVT group ($p = 0.78$). Additional adjustments for age or stroke severity also did not uncover significant discrepancies between the two groups.

Safety Outcomes

Mortality was high in both groups (33.8 vs. 36.2%, $p = 0.73$). Patients of the BMT plus EVT group showed a statistically non-significant higher rate of intracerebral bleeding complications (1.5 vs. 0.8%, $p = 0.53$) and were more frequently treated in intensive care units (82.6 vs. 42.9%, $p < 0.001$). Besides, we observed a lower rate of pneumonia in this group (27.0 vs. 82%, $p = 0.05$).

DISCUSSION

The present study provides consecutive and non-selective prospective real-world data on the management and treatment results of patients with acute BAO. At the time of hospital discharge, there was no significant difference in terms of favorable outcome (mRS 0–3) between patients treated with BMT alone and patients treated with BMT and EVT. However, our data suggest that patients with severe stroke might benefit from additional EVT.

These results are in line with recently presented results of the randomized-controlled BASICS trial conducted in the Netherlands, Switzerland, Germany, Italy, Norway, and Brazil,

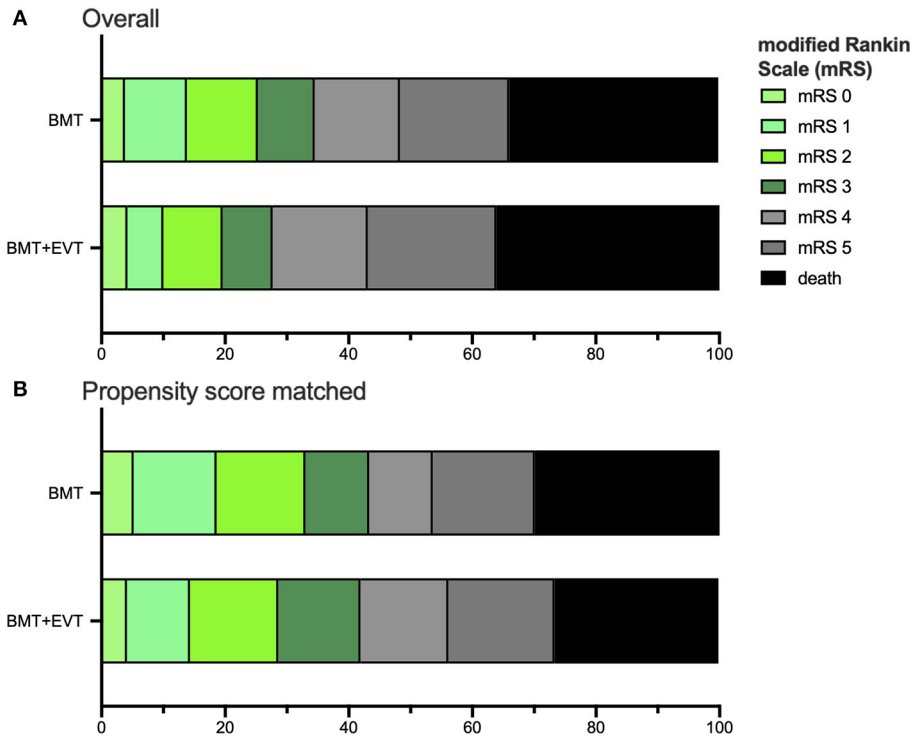

FIGURE 1 | Distribution of the modified Rankin scale (mRS) in all patients **(A)** and the Propensity Score matched data set **(B)** for age, mRS at admission, baseline NIHSS, and medical history, such as diabetes mellitus, arterial hypertension, and prior stroke. Comparing BMT vs. BMT plus EVT group, the mRS shift was not significant, neither for the all patients [OR 0.81 (0.56–1.19)] nor for Propensity Score matched patients [OR 0.98 (0.60–1.61)]. The ratio was estimated with ordinal logistic regression.

which randomized 300 patients from 2011 to 2019 with a BAO (<6 h since onset) to best medical management plus EVT or best medical management alone (8). The primary endpoint of favorable outcome defined as mRS $\leq$ 3 after 90 days did not differ significantly between groups (oral presentation ESOC 2020, Vienna, Austria, https://eso-wso-conference.org/eso-wso-may-webinar/). The authors discussed a higher-than-expected rate of favorable outcome in the BMT-only group (37.7% reached mRS 0–3 after 90 days) as one of the factors for the neutral result of the trial. Furthermore, regarding the prespecified subgroup analysis, the authors stated that especially in severely affected patients (NIHSS > 10), EVT might be more effective, whereas in NIHSS, <10 BMT seems to be superior.

The randomized-controlled BEST trial conducted in China was terminated early after enrollment of 131 patients due to slow recruitment and a high crossover rate into the EVT arm (9). The primary intention-to-treat analysis was neutral despite numerically more patients reaching mRS $\leq$ 3 at 90 days. There was no effect of additional EVT on mortality in the primary analysis. Secondary "per protocol" and "as treated" analyzing crossover patients in the EVT pointed toward a superior efficacy of EVT. Of note, there was a numerically higher rate of hemorrhagic complications in the arm with additional EVT (9).

BASILAR, a large Chinese registry that consecutively enrolled 829 adult patients with angiographically proven acute BAO with symptom onset < 24 h, showed a clear treatment preference toward additional endovascular therapy that was delivered to 78% of patients (10). A non-selected analysis as well as an analysis after propensity score matching for age, systolic blood pressure, baseline pc-ASPECTS, baseline NIHSS, TOAST classification, occlusion site, and medical history found significantly better outcomes in a mRS shift analysis and significantly more patients with mRS $\leq$ 3 at 90 days as well as a significantly lower mortality in patients receiving additional EVT. With a median NIHSS of 27 points, patients in the BASILAR registry were more severely affected than in the BASICS study (median 21 and 22, respectively) and significantly more severely affected than in our registry. Together with the indications of a higher additional efficacy of EVT in more severely affected patients with BAO from the BASICS trial, we hypothesize that the differences between this and the present registry data might be at least partially attributable to the higher rate of severe strokes in the BASILAR registry. This is supported by a relevantly lower mortality rate in our registry that did not differ significantly between both treatment groups. Given the quasi-population based nature of our registry data from a mandatory quality assurance database, we think that our data are representative for a central European stroke patient population.

When considering both registries, it should be noted that our patients were included for the most part up to 24 h after symptom

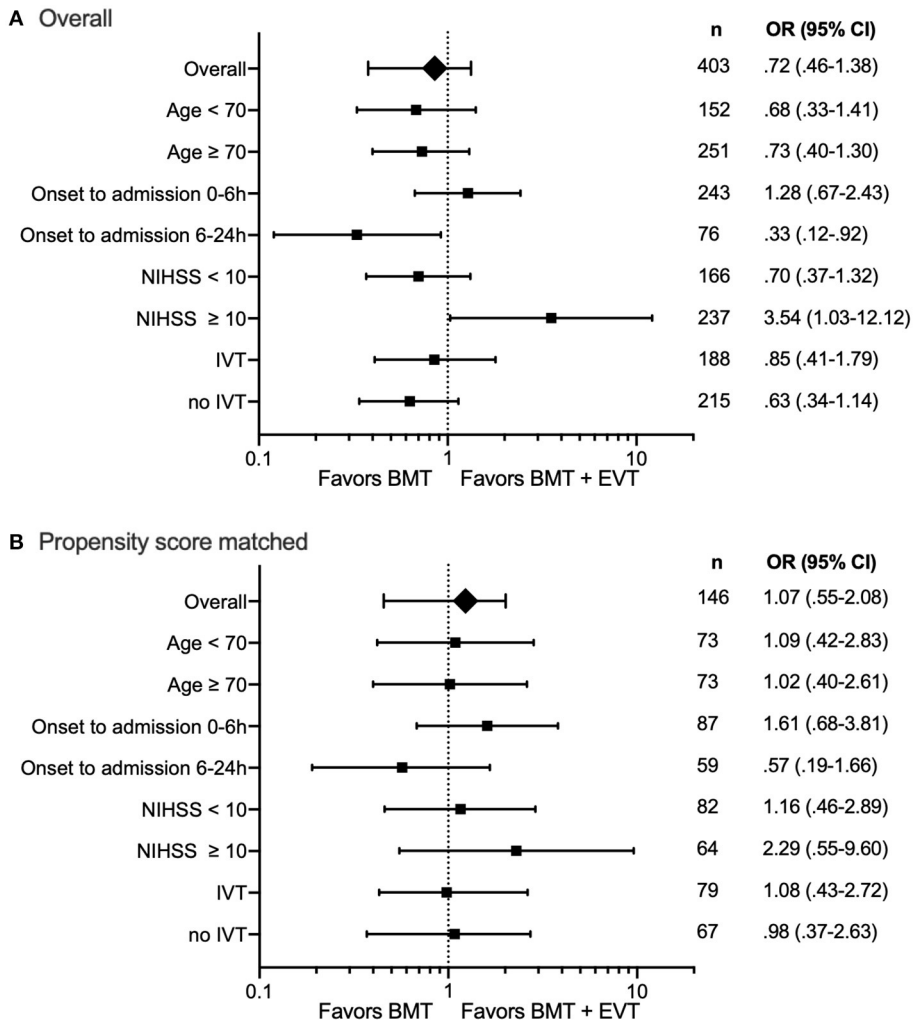

FIGURE 2 | Forest plot of additional endovascular therapy (EVT) on favorable outcome (mRS 0–3) at discharge from hospital. **(A)** includes all patients ($n = 403$). **(B)** Propensity Score matched data set ($n = 146$) for age, care situation prior to admission (independent at home, care at home, and care in institution), mRS at admission, baseline NIHSS, and medical history, such as diabetes mellitus, arterial hypertension, prior stroke, and time from onset to admission <24 h. Number of patients and odds ratio (OR) with 95% CI are presented.

onset, and, in addition, in a small part, no symptom onset was known at all, differing from the randomized-controlled trials BASICS and BEST with intervals up to 6 and 8 h after onset, respectively. The currently ongoing randomized BAOCHE trial conducted at multiple sites in China aims to shed more light on the efficacy of additional EVT in the late time window.

The three sources of evidence discussed above (BASICS, BEST, and BASILAR) and our data do not show an excess risk of additional EVT in patients with acute BAO of all degrees of severity. A secondary analysis from the BASICS trial as well as our analysis dichotomizing the population by an NIHSS score of 10 suggest a superior efficacy of additional EVT in patients with acute BAO and severe stroke. Looking at the subgroup analysis of our study, for patients with symptom onset to admission 6–24 h, BMT appears superior. Nevertheless, we believe that the data of our study are not sufficient to argue in principle against EVT beyond 6 h. This is also supported by the fact that the effect was no longer detectable after propensity score matching. In contrast to our study, the BASILAR study could show an efficacy of EVT for this subgroup (10).

A limitation of our study is the fact that our quality assurance database only captures the inpatient stay as we do not have access to the functional status beyond the mRS at discharge. On the other hand, our data reveal population-based information on acute treatment of BAO with little selection bias. In addition, an observation period of 3 months may also be too short to adequately reflect recovery in the most severely affected patients.

Recent data on the use of tenecteplase for BAO and consecutive EVT have demonstrated an increased likelihood of reperfusion (12). However, based on our data, we cannot comment on this because the type of thrombolytic agent used is not recorded.

In summary, our study showed no significant difference between BMT plus EVT vs. BMT alone on short-term functional outcome. Taking into account the recently published BASICS and BEST trials and the data from the BASILAR registry, it can be assumed that additional EVT is safe and that severely affected patients seem to benefit from additional EVT. Further clinical studies are necessary to better define the patient population with a high likelihood of clinical benefit from additional EVT for acute BAO.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available because due to legal restrictions, the data cannot be made available. Requests to access the datasets should be directed to Dr. Ferdinand Bohmann, ferdinand.bohmann@kgu.de.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FB and WP conceived the study. FB and KG managed the data and performed the statistical analysis. BM runs the state-wide prospective quality assurance database. All authors contributed to manuscript revision, and read and approved the submitted version.

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Comparison of Risk Factors, Safety, and Efficacy Outcomes of Mechanical Thrombectomy in Posterior vs. Anterior Circulation Large Vessel Occlusion

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Background and Purpose: It is believed that stroke occurring due to posterior circulation large vessel occlusion (PCLVO) and that occurring due to anterior circulation large vessel occlusion (ACLVO) differ in terms of their pathophysiology and the outcome of their acute management in relation to endovascular mechanical thrombectomy (MT). Limited sample size and few randomized controlled trials (RCTs) with respect to PCLVO make the safety and efficacy of MT, which has been confirmed in ACLVO, difficult to assess in the posterior circulation. We therefore conducted a meta-analysis to study to which extent MT in PCLVO differs from ACLVO.

Materials and Methods: We searched the databases PubMed, Cochrane, and EMBASE for studies published between 2010 and January 2021, with information on risk factors, safety, and efficacy outcomes of MT in PCLVO vs. ACLVO and conducted a systematic review and meta-analysis; we compared baseline characteristics, reperfusion treatment profiles [including rates of intravenous thrombolysis (IVT) and onset-to-IVT and onset-to-groin puncture times], recanalization success [Thrombolysis In Cerebral Infarction scale (TICI) 2b/3], symptomatic intracranial hemorrhage (sICH), and favorable functional outcome [modified Rankin Score (mRS) 0–2] and mortality at 90 days.

Results: Sixteen studies with MT PCLVO (1,172 patients) and ACLVO (7,726 patients) were obtained from the search. The pooled estimates showed higher baseline National Institutes of Health Stroke Scale (NIHSS) score (SMD 0.32, 95% CI 0.15–0.48) in the PCLVO group. PCLVO patients received less often IVT (OR 0.65, 95% CI 0.53–0.79). Onset-to-IVT time (SMD 0.86, 95% CI 0.45–1.26) and onset-to-groin puncture time (SMD 0.59, 95% CI 0.33–0.85) were longer in the PCLVO group. The likelihood of obtaining successful recanalization and favorable functional outcome at 90 days was comparable between the two groups. PCLVO was, however, associated with less sICH (OR 0.56, 95% CI 0.37–0.85) but higher mortality (OR 1.92, 95% CI 1.46–2.53).

Conclusions: This meta-analysis indicates that MT in PCLVO may be comparably efficient in obtaining successful recanalization and 90 day favorable functional outcome just as in ACLVO. Less sICH in MT-treated PCLVO patients might be the result of the lower IVT rate in this group. Higher baseline NIHSS and longer onset-to-IVT and onset-to-groin puncture times may have contributed to a higher 90 day mortality in PCLVO patients.

Keywords: acute ischemic stroke, mechanical thrombectomy, endovascular stroke treatment, endovascular thrombectomy, posterior circulation, anterior circulation, large vessel occlusion

Subject Terms: Mechanical Thrombectomy/Endovascular treatment, Ischemic Stroke, Large Vessel Occlusion

INTRODUCTION

Intravenous thrombolysis (IVT) has become the mainstay of acute intervention in ischemic stroke presenting within 4.5 h of symptom onset when other contraindications have been excluded (1). However, IVT has been shown to be less effective in proximal large vessel occlusion (LVO), mainly in the terminal internal carotid artery, proximal middle cerebral artery, and basilar artery, than in more distal occlusion (2). Therefore, clinical worsening is to be expected in many cases of LVO unless endovascular mechanical thrombectomy (MT) is initiated (2).

The second-generation MT devices that were introduced in the last decade have shown superiority to first-generation MT devices and, hence, have been widely used in MT since then (3–5). Consequently, it could be argued that most studies on MT conducted before the surge of second-generation MT devices could have been compromised by the inferiority of first-generation MT devices. Nowadays, MT in LVO may be conducted up to 24 h without waiting for IVT outcome (6–8).

To date, many randomized controlled trials (RCTs) have reported the safety and efficacy of MT in acute ischemic stroke due to anterior circulation LVO (ACLVO). However, there is lack of substantial data on the safety and efficacy of MT in posterior circulation LVO (PCLVO) (5, 6, 9).

Posterior circulation stroke is defined as the development of ischemic lesions occurring in the vascular territories supplied by branches of the vertebrobasilar arterial system (10). It occurs in about 20–25% of all ischemic strokes (11, 12), and neurological deficits caused by PCLVO have been described as catastrophic with severe disability and death occurring in about 68% of patients (13, 14). The rarity of PCLVO poses the challenge of obtaining a significant sample size for conducting observational and controlled trials in comparison to anterior circulation stroke.

MT in ACLVO has been accepted in most clinical settings as the best way for obtaining recanalization, and therefore, the randomization of patients with PCLVO into groups including no-MT is considered mostly unethical. Among the very few RCTs that focused on posterior circulation stroke, the Basilar Artery Occlusion Endovascular Intervention vs. Standard medical Treatment (BEST) RCT was terminated due to loss of equipoise, which resulted from a high crossover rate and was topped by a small sample size. This trial, however, reported no difference in favorable outcomes of MT patients and those receiving only standard medical treatment including IVT (15). On the other hand, a larger non-randomized cohort study, the Endovascular Treatment for Acute Basilar Artery Occlusion (BASILAR) study, reported that MT within 24 h of estimated occlusion time in basilar artery occlusion patients is associated with better functional outcomes and reduced mortality (16). Data on the safety and efficacy of MT in PCLVO from the randomized controlled Basilar Artery International Cooperation Study (BASICS) and Basilar Artery Occlusion Chines Endovascular Trial (BAOCHE) trials are pending (17, 18). Available data show a strong probability of differences in MT in PCLVO and ACLVO, which may contribute to their safety and efficacy outcomes (19, 20). An improved functional outcome and reduced mortality in moderate-to-severe ACLVO stroke patients have been shown to be dependent on a small infarct core, moderate-to-good collateral circulation, and rapid MT (21). Some PCLVO studies have associated MT with a poor outcome despite having a high recanalization rate, and this has raised interest in possible predicting factors of outcome in PCLVO such as initial stroke symptom severity, collateral status, age, infarct volume, stroke etiology, respiratory insufficiency, and other comorbidities (22–26). Bad outcome could also be a consequence of a delayed treatment since symptoms of posterior circulation stroke are known to be often fluctuating with about 55–63% cases of prodromal transient ischemic attack in spite of a persistent vessel occlusion (14).

Due to the conflicting nature of available studies, we conducted a systematic review and meta-analysis on studies published from 2010 to January 2021 with data comparing MT in PCLVO vs. ACLVO in order to assess the differences of risk factors, as well as safety and efficacy outcomes between both circulations.

MATERIALS AND METHODS

This study was conducted in accordance with the guidelines of the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) (27).

Data Source and Searching

We conducted a database search in PubMed, Cochrane library, and EMBASE before January 23, 2021, for literature from 2010 to 2021 using the following medical search heading (MeSH) and keywords: "acute stroke," "mechanical

thrombectomy," "endovascular treatment," "posterior circulation," "vertebrobasilar occlusion," "anterior circulation," and "large vessel occlusion" (see **Supplementary Methods**). The PubMed search strategy was adapted for use in Cochrane library and EMBASE search databases. No restrictions were made in relation to literature type and text availability. Literature was however screened for study suitability based on title and abstract. Only subject-relevant studies were therefore assessed for eligibility.

Study Selection and Data Extraction

Studies were included if they met the following criteria: (1) retrospective or prospective observational studies with a combined sample size for PCLVO and ACLVO of at least 40, (2) comparison of baseline characteristics and at least two reperfusion treatment profile parameters (i.e., rate of IVT, onset-to-IVT time, onset-to-groin puncture time, onset-to-recanalization time, and number of passages) in PCLVO and ACLVO as main and/or subgroup analysis, and (3) outcome defined by at least two of the following: Thrombolysis In Cerebral Infarction scale (TICI) 2b/3 (28), symptomatic intracranial hemorrhage (sICH), modified Rankin Scale score (mRS) 0–2 at 90 days, and mortality at 90 days. Exclusion criteria included the following: (1) non-English literature, (2) no MT conducted, (3) duplicate literature, (4) insufficient data for comparison purposes, and (5) same datasets used by multiple studies. Duplicates were identified and eliminated using EndNote X9 citation manager software (Clarivate, Philadelphia, PA, USA).

Data extracted from the included studies were patient age, sex, comorbidities/cardiovascular risk factors, stroke etiology, baseline NIHSS, site of LVO, reperfusion treatment profile (rate of IVT, onset-to-IVT time, onset-to-groin puncture time, onset-to-recanalization time, and number of passages), TICI 2b/3, sICH, 90 day mRS 0–2 and mortality.

Quality Assessment

Quality assessment by means of Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) was performed to assess the methodological quality of all included studies under which studies were rated as having either a high, a low, or an uncertain risk of bias (29).

Data search, eligibility assessment, selection, and extraction as well as quality assessment were conducted and crosschecked by two independent investigators and contentions were resolved through a consensus between the two. Publication bias was assessed by means of a funnel plot asymmetry.

Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan) [Computer program], version 5.4.1 (30). We used the Mantel–Haenszel statistical method and a random or fixed effects analysis model for studies with moderate/high and low heterogeneity, respectively, to estimate the pooled effect size. Cochrane I^2 statistics was used to assess heterogeneity. We defined high heterogeneity as $I^2 > 75\%$, moderate heterogeneity as $25\% < I^2 < 75\%$, and low heterogeneity as $I^2 < 25\%$ (31).

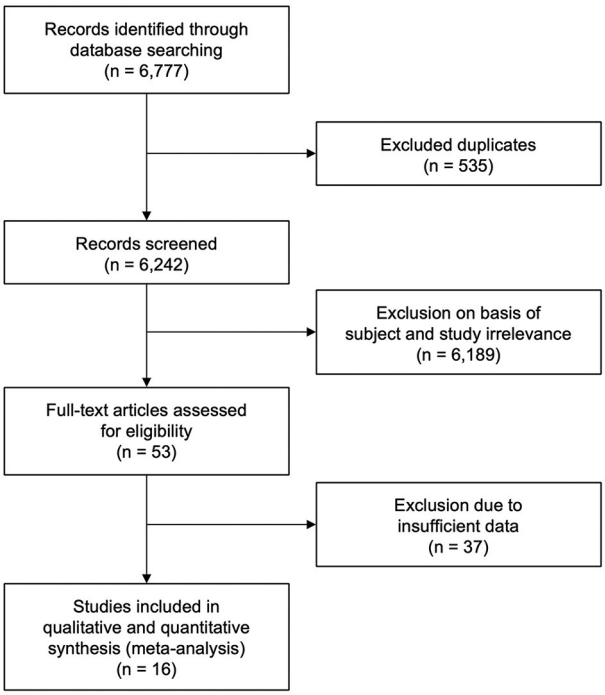

FIGURE 1 | Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram showing study selection (27).

PCLVO and ACLVO were the comparison groups, and the corresponding meta-analysis was performed for each outcome of interest.

Sensitivity analysis was performed for baseline characteristics and recanalization treatment profiles in which retrospective studies were excluded due to higher risk of selection bias (29). We furthermore conducted subgroup analyses in which we excluded studies with <20 patients with PCLVO due to a possible risk of lack of representation of PCLVO with low sample sizes in the real world and studies that primarily recruited patients who received MT until 2012, with the presumption that results could have been compromised by the use of first-generation MT devices (32).

Odds ratios (ORs) and standardized mean difference (SMD) were calculated with 95% confidence intervals (CIs) and $p < 0.05$ was considered significant. For continuous data, the corresponding estimated mean and estimated standard deviation were calculated (33).

RESULTS

Search Results and Study Characteristics

The database search yielded 6,777 citations of literature published between January 1, 2010 and January 23, 2021. A total of 535 duplicate studies were excluded. A total of 6,242 studies were screened, out of which 6,189 were eliminated on the basis of subject and study irrelevance. The remaining 53 studies were individually assessed for eligibility by means of full-text review

TABLE 1 | Baseline characteristics reported in included studies.

Publication	Posterior circulation					Anterior circulation				
	N	Age, years	Female sex	Baseline NIHSS	Occluded vessel	*N*	Age, years	Female sex	Baseline NIHSS	Occluded vessel
Mourand et al. (44)	15	–	–	21 (3–38)	14 BA, 1 VA	25	–	–	17 (9–23)	16 MCA, 9 ICA
Abilleira et al. (34)	65	64 ± 14	21	16 (8–27)	–	471	68 ± 13	221	18 (14–21)	–
Lefevre et al. (45)	26	–	–	–	25 BA, 1 PCA	36	–	–	–	20 ICA, 16 MCA
Fockaert et al. (35)	15	56 (22–86)	2	33 (7–42)	15 PCA	65	64 (22–86)	43	15 (6–42)	47 MCA, 18 ICA
Serles et al. (36)	43	72 (63–77)	19	19 (13–30)	40 BA, 3 VA	258	70 (60–77)	133	17 (13–20)	189 MCA, 65 ICA, 1 ACA
Alonso De Lecinana et al. (26)	52	64 (50–74)	17	11 (6–23)	52 VBA	427	70 (60–77)	214	18 (14–21)	284 MCA, 100 ICA, 43 tandem occlusion
Hu et al. (46)	24	66 (32–85)	11	14 (2–34)	24 VBA	137	66 (22–87)	59	10 (3–26)	94 MCA, 42 ICA, 1 ACA
Khoury et al. (37)	5	–	–	–	5 VBA	35	–	–	–	29 MCA, 6 ICA
Singh et al. (38)	25	56 ± 9	9	19 ± 9	25 BA	112	58 ± 13	41	16 ± 13	61 MCA, 51 ICA
Alawieh et al. (47)	56	27 ± 48	8	17 ± 11	–	380	67 ± 15	192	15 ± 7	–
Meinel et al. (39)	165	70 (59–80)	69	18 (8–30)*	–	1,574	73 (61–82)	810	17 (12–20)**	–
Weber et al. (40)	139	65 ± 16	–	12 (6–21)	–	961	69 ± 14	–	15 (12–19)	–
Wollenweber et al. (41)	303	–	–	–	250 BA, 69 PCA, 59 VA	2,265	–	–	–	1,890 MCA, 666 ICA, 86 ACA
Uno et al. (48)	50	73 (65–79)	17	25 (13–32)	–	295	77 (69–84)	151	18 (13–22)	–
Renieri et al. (43)	44	–	–	–	38 BA, 4 VA, 2 PCA	90	–	–	–	53 MCA, 37 ICA
Huo et al. (42)	145	64 ± 13	37	20 (11–26)	–	596	64 ± 14	216	16 (12–21)	–

**n = 155, **n = 1,558; – = not available, ACA, anterior cerebral artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; N, number of patients; n, reference number of patients; NIHSS, National Institutes of Health Stroke Scale score; PCA, posterior cerebral artery; VA, vertebral artery; VBA, vertebrobasilar arteries.*

with 37 studies being excluded due to lack of sufficient data. Sixteen eligible studies that met the study inclusion criteria were therefore included in our meta-analysis (**Figure 1**). Data from 11 studies (26, 34–43) were acquired from multiple centers and data from 5 studies (44–48) were acquired from single centers. Among these studies, 6 were retrospective (35, 39, 44–47) and 10 were prospective studies (26, 34, 36–38, 40–43, 48). This study comprised a total of 8,898 patients with 1,172 belonging to PCLVO and 7,726 belonging to ACLVO.

Risk of Bias Assessment

Data on risk of bias are shown in **Supplementary Figure 1**; generally, there was a high risk of bias with respect to patient selection, confounding variables, and outcome reporting and a lower risk of incomplete data across all studies.

The funnel plots showed no asymmetry with respect to sICH, indicating a low probability of publication bias across the included studies for sICH. Asymmetry was, however, observed for recanalization success, favorable functional outcome, and mortality (**Supplementary Figure 2**).

Baseline Characteristics

Results of age, sex, baseline NIHSS, and site of LVO for the included studies are reported in **Table 1**. PCLVO patients were younger than ACLVO [SMD = −0.31 (95% CI 0.59–0.03), $p = 0.03$] ($I^2 = 92\%$, $p < 0.00001$) (**Figure 2**). Further results showed less females in the PCLVO group [OR = 0.54 (95% CI 0.39–0.73), $p < 0.0001$] ($I^2 = 59\%$, $p = 0.008$) (**Figure 3**).

Hypertension seemed to be the predominant comorbidity in both PCLCO (56.0%) and ACLVO (62.6%) (**Supplementary Table 1**). Although the pooled results showed hypertension to be comparable in both circulations, there seemed to be a tendency of fewer cases of hypertension as a comorbidity in PCLVO [OR = 0.76 (95% CI 0.54–1.09), $p = 0.14$] ($I^2 = 76\%$, $p < 0.0001$) (**Supplementary Figure 3**). In addition, atrial fibrillation [OR = 0.62 (95% CI 0.50–0.77), $p < 0.00001$] ($I^2 = 0\%$, $p = 0.71$) and hyperlipidemia [OR = 0.73 (95% CI 0.61–0.89), $p = 0.001$] ($I^2 = 9\%$, $p = 0.36$) were less likely comorbidities of PCLVO, with smoking being a more likely comorbidity of PCLVO [OR = 1.22 (95% CI 1.01–1.48), $p = 0.004$] ($I^2 = 0\%$, $p = 0.47$) (**Supplementary Figures 4–6**, respectively). Diabetes mellitus [OR = 0.98 (95% CI 0.72–1.34), $p = 0.91$] ($I^2 = 51\%$, $p = 0.04$), coronary artery disease [OR = 0.64 (95% CI 0.36–1.27), $p = 0.22$] ($I^2 = 62\%$, $p = 0.02$), and previous stroke/TIA [OR = 1.21 (95% CI 0.96–1.53), $p = 0.11$] ($I^2 = 17\%$, $p = 0.30$) were, however, comparable between both groups (**Supplementary Figures 7–9**, respectively).

The average baseline NIHSS was higher in PCLVO [SMD = 0.32 (95% CI 0.15–0.48), $p = 0.0001$] ($I^2 = 75\%$, $p < 0.00001$) (**Figure 4**). In ACLVO, middle cerebral artery occlusion was the most prevalent site of LVO (31.0%) followed by internal carotid artery (13.1%). Basilar artery occlusion was the predominant

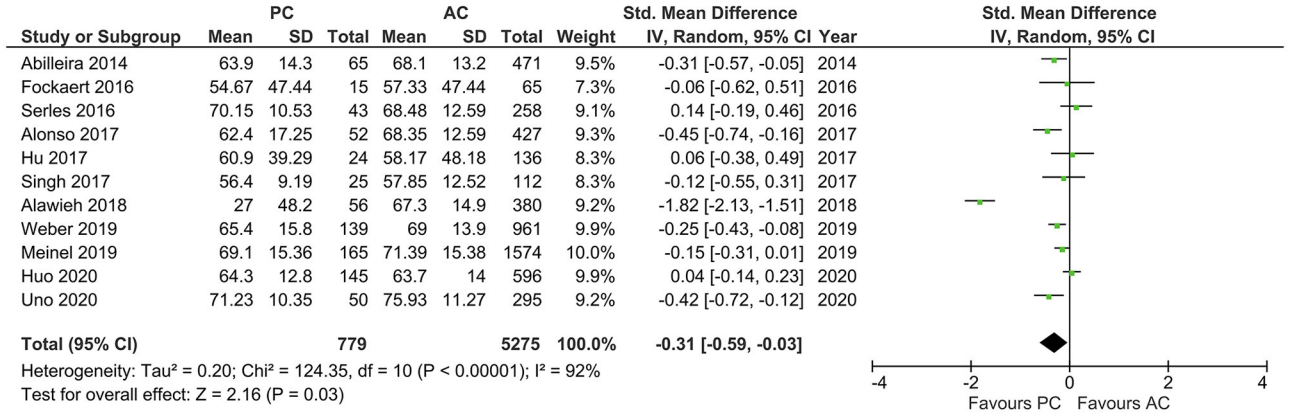

FIGURE 2 | Forest plot comparing "age" of patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; IV, weighted mean difference; *P*, *p*-value; SD, standard deviation; Std., standardized; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

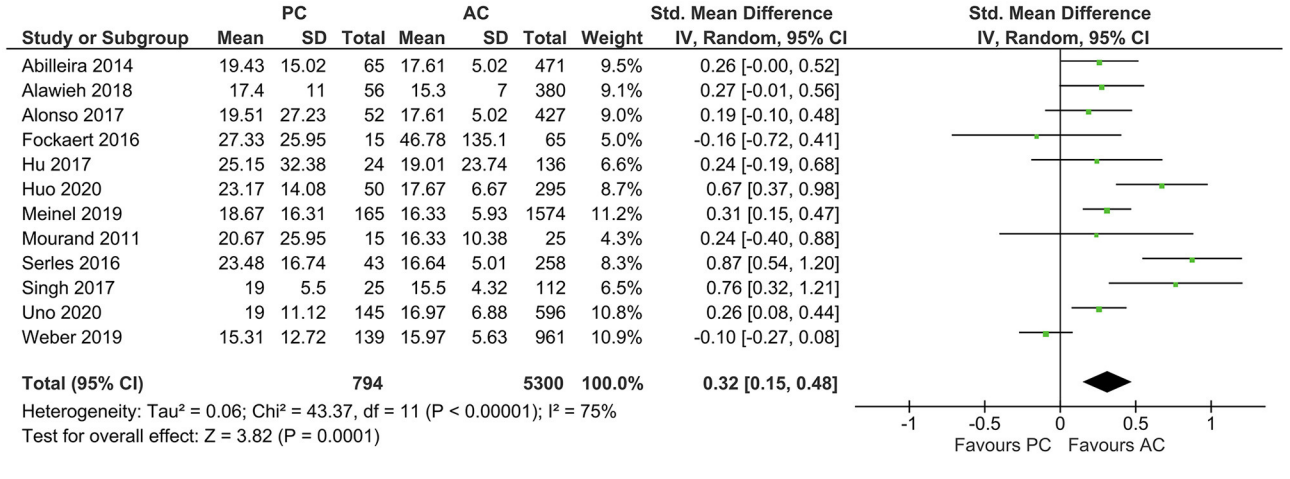

FIGURE 3 | Forest plot comparing the baseline characteristic "female sex" of patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

lesion location in the PCLVO (33.5%) followed by posterior cerebral artery (7.4%).

Large artery atherosclerosis was a more likely stroke etiology in PCLVO [OR = 1.55 (95% CI 1.26–1.91), $p < 0.0001$] ($I^2 = 0\%$, $p = 0.76$) in comparison to ACLVO (**Supplementary Figure 10**). On the other hand, cardiac embolism was a less likely stroke etiology in PCLVO [OR = 0.63 (95% CI 0.52–0.75), $p < 0.0001$] ($I^2 = 0\%$, $p = 0.67$) in comparison to ACLVO (**Supplementary Figure 11**). Results obtained from sensitivity analyses conducted for the baseline characteristics age, sex, admission NIHSS, stroke etiology, and all comorbidities except "prior stroke or transient ischemic attack" had no influence on their respective results (**Supplementary Figures 3–8, 10–14**). However, sensitivity analysis showed "prior stroke or transient ischemic attack" being more likely in PCLVO [OR = 1.39 (95% CI 1.06–1.82), $p = 0.02$] ($I^2 = 0\%$, $p = 0.51$) (**Supplementary Figure 9**).

Recanalization Treatment Profiles

Studies that reported number of IVT showed moderate heterogeneity ($I^2 = 27\%$, $p < 0.0001$). The pooled results indicated a lower frequency of IVT in PCLVO patients [OR = 0.65 (95% CI 0.53–0.79), $p < 0.0001$] (**Figure 5**).

With a high heterogeneity across the studies reporting onset to IVT ($I^2 = 79\%$, $p = 0.008$), the pooled estimates showed a longer onset to IVT in PCLVO [SMD = 0.86 (95% CI 0.45–1.26), $p < 0.0001$] (**Figure 6**). Further analyses also showed a longer onset-to-groin puncture time in PCLVO [SMD = 0.59 (95% CI 0.33–0.85), $p < 0.00001$] ($I^2 = 86\%$, $p < 0.00001$) (**Figure 7**). Results from onset-to-recanalization time in PCLVO, however, did not show any difference compared to ACLVO [SMD

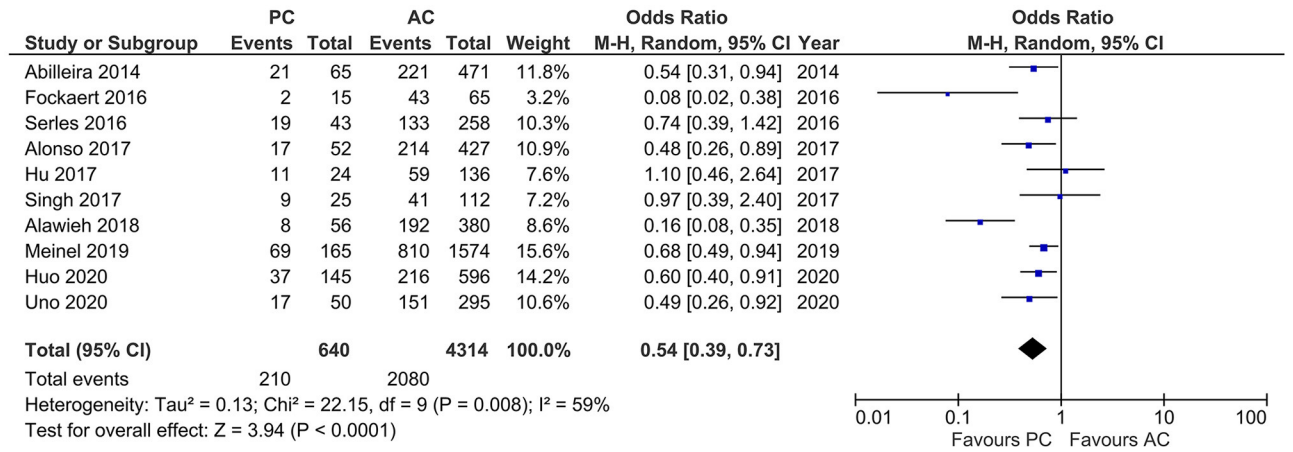

FIGURE 4 | Forest plot comparing "admission NIHSS" of patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; IV, weighted mean difference; *P*, *p*-value; SD, standard deviation; Std., standardized; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

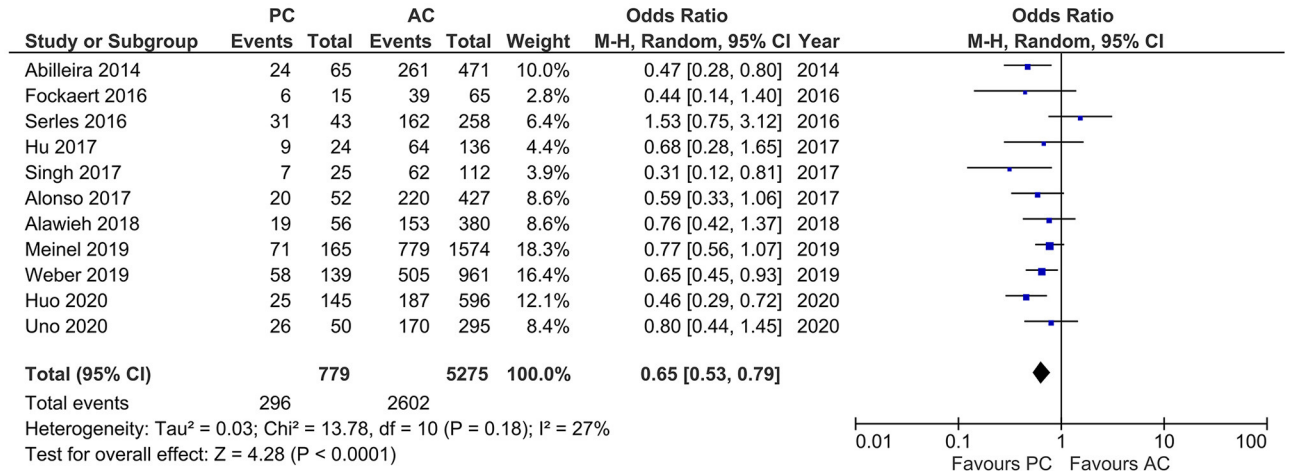

FIGURE 5 | Forest plot comparing rate of intravenous thrombolysis in patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

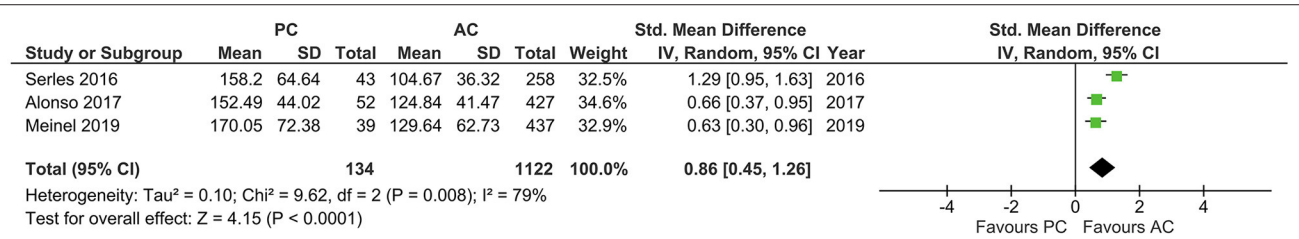

FIGURE 6 | Forest plot comparing "onset-to-intravenous thrombolysis time" in patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; IV, weighted mean difference; *P*, *p*-value; SD, standard deviation; Std., standardized; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

= 0.29 (95% CI −0.04–0.60), $p = 0.08$] ($I^2 = 90\%$, $p < 0.00001$) (**Supplementary Figure 15**). Pooled results for the number of passages did not reveal a difference between PCLVO and ACLVO [SMD = 0.21 (95% CI −0.05–0.46), $p = 0.11$] ($I^2 = 79\%$, $p = 0.0008$) (**Supplementary Figure 16**).

Sensitivity analyses performed for rates of IVT, onset-to-IVT time, onset-to-groin puncture time, and number of passages had no influence on their respective results (**Supplementary Figures 16–19**). However, sensitivity analysis showed PCLVO to be associated with a longer onset-to-recanalization time [SMD = 0.43 (95% CI 0.10–0.77), $p = 0.01$] ($I^2 = 89\%$, $p < 0.00001$) (**Supplementary Figure 15**).

Outcomes of Study

Results of TICI 2b/3, sICH, mRS 0-2 at 90 days, and mortality for the included studies are reported in **Table 2**.

Successful Recanalization

Studies that reported successful recanalization (i.e., TICI 2b/3) showed moderate heterogeneity ($I^2 = 50\%$, $p = 0.01$). The pooled estimates showed no difference in outcomes in both PCLVO and ACLVO [OR = 1.07 (95% CI 0.81–1.42), $p = 0.44$]. In a subgroup analysis in which three studies were excluded on the basis of <20 PCLVO patients and patient recruitment primarily until 2012, the remaining studies showed similar results [OR

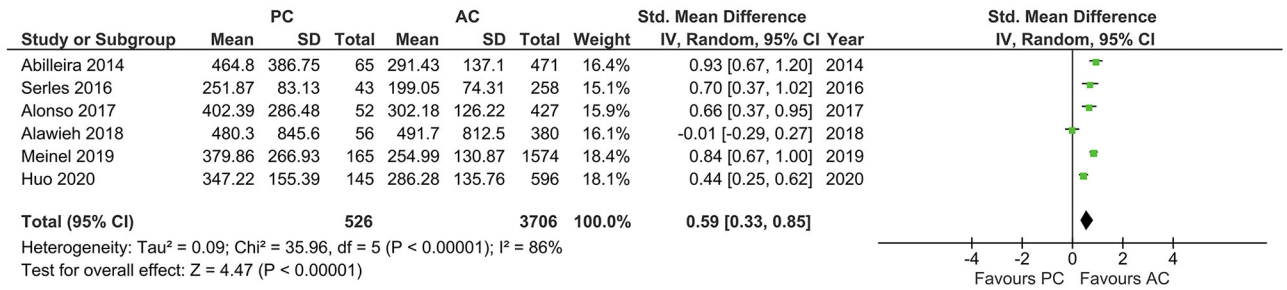

FIGURE 7 | Forest plot comparing "onset-to-groin puncture time" in patients with large vessel occlusion in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; IV, weighted mean difference; *P*, *p*-value; SD, standard deviation; Std., standardized; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

TABLE 2 | Outcomes reported in included studies.

	Posterior circulation					Anterior circulation				
Publication	***N***	**Successful recanalization**	**sICH**	**mRS 0–2 at 90 days**	**Mortality**	***N***	**Successful recanalization**	**sICH**	**mRS 0–2 at 90 days**	**Mortality**
Mourand et al. (44)	15	11	–	5*	7	25	15	–	9	8‡
Abilleira et al. (34)	65	48	5	25	22	471	348	25	207	97
Lefevre et al. (45)	26	23	–	14	–	36	23	–	11	–
Fockaert et al. (35)	15	15	2	–	7	65	47	2	–	14
Serles et al. (36)	43	35	0	–	10	258	207	18	–	24
Alonso De Lecinana et al. (26)	52	39	1	21	17	427	359	23	237	48
Hu et al. (46)	24	19	1	–	4	137	110	12	–	8
Khoury et al. (37)	5	–	–	1	4	35	–	–	19	7
Singh et al. (38)	25	21	–	–	2	112	104	–	–	7
Alawieh et al. (47)	56	54	3	24	16	380	351	20	164	68
Meinel et al. (39)	165	149	8	55**	55**	1,574	1,299‡‡	98‡‡‡	604§§	344§§
Weber et al. (40)	139	96#	0	35***	31***	961	719§	29	281§§§	203§§§
Wollenweber et al. (41)	303	246	–	100##	82##	2,265	1,857	–	732†	570†
Uno et al. (48)	50	50	0	27###	4###	295	250	38†††	105††	22††
Renieri et al. (43)	44	33	–	–	–	90	65	–	–	–
Huo et al. (42)	145	119	4	–	49	596	520	44	–	98

*n = 14, **n = 152, ***n = 92, #n = 134, ##n = 265, ###n = 42, ‡n = 22, ‡‡n = 1571, ‡‡‡n = 1,562, §n = 964, §§n = 1,409, §§§n = 660, †n = 1,997, ††n = 213, †††n = 290; – = not available, sICH, symptomatic intracranial hemorrhage; mRS, modified ranking score; N, number of patients; n, reference number of patients.

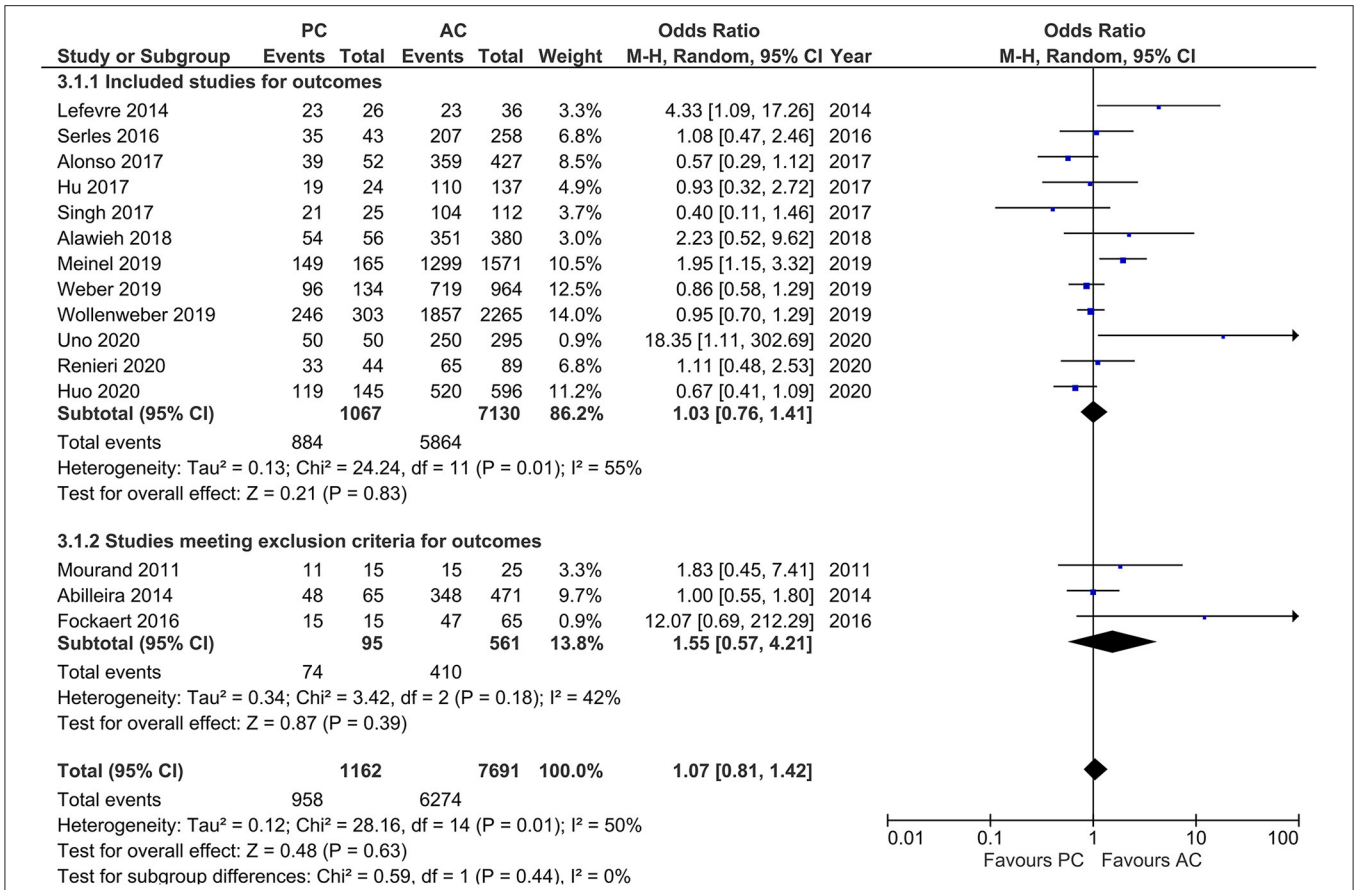

FIGURE 8 | Forest plot of main and subgroup analyses comparing "successful recanalization" defined as thrombolysis in cerebral infarction scale (TICI) 2/3 in patients with large vessel occlusion (LVO) in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Three studies with <20 PCLVO patients and/or patient recruitment primarily until 2012 were excluded from subgroup analysis. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

= 1.03 (95% CI 0.76–1.41), $p = 0.83$] ($I^2 = 55\%$, $p = 0.01$) (**Figure 8**).

Symptomatic Intracerebral Hemorrhage

Studies that reported sICH showed moderate heterogeneity ($I^2 = 42\%$, $p = 0.08$). Our results indicated a lower likelihood of sICH in PCLVO [OR = 0.56 (95% CI 0.37–0.85), $p = 0.006$]. In our subgroup analysis (exclusion of two studies based on <20 PCLVO patients and patient recruitment primarily until 2012), the studies showed a rather reduced heterogeneity ($I^2 = 19\%$, $p = 0.28$). The pooled estimates once again indicated a lower likelihood of sICH in PCLVO compared to ACLVO [OR = 0.44 (95% CI 0.27–0.71), $p = 0.0008$] (**Figure 9**).

Favorable Functional Outcome at 90 Days

Studies that reported favorable functional outcome, defined by mRS ≤ 2 at 90 days, showed a moderate heterogeneity ($I^2 = 41\%$, $p = 0.08$) with comparable likelihood of favorable functional outcome in both PCLVO and ACLVO [OR = 0.92 (95% CI 0.73–1.16), $p = 0.48$]. The subgroup analysis (after exclusion of three studies based on <20 PCLVO patients and patient recruitment primarily until 2012) showed similar findings ($I^2 = 55\%$, $p = 0.04$) [OR = 0.97 (95% CI 0.73–1.27), $p = 0.80$] (**Figure 10**).

Mortality

Studies reporting mortality showed a moderate heterogeneity ($I^2 = 57\%$, $p = 0.004$). MT in PCLVO was associated with a higher likelihood of mortality as compared to ACLVO [OR = 1.92 (95% CI 1.46–2.53), $p < 0.00001$]. The subgroup analysis (after exclusion of four studies due to <20 PCLVO patients and patient recruitment primarily until 2012) likewise showed a higher likelihood of mortality in PCLVO patients [OR = 1.82 (95% CI 1.33–2.48), $p = 0.0002$] ($I^2 = 65\%$, $p = 0.003$) (**Figure 11**).

DISCUSSION

To the best of our knowledge, until the conduction of this meta-analysis, there had been two prior meta-analyses comparing MT in anterior and posterior circulation stroke with both

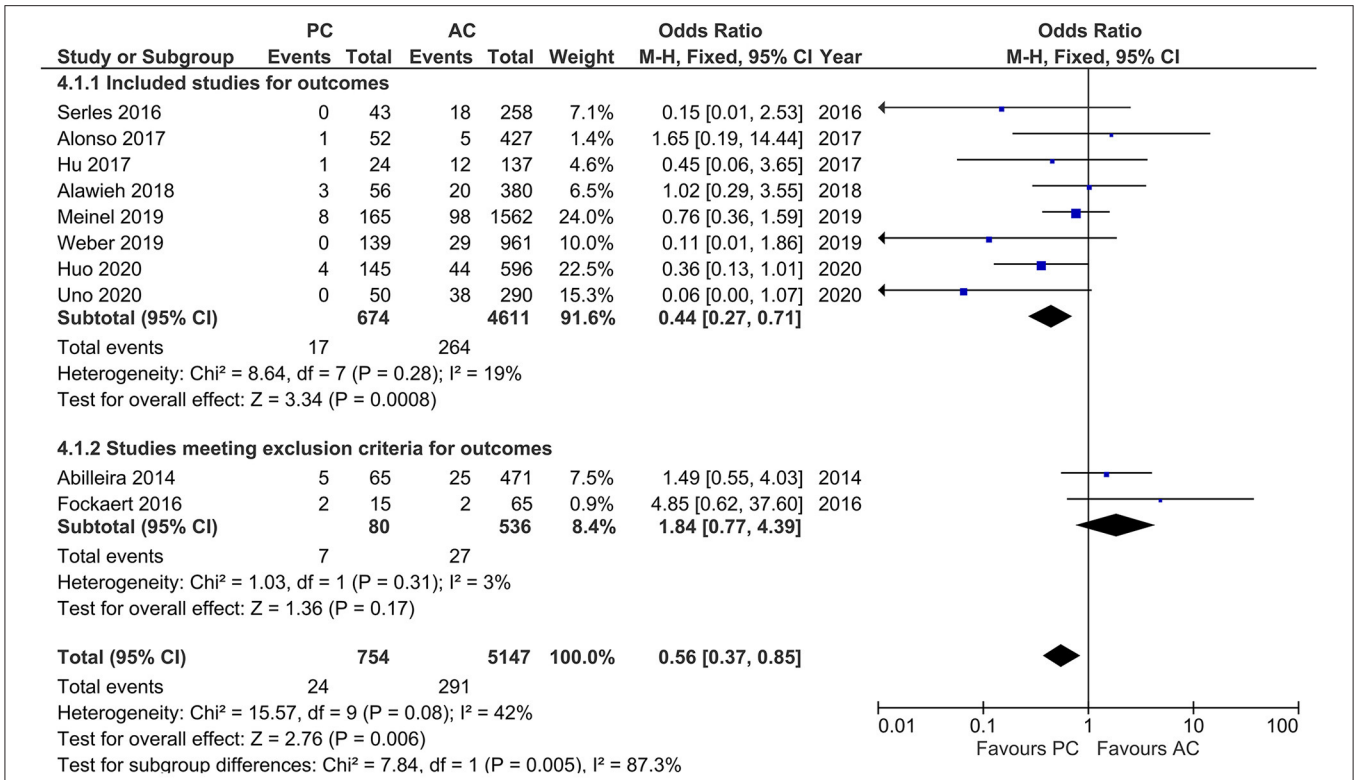

FIGURE 9 | Forest plot comparing "symptomatic intracranial hemorrhage" in patients with large vessel occlusion (LVO) in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Two studies with <20 PCLVO patients and/or patient recruitment primarily until 2012 were excluded from subgroup analysis. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; *Z*, *Z* statistic.

studies, however, focusing on MT safety and efficacy outcomes (19, 20). This study, conducted independently from previous studies, included more recent literature on MT in PCLVO and ACLVO and, in a detailed meta-analysis, further sought to compare demographics and baseline characteristics, risk factors, as well as recanalization treatment profiles between the two brain circulations. Hence, this study presents at the time of publication the most current data on MT in PCLVO vs. ACLVO.

Results on etiology of LVO in our meta-analysis show large artery atherosclerosis (36.7% and 23.1%) and cardiac embolism (34.8 and 47.0%) to be the most common causes of PCLVO and ACLVO, respectively (**Supplementary Table 2**), with large artery atherosclerosis and cardiac embolism being an equally likely etiology in PCLVO. This was consistent with reports from previous literature that reported 26–36% for large artery atherosclerosis and 30–35% for cardiac embolism in PCLVO, although this was based only on basilar artery occlusion (14). The difference in stroke etiologies for the other classification groups such as other determined LVO etiologies (dissection, thrombophilia, paraneoplastic, etc.) and unknown causes, might, however, be inconclusive due to a possible lack of standardized classification of etiology across studies (49).

It is thought that NIHSS gives more weight to neurological deficits in anterior circulation stroke due to factors such as aphasia, facial palsy, and hemiparesis as opposed to limb ataxia, oculomotor disorders, and hemianopia in posterior circulation stroke. However, depending on the level of occlusion, some cases of PCLVO are accompanied by hemiparesis, facial palsy, and dysarthria. It could therefore be argued that a substantial overlap in clinical characteristics exists in both anterior and posterior circulation strokes (14, 50). Contrary to the presumption that NIHSS gives more weight to neurological deficits in anterior circulation strokes, our study detected a higher admission NIHSS in PCLVO than in ACLVO (**Figure 4**). This could be due to more PCLVO patients with reduced consciousness on admission although we do not have data to support this presumption.

Our meta-analysis showed that fewer PCLVO patients are likely to receive IVT in comparison to ACLVO (**Figure 5**). Previous literature have reported prodromal symptoms in up to 60% cases of PCLVO, which, in most cases, is a reason for misdiagnosis and wrong specialty consultation (17, 51). As a result, PCLVO patients may not succeed presenting within the widely accepted 4.5-h time window to receive IVT (52).

Furthermore, the delay in neurological intervention in patients with posterior circulation stroke was reflected in the longer onset-to-IVT and onset-to-groin puncture times in PCLVO (**Figures 6**, **7**). This association is supported by previous studies (53). In spite of the longer onset-to-IVT and

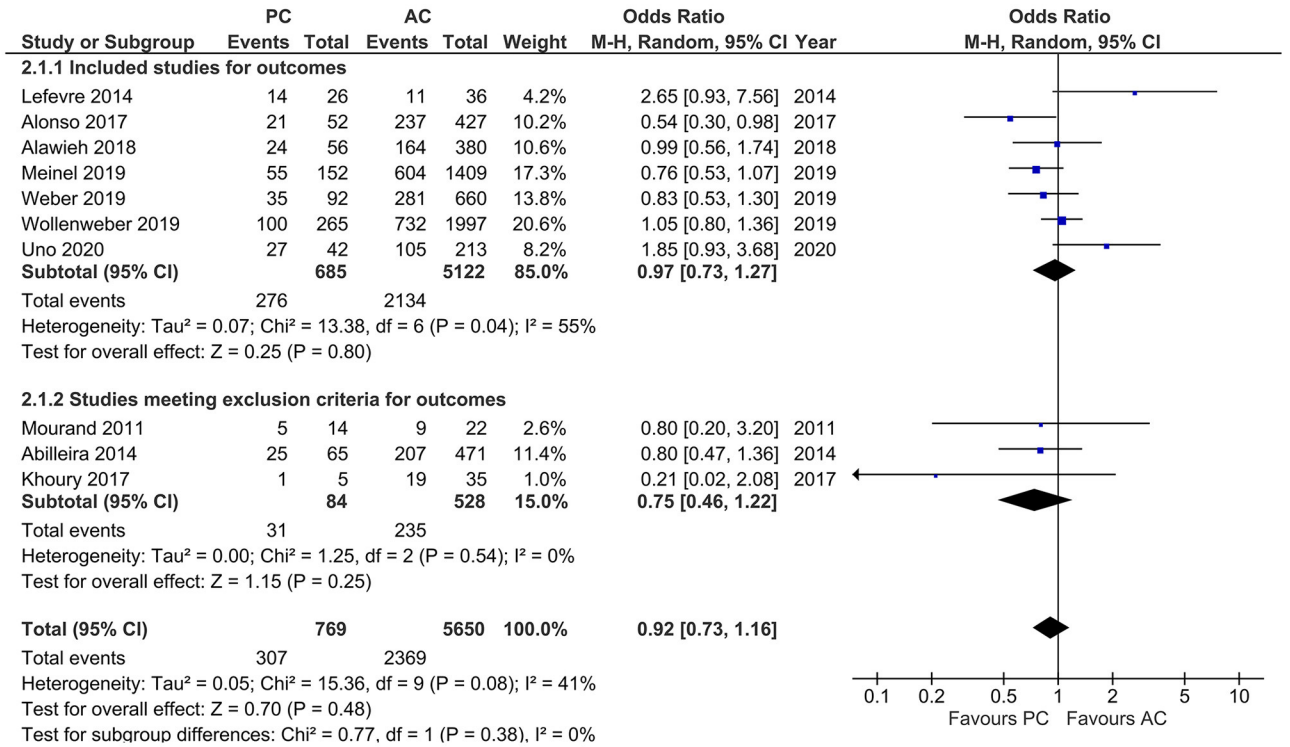

FIGURE 10 | Forest plot comparing "favorable functional outcome (defined as modified Rankin Scale score 0–2) at 90 days" in patients with large vessel occlusion (LVO) in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Three studies with <20 PCLVO patients and/or patient recruitment primarily until 2012 were excluded from subgroup analysis. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

onset-to-groin puncture times in PCLVO, a favorable 90 day functional outcome in PCLVO is, however, equally possible just as in ACLVO (**Figure 10**). This could support the hypothesis that salvageable brain tissue in posterior circulation stroke persists for a longer time as compared to anterior circulation stroke possibly due to a better collateralization in the brainstem (54). Shorter onset-to-IVT and onset-to-groin puncture times could therefore influence a better functional MT outcome in PCLVO. Although onset-to-recanalization time and number of passages were comparable between PCLVO and ACLVO, they tended to be increased in PCLVO patients (**Supplementary Figures 7, 8**). MT in PCLVO was, however, shown to be associated with longer onset-to-recanalization times in the sensitivity analysis, which was not surprising due to the known delays in hospital admission and intervention of PCLVO patients (14, 53).

In our study, we found lower likelihood of sICH in PCLVO (**Figure 9**). Previous literature has attributed the scarcity of sICH in posterior circulation stroke to relatively smaller infarct volumes and the anatomically smaller nature of vessels that supply the brainstem and cerebellum (55, 56). However, this could also be attributed to the lower number of PCLVO patients who receive IVT (**Figure 5**). Several other studies have shown IVT in posterior circulation stroke to be associated with lower occurrence of sICH than IVT in anterior circulation stroke (57, 58). Similar results have been demonstrated by a more recent meta-analysis that indicated a lower likelihood of sICH after IVT in posterior circulation stroke (59). On the other hand, a randomized clinical trial that enrolled 656 patients showed no significant difference in sICH in IVT and non-IVT patients although this study included patients with either ACLVO or PCLVO (60). This raises the question as to whether sICH after MT in PCLVO could therefore be independent of IVT administration. In the anterior circulation, however, MT in addition to IVT has been identified as a significant independent predictor of ICH (56, 61).

Studies by previous meta-analyses showed no statistical difference between PCLVO and ACLVO in both recanalization success and 90 day functional outcome (19, 20). A comparable likelihood of obtaining successful recanalization (**Figure 8**) and 90 day favorable functional outcome (**Figure 10**) was also found in our meta-analysis that included more recent studies. A successful recanalization could therefore influence a good functional outcome irrespective of the circulation involved. Although this study makes a comparison between MT in PCLVO vs. ACLVO, we believe that RCTs are warranted to study if MT in PCLVO is generally efficient.

The incidence of higher mortality in PCLVO has been discussed in numerous previous studies (19, 20). Our study likewise provided data to support the claim that MT in PCLVO is associated with a higher mortality as compared to ACLVO

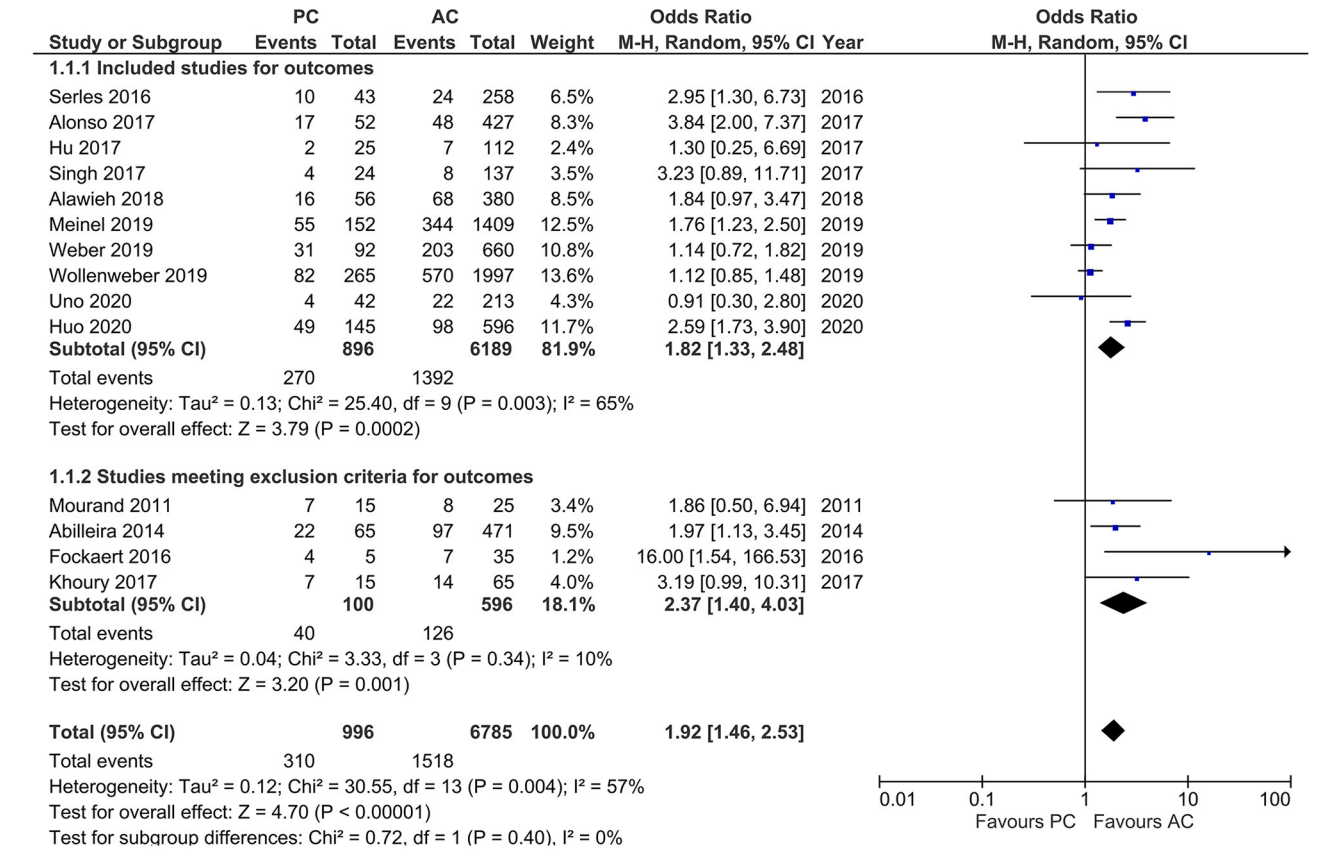

FIGURE 11 | Forest plot comparing "mortality at 90 days" in patients with large vessel occlusion (LVO) in the posterior circulation (PC) vs. anterior circulation (AC) who were treated with endovascular mechanical thrombectomy. Four studies with <20 PCLVO patients and/or patient recruitment primarily until 2012 were excluded from subgroup analysis. Chi^2, chi-square statistic; CI, confidence interval; df, degrees of freedom; I^2, *I*-square heterogeneity statistic; M-H, Mantel–Haenszel statistic; *P*, *p*-value; Tau^2, estimated variance of underlying effects across studies; *Z*, *Z* statistic.

(**Figure 11**). Although it is believed that younger patients tend to have a better stroke outcome in comparison to older patients (55, 56), this study shows that PCLVO patients are younger but yet are still associated with a higher mortality than ACLVO patients.

Futile recanalization, a phenomenon defined as poor functional outcome with mRS 4–6, despite successful recanalization by MT, have been reported in individual studies as being significantly higher in PCLVO than ACLVO [OR = 2.15 (95% CI 1.27–3.63)] (39).

Due to the higher probability of futile recanalization, physicians may be more conservative and may not attempt MT in older PCLVO patients, hence creating a selection bias with higher numbers of younger patients being considered for MT. It is, however, worth mentioning that this study does not include data on futile recanalization and physicians' patient management.

The higher rate of mortality in PCLVO compared to ACLVO could be partly due to the relatively higher NIHSS on admission and, hence, stroke severity in posterior circulation stroke (**Figure 4**). This is in line with previous suggestions that stroke severity on admission is an important predictor of stroke outcome, especially in the posterior circulation, and that higher baseline NIHSS in PCLVO is associated with a poor outcome (24, 62).

In addition, stroke due to basilar artery occlusion has been described as severe in relation to other occlusion sites in PCLVO (63). We reported basilar artery occlusion as the most frequent site of PCLVO (33.5%) (**Table 1**), which may also have contributed to the higher mortality. This study therefore suggests onset-to-IVT and onset-to-groin puncture times, NIHSS, and basilar artery occlusion as factors that could influence outcome in PCLVO. As a reason for high mortality in PCLVO, we propose a subtle progressive-over-time damage or a non-life supporting damage in the posterior circulation, possibly due to the gravity and irreversible nature of the damage to support life despite neurorehabilitation. Such damages have been described as a comatose state or locked-in syndrome, dysphagia, tracheostomy, hypostatic pneumonia, and complications as a result of being long-term bedridden (42). However, this hypothesis cannot be supported by the present study and we therefore encourage further studies to detect causes of higher mortality of MT in PCLVO.

Limitations

Although we implemented measures to limit setbacks in this study, we were nonetheless posed with a couple of challenges. Firstly, such a meta-analysis with several studies over such long duration faces the problem of high heterogeneity with respect to stroke management across studies. Secondly, although efforts were made to exclude the possible effects of the use of first-generation MT devices, there was no 100% guarantee that all remaining studies included in our subgroup analyses exclusively used second-generation MT devices. Thirdly, there was a huge disparity in number of PCLVO and ACLVO patients. Finally, the lack of RCT in both groups introduces selection bias.

CONCLUSION

Although MT in PCLVO differs characteristically and also in terms of outcome from ACLVO, our meta-analysis indicates that MT in PCLVO may be equally efficient just as in ACLVO in achieving successful recanalization and a favorable 90 day functional outcome. Although MT in PCLVO is associated with lower likelihood of sICH, possibly due to fewer PCLVO patients receiving IVT because of late recognition and presentation, PCLVO is associated with a higher occurrence of mortality. This higher mortality could be explained through the high baseline NIHSS, longer onset-to-IVT and onset-to-groin puncture times, and basilar artery occlusion being the most predominant site of PCLVO.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JM and SP conceived and designed the study, undertook data extraction, analyzed the data, and drafted the manuscript. KP and JT independently rechecked all extracted data and analysis. AG-E, YW, KF, and AM helped with data analysis. UZ helped interpret the data. SP had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.687134/full#supplementary-material

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REVIEW
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Pitfalls in the Diagnosis of Posterior Circulation Stroke in the Emergency Setting

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Posterior circulation stroke (PCS), caused by infarction within the vertebrobasilar arterial system, is a potentially life-threatening condition and accounts for about 20–25% of all ischemic strokes. Diagnosing PCS can be challenging due to the vast area of brain tissue supplied by the posterior circulation and, as a consequence, the wide range of—frequently non-specific—symptoms. Commonly used prehospital stroke scales and triage systems do not adequately represent signs and symptoms of PCS, which may also escape detection by cerebral imaging. All these factors may contribute to causing delay in recognition and diagnosis of PCS in the emergency context. This narrative review approaches the issue of diagnostic error in PCS from different perspectives, including anatomical and demographic considerations as well as pitfalls and problems associated with various stages of prehospital and emergency department assessment. Strategies and approaches to improve speed and accuracy of recognition and early management of PCS are outlined.

Keywords: emergency department, diagnostic error, misdiagnosis, stroke, posterior circulation

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INTRODUCTION

Physicians long viewed posterior circulation stroke (PCS) as an entity sufficiently distinct from anterior circulation stroke (ACS) to justify focusing on particulars of management rather than attempting to identify stroke etiology and deriving therapeutic recommendations (1). The initiation of the New England Medical Center Posterior Circulation Registry (NEMC PCR) in 1988 constituted a critical turning point, as this research provided a large body of new clinical and imaging information which challenged this historical view and emphasized that PCS and ACS were, in fact, more alike than they were different. In the wake of this work, the number of publications dealing with a wide range of PCS-related topics increased dramatically. Nevertheless, despite advancing knowledge about PCS, rates of misdiagnosis still exceed those in ACS, which is related to several functional-anatomical properties of the posterior circulation and the clinical consequences resulting from acute vascular pathology. These inherent characteristics furthermore lead to several challenges concerning the correct recognition and diagnosis of PCS in the emergency department.

WHY PCS POSES A CHALLENGE TO CORRECT DIAGNOSIS

Differences in Vascular Anatomy and Susceptibility to Pathology

While the general nature of stroke in the anterior and posterior circulation is similar in many respects, there are distinct anatomical differences between the carotid and the vertebrobasilar vascular anatomy contributing to some of the differences in the way PCS is conceptually approached. The posterior circulation consists of the vertebral arteries arising from the subclavian

arteries, three paired cerebellar arteries, the basilar artery, and the posterior cerebral arteries. Unlike the internal carotid artery, which gives rise to many smaller branches, the bilateral vertebral arteries join to form one large single midline vessel, the basilar artery, which supplies the brainstem, occipital lobes, and thalamus. Vascular pathology of various kinds can lead to multi-level strokes in different anatomical regions of the posterior circulation (2, 3). Long circumferential arteries with a superficial course supply the lateral parts of the brainstem and the cerebellum, while small penetrating arteries direct blood to the medial portions of the brainstem and the base of the pons (4). In comparison to the anterior circulation, larger parts of the posterior circulation are fed by penetrating vessels with typical distributions of arterial supply. As these arteries do not form collaterals, vascular occlusion causes a lacunar stroke.

The anatomical and functional complexity of the structures in the brainstem may make localization of clinical signs and identification of the site of infarction in the posterior circulation difficult. Most of the more recent posterior circulation stroke registries (5, 6) categorized stroke locations into the proximal, middle and distal vertebrobasilar artery territory as initially suggested by Caplan et al. (7) and demonstrated in **Figure 1**. In the NEMC PCR, most of the infarcts occurred in the distal territory (40%), followed by proximal (18%) and middle (16%) territory sites of infarction.

Atherosclerosis is the most common disease of the posterior circulation arteries. *In situ* thrombosis often leads to complete vessel occlusion, which in case of the basilar artery has devastating consequences with mortality rates of up to 90% (8). Embolism from the heart or proximal supplying vessels accounts for 20–30% of posterior circulation infarcts (9). Especially in young patients, vertebral artery dissections—due to trauma or hereditary disorders—can give rise to PCS. Small vessel disease often affects the paramedian branches of the basilar artery penetrating pontine tissue. While 40% of the brain's blood supply is provided by each internal carotid artery, ∼20% of cerebral blood flow is attributable to the vertebrobasilar circulation (10). This predicts one out of five isolated cardioembolic strokes to be in the posterior circulation, as has been shown by diffusion-weighted MRI studies analyzing lesion patterns and stroke subtypes (9). The geometry of the vertebral artery origin from the subclavian artery differs compared to the carotid system since the vertebral artery has a nearly 90° take-off and is much smaller than its parent artery, thus increasing the risk factors for local atherosclerosis (11). Perhaps one of the most striking features of the vertebrobasilar circulation is the high frequency of anatomical variants—congenital anomalies, hypoplastic arteries, and adult retention of fetal arterial communications and patterns, to name the most relevant (12–14). Most are clinically insignificant, but some may impact stroke risks. For example, vertebral artery hypoplasia has been observed disproportionately frequently in strokes affecting the posterior inferior cerebellar artery (15), even though this has not been found to affect lesion size and clinical severity (16). In addition, knowledge about anatomical variants and anomalies in an individual may be relevant for identifying stroke etiology and the ensuing therapeutic consequences (17).

Atypical Presentation as an Obstacle to Pre- and Early Intrahospital Symptom Awareness and Recognition

Positive outcome after ischemic stroke heavily relies on early treatment, which again depends on the fast and correct recognition and interpretation of stroke symptoms by patients and bystanders as well as by emergency medical service (EMS) and emergency department (ED) staff in both the pre- and early intrahospital phase. In this context, less classic or less commonly-known symptoms and atypical patient characteristics may represent specific challenges to PCS identification.

Lower Awareness for PCS Signs and Symptoms

A high level of public awareness of stroke symptoms and the need to seek immediate medical attention is crucial for effective acute stroke treatment. Although no study has specifically focused on signs of PCS, research indicates that overall, there is much room for improvement. A study focusing on temporal trends in public awareness between 1995 and 2005 in Cincinnati found that knowledge of stroke warning signs only slightly improved: those able to name three warning signs rose from 5 to 16%, while there was no improvement in the ability of the public to name at least one warning sign (18). Not surprisingly, of typical stroke symptoms, the one named least frequently was trouble seeing/visual impairment. Interestingly, visual field abnormalities are among the most common manifestations of PCS yet constitute a symptom of which patients are often unaware (19). Finally, a Korean survey noted an underappreciation of stroke warning signs other than sudden paresis or numbness (20). Subsequently, it is not surprising that process times like onset-to-door and door-to-imaging times are significantly higher for PCS (21). A recent systematic review aimed to identify the characteristics of acute stroke presentations associated with inaccurate identification by EMS (22). The authors conclude from data reported in 21 studies that between 2 and 52% of all stroke presentations transported by EMS are not diagnosed on-site. The most common stroke presentations in these cases included posterior circulation symptoms such as nausea/vomiting, dizziness, and visual disturbance/impairment. Clinical manifestations of PCS and differential diagnoses to consider are presented in **Table 1**, **Figure 2**. While present in patients with an acute stroke, most frequently in those with PCS, these symptoms may occur in a wide range of conditions and thus possess a low signal-to-noise ratio when it comes to stroke detection. Mental status alterations—a term way too imprecise for a wide variety of cognitive and behavioral symptoms reported in PCS—have been reported in up to 25% of missed stroke cases (26–28). However, due to the anatomical features and idiosyncrasies discussed above, it is essential to recognize that these symptoms rarely occur in an isolated fashion in acute stroke. PCS can present with a wide range and combination of symptoms and signs, some of which overlap with those caused by ACS.

As PCSs often present with non-specific symptoms such as dizziness, headache, nausea, and vomiting (2, 24), these

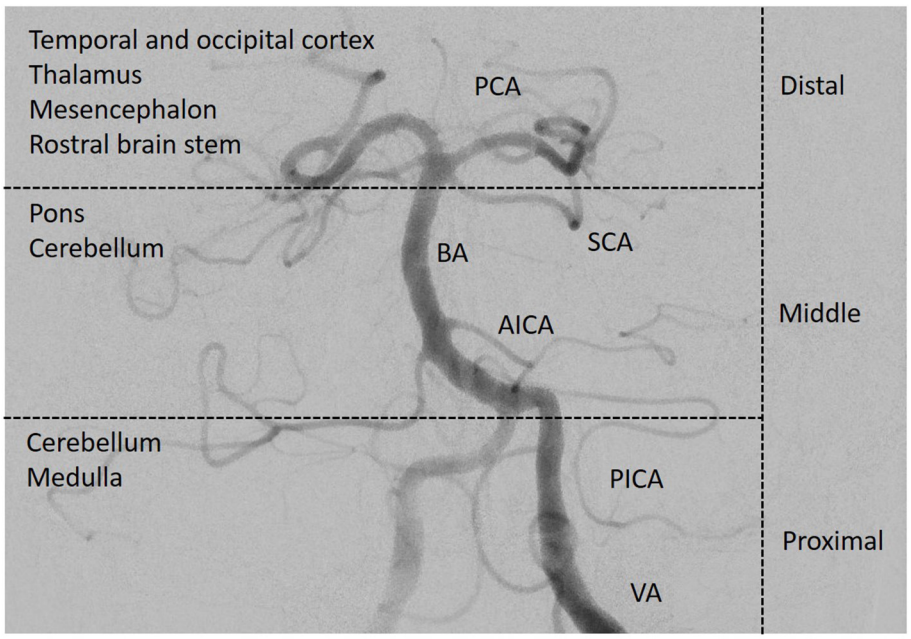

FIGURE 1 | Posterior circulation vasculature. The vessels of the posterior circulation can cause multi-level strokes in different anatomical regions of the posterior circulation. The complexity of especially the structures in the brainstem makes localization of clinical signs and the site of infarction more difficult than in the anterior circulation. Angiography of the left vertebral and basilar artery. PCA, posterior cerebral artery; SCA, superior cerebellar artery; BA, basilar artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery; distribution according to the New England Medical Center Posterior Circulation Stroke Registry (3). (*Image courtesy of C. Herweh, Frankfurt*).

are usually not interpreted as potential stroke symptoms by prehospital care providers and subsequently not assessed in this context. On the contrary, Andersson et al. (29) found that precisely those symptoms were more frequently documented and evaluated in patients in whom no stroke was suspected. This is extremely important to acknowledge in particular because the framing of a call as a potential stroke significantly impacts emergency department processes. The positive impact of early stroke identification and ED pre-notification in general (30) may generate a false sense of security with ED personnel over-relying on EMS staff's diagnostic impression and decision-making (31). Similarly, widely-used triage tools have been shown to under-appreciate the idiosyncrasies of neurological emergencies (32, 33). Atypical stroke symptoms may not only obscure subtler neurological abnormality, but they may also make the clinical assessment, especially by non-neurologists, difficult. Not surprisingly, there are also reports showing that clinical deficits in hyperacute stroke assumed to be caused by pathology in the anterior circulation eventually turn out to be PCS (34). Localizing capacities are thus brought to their limits, which would not be worrisome if a stroke is recognized as such and the necessary diagnostic and therapeutic measures ensue. All of the challenges mentioned above contribute to a lower likelihood of early arrival of PCS patients in the ED (35) and more frequent delays in neurological evaluation after initial ED assessment and delayed intravenous tissue plasminogen activator administration compared with ACS patients (36).

Recent studies indicate that 20–60% of acute ischemic strokes are missed in the emergency room setting (37, 38). Of these, PCSs are nearly three times more likely than ACSs to be missed, especially when presenting with nausea/vomiting and dizziness (37). The risk of misdiagnosis is high when presenting complaints are mild, non-specific, or transient, suggesting that many cases of diagnostic error relate to symptom-specific factors and perceived degree of impairment (38). While these data refer to general ED populations, stroke is even less frequently suspected in the young due to the lack of cardiovascular risk factors and a different range of potential etiologies. According to a recent study, these aspects underlie about 30% of missed strokes in young patients in the ED (39). Clinical signs that were initially missed in 50% of patients later identified by the first neurological consultation included Horner's syndrome, mild focal weakness (monoparesis or hemiparesis), ataxia, nystagmus, and hemianopia. Misdiagnosed patients were more frequently females, had a significantly higher prevalence of dissections and stroke involving the posterior circulation. Another study found that patients aged 35 years or below with PCS were more likely to be misdiagnosed (40). An especially vulnerable population are women: several studies found that women present more often with atypical stroke symptoms than men (39, 41). This situation is made even more difficult because there is a higher incidence of benign causes of symptoms such as headache or vertigo in women and that several stroke mimics share these characteristics with stroke chameleons, i.e., atypical stroke presentations (42, 43).

TABLE 1 | Clinical manifestations of posterior circulation stroke.

Territory	Affected territory	Clinical manifestation
Distal	Posterior cerebral artery	Occipital cortex: visual field defect with contralateral homonymous hemianopia, photopsia, and visual illusion; bilateral: cortical blindness, amnesia and agitation (Anton's syndrome) Thalamus: impairment of arousal and orientation, learning and memory, personality, and executive function; contralateral hemisensory loss, hemiparesis and hemiataxia, and pain syndromes, visual field deficits, sensory loss, weakness, and dystonia left: language deficits; right: visual-spatial deficits
	Top of the basilar artery	Mesencephalon, thalamus and occipital and temporal lobe: unconsciousness, oculomotor disturbances, cortical blindness, neuropsychological and mnestic deficits
Middle	Common brainstem syndromes	Weber's syndrome/paramedian and lateral midbrain infarct: ipsilateral III nerve palsy, contralateral hemiplegia Foville's syndrome/pontine tegmentum: Unilateral horizontal-gaze palsy, contralateral hemiparesis Wallenberg's syndrome/lateral medullary infarct: ataxia, vertigo, nystagmus, nausea and vomiting, loss of pick sensation in the ipsilsateral side of the face and contralateral side of the body, dysphagia, dysarthria, ipsilateral Horner's syndrome
Proximal	Superior cerebellar artery (from upper basilar artery)	Ipsilateral: limb dysmetria, Horner's syndrome; contralateral: loss of sensation for temperature and pain, IV nerve palsy, hearing loss, sleep disorder
	Posterior inferior cerebellar artery (from intracranial vertebral artery)	When infarct spares the medulla: vertigo, headache, gait ataxia, appendicular ataxia, horizontal nystagmus, with medullary involvement: Wallenberg's syndrome
	Anterior inferior cerebellar artery (from lower basilar artery)	Vertigo, vomiting, tinnitus, dysarthria, dysphagia, Ipsilateral conjugate-lateral gaze palsy Ipsilateral: Limb motor weakness, facial palsy, hearing loss, trigeminal sensory loss, Horner's syndrome, appendicular dysmetria

Differential diagnosis of posterior circulation stroke: intoxication, infectious disorders, posterior reversible encephalopathy syndrome, migraine, seizure, benign paroxysmal peripheral vertigo, Meniere's disease, Wernicke's encephalopathy, central pontine myelinolysis, electrolytse disturbances

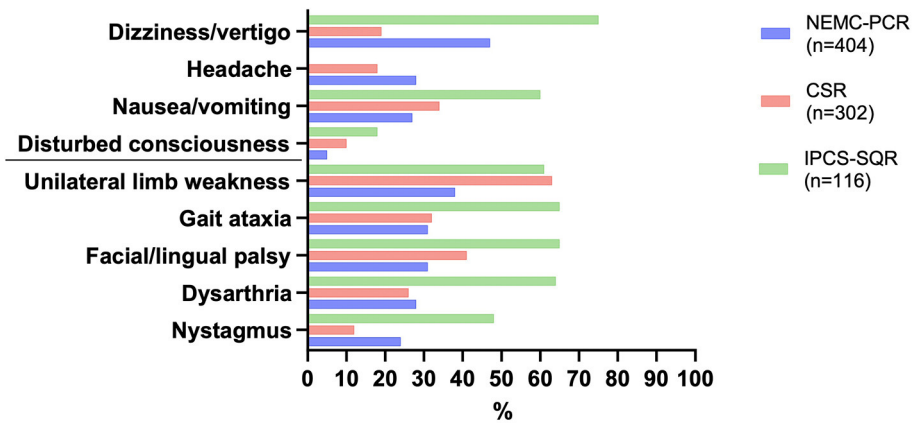

FIGURE 2 | Most common symptoms in posterior circulation stroke as reported in the three large registries. NEMC-PCR, New England Medical Center Posterior Circulation Registry (23); CSR, Chengdu Stroke Registry (24); IPCS-SQR, Ischaemic Posterior Circulation Stroke in the state of Qatar Registry (25).

Shortcomings of Pre- and Early Intrahospital Scales and Tools

Different instruments for rapid stroke recognition have been developed, most of these predominantly intended for prehospital assessment by EMS personnel. The Face Arm Speech Test (FAST) is perhaps the most popular, also designed to aid stroke sign recognition by the general public. Prehospital stroke detection scales have been found to have similar shortcomings, with e.g., FAST missing about half of PCS (44, 45). Furthermore, patients with stroke misdiagnosis were commonly FAST-negative with non-specific symptoms including altered mental status, dizziness, and nausea/vomiting often associated with PCS, a finding that provides a false sense of security during ED assessment (46). In addition, recent years have seen a relative predominance of research concerning the suitability of prehospital stroke scales to recognize patients with large-vessel occlusion, who—as potential candidates for endovascular therapy (EVT)—require fast allocation to an EVT-capable stroke center (47). The primary focus here has been the detection of anterior circulation pathology rather than consideration of a subgroup of stroke

patients with atypical symptoms and less-clear long-term benefit from acute interventions.

The National Institutes of Health Stroke Scale (NIHSS) is the most widely used deficit rating scale for assessing patients with acute ischemic stroke. While it has been shown to have a significant association with vessel occlusions in patients with ACS, performance in patients with PCS is poorer (48). Accordingly, PCS patients from the Acute Stroke Registry and Analysis of Lausanne had lower NIHSS at admission than ACS patients (49). The vast majority of PCS patients have a baseline NIHSS scores $\leq$4 (50), and even a value of 0 cannot rule out the presence of stroke, a finding reported in PCS patients in particular. In those patients commonly presenting with symptoms like headache, vertigo, and nausea and truncal ataxia as the most common neurologic signs (51), the NIHSS drastically underestimates the degree of stroke-associated functional impairment.

The Risk of False-Negative Neuroimaging of the Posterior Fossa

Brain imaging plays a pivotal role in the differential diagnosis of neurological deficits, and CT is usually employed in the emergency setting because of its wide availability and speed of the examination. Due to bone-related artifacts and suboptimal brainstem resolution, however, the ability of this imaging modality to visualize small—in particular pontine and medullar—lesions is limited. Studies suggest that the sensitivity of CT for the detection of acute PCS is low (52) and that a negative CT may lead to false reassurance and missed stroke diagnoses in the emergency setting, especially in patients with less severe or inconclusive symptoms (53). To some extent, this disadvantage is attenuated when multimodal CT-imaging (CT angiography and CT perfusion) is employed, as reported for patients with acute vestibular syndrome who received intravenous thrombolysis triggered by information supplied by these procedures (54). One study found that while there were lower rates of early ischemic signs on admission CT and overall arterial pathology in PCS than in ACS, intracranial arterial pathology was more prevalent in the former (49). On a related note, in certain constellations of high clinical certainty of an acute cerebrovascular event, CT angiography is mandatory for demonstrating the site of vascular occlusion, thereby guiding treatment decisions (55). Compared to digital subtraction angiography (DSA), CT angiography is a reliable method for detecting lesions in the posterior circulation. It may, due to its relative ease of applicability, frequently be used instead of DSA. Similarly, adding CT perfusion to the scanning protocol may improve diagnostic accuracy (56). However, particularly in vertebral artery imaging, DSA remains superior (57).

Diffusion-weighted MRI (DWI) was introduced and established as a routine imaging procedure in acute ischemic stroke in the late 1990s; since then, many studies covering numerous different facets of ischemic stroke diagnostics have been published. DWI is exquisitely sensitive and able to demonstrate even minutely-sized acute ischemic lesions (58). The impaired mobility of water protons in ischemic tissue generates a strong signal against the background of healthy tissue on DWI, which provides high contrast of the lesion. The characterization of especially brainstem ischemic stroke lesions via imaging—previously only possible in post-mortem neuroanatomical studies—has since seen tremendous improvement (59). The number of publications dealing with routine clinical use of DWI related to specific aspects of PCS has risen substantially, and various clinical-anatomical facets have been explored (60, 61). However, despite the obvious advantages of DWI, a considerable number of infarcts may still be missed in cases of false-negative imaging (62), which was reported in the context of small lacunar lesions (63), in association with minor clinical deficits of <5 NIHSS points (64), and when MRI was performed very shortly after symptom onset (65). In addition, false negativity of DWI was found to occur five times more often in PCS (66). This phenomenon has been attributed to a different temporal evolution of DWI hyperintensities in acute brainstem infarcts compared to hemispheric stroke in the anterior circulation (67). As sensitivity increases over time, an early negative MRI, in particular, should not be relied upon too readily to rule out PCS, especially when symptoms persist.

DIAGNOSTIC ERROR IN THE EMERGENCY CONTEXT

Diagnostic error constitutes a substantial hazard to patient safety, and its potential consequences such as permanent disability or death are dire (68). It disproportionally affects neurological disorders and cerebrovascular events like stroke in particular (38, 41, 69–71). As a result, time-sensitive treatments may not be administered, and established standards of stroke care or secondary preventive measures may not be implemented. These missed opportunities bear significant medical and socioeconomic ramifications like higher rates of disability and mortality (72), higher hospital readmission (37), and prolonged hospitalization (70).

Bedside examination and clinical reasoning and decision-making are particularly prone to error (73, 74). In the latter two, clinicians employ heuristics in order to process complex information and plan work-up and treatment efficiently. They are indispensable in day-to-day practice, but in particular in the prehospital and emergency department context, which are fast-paced environments where there is often only limited or incomplete information available upon which part of the diagnostic considerations are based. In addition, time and resource constraints, frequent interruptions, and the need to multitask characterize these workplaces. Despite their undeniable value, heuristics are associated with certain pitfalls, which may lead to diagnostic error (75, 76). Accordingly, failed heuristics have been identified as one type of cognitive error occurring in the ED (77). Some of the diagnostic challenges presented by PCS and discussed above may be linked to different kinds of cognitive errors, such as diagnostic anchoring when EMS staff initially do not consider stroke, and later it is not introduced into the spectrum of differential diagnoses. Similarly, false reassurance by a negative CT scan can be considered an

instance of blind obedience (76). These heuristics need to be viewed in the context of two different modes of information processing and management, a Type 1 "intuitive" and a Type 2 "analytical" mode of thinking, each of them possessing distinct merits and weaknesses (78). A number of strategies and interventions have been suggested to address these cognitive factors and the employment of Type 1 and Type 2 thinking, e.g., through debiasing techniques, reflective practice, or cross-checks. However, evidence for their effectiveness especially in the emergency care system is limited (79). There are no initiatives directly addressing cognitive errors in missed diagnoses of stroke in general and PCS in particular but a variety of solutions targeting different stages of the process of recognizing and diagnosing stroke have been suggested, and both implicit and explicit reverberations of cognitive phenomena and corresponding corrective strategies can be identified therein.

APPROACHES TO SOLVING THE PROBLEM OF PSC MISDIAGNOSIS

Improving Symptom Recognition Prehospitally and During Triage

Timely recognition of stroke symptoms in the prehospital context as the first link in the chain of acute stroke care is an essential precondition for all following phases and refinement efforts. The need for improvement here is underscored by the fact that onset-to-door times have seen comparatively little change in comparison to intrahospital process times (30, 80, 81). Campaigns targeted at raising public stroke awareness may aid in increasing knowledge about stroke symptoms and the subsequent motivation to seek medical advice (82), even though help-seeking behavior has been found to be more dependent on perceived symptom severity than on actual symptom knowledge (83). The dominant representation of motor and speech disturbances in many public campaigns and the more pronounced functional impairment frequently associated with them may further increase disparities regarding the appropriate recognition and interpretation of atypical stroke symptoms or mild deficits. One challenge to address in the future will be to adequately represent these stroke manifestations without sacrificing brevity and memorability for application in public incentives. One of these respective attempts concerns the extension of the FAST mnemonic to include an assessment of balance and eye movement abnormalities, BE-FAST (84). Despite the lack of prospective studies, this modification of a screening method used by laypersons as well as EMS dispatchers and providers alike may be a promising strategy to pursue. In a retrospective study, BE-FAST was found to be a very sensitive tool for screening among hospitalized patients evaluated through an inpatient stroke alert system (85). Even though shortcomings of preclinical stroke screening instruments regarding PCS diagnosis have been appreciated, there have been relatively few efforts to supplement them with additional tools for PCS recognition (86). The same holds for severity scales like the NIHSS, for which an extended version, the eNIHSS, appreciating the posterior circulation has been offered (87) but does not appear to have gained much practical traction. Increasing knowledge and awareness in EMS staff regarding atypical stroke syndromes as those frequently found in PCS will be an important target for future work to reduce prehospital delays and errors in the early stages of patient assessment and allocation. One ambulance service in the UK added nausea to their prehospital stroke screening tool, which also includes vertigo, visual problems, and ataxia as further signs indicative of PCS (88). Another study demonstrated that an initiative as simple as training paramedics to perform the finger-to-nose test may facilitate PCS identification (89). The particular relevance of such efforts is also emphasized in the context of a recent study suggesting that ED staff does appear to rely on EMS staff's diagnostic impression (31). Hence, when EMSs fail to recognize stroke and do not pre-notify the ED, ED processes are negatively impacted. It follows that triage nurses are another important target population for initiatives aimed at increasing knowledge about and awareness of atypical stroke presentations. With regard to the shortcomings of established triage instruments, these may either be complemented by a neurological assessment, or dedicated neurological triage instruments (90) may be applied. In addition, the use of "do not-to-miss" diagnoses checklists for common complaints such as headache or dizziness has been advocated (91, 92), and their potential impact on ED diagnostic quality and processes deserves further prospective exploration.

Strategies to Improve Diagnostic Yield in ED Clinical Assessment and Imaging

Considerable efforts have been devoted to improving the diagnostic accuracy of patients presenting with vertigo. In view of the costs caused by overdiagnosis and overtreatment of benign causes of dizziness as well as inadequate use of diagnostic methods in the diagnosis of stroke, in particular imaging, a sensitive yet quick and cost-effective assessment of patients with vertigo is much needed (93). In this regard, much attention has been drawn to an improved approach to history taking focusing on timing and triggers rather than symptom quality (94, 95), allowing for categorization of vestibular syndromes as either acute, triggered-episodic, spontaneous-episodic, or chronic, and the development of clinical pathways and algorithms to differentiate potential etiologies and guide an adequate syndrome-specific work-up (96). The HINTS (head impulse test, nystagmus, test of skew) diagnostic triad has been extensively investigated (97), and several modifications such as additional bedside assessment of hearing (98) or ataxia (99) have been proposed. Importantly, the head impulse test (HIT) as an essential component of these targeted forms of examination is underutilized in the ED: one study (100) found it was applied to patients with dizziness in only 5% of cases and in ∼7% of cases with acute vestibular syndrome, for which it is most suited. This is all the more relevant since appropriately trained ED physicians are able to accurately administer the assessment (101). To reduce inter-observer variability and increase reliability, the test may be performed using video goggles, allowing for quantification of vestibular function and skew deviation (97). Such a procedure is assessed in an ongoing multicenter phase II trial, the AVERT

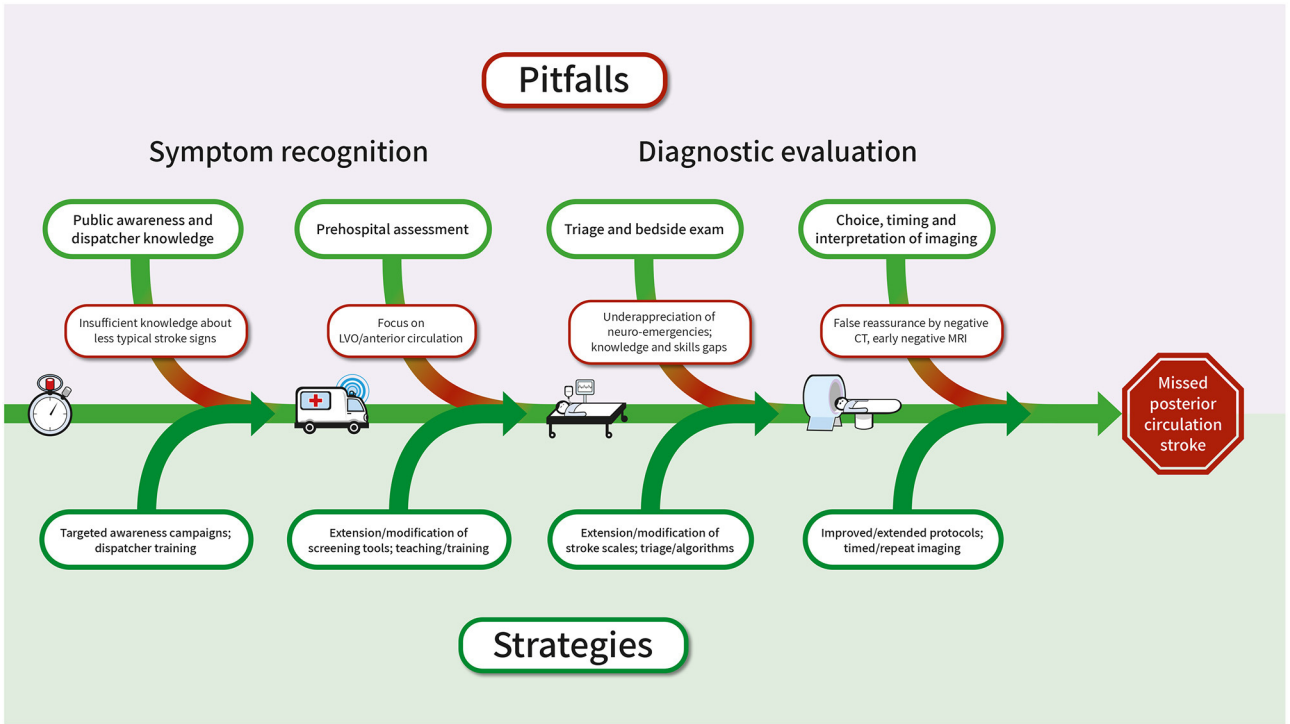

FIGURE 3 | Pitfalls associated with the diagnosis of PCS in the chain of acute stroke care and suggested approaches to solution. CT, computed tomography; MRI, magnetic resonance imaging; PCS, posterior circulation stroke.

(Acute Video-Oculography for Vertigo in Emergency Rooms for Rapid Triage) trial (102). With some of the available systems providing feedback regarding the correct velocity of a given impulse, their usefulness in the ED setting with examiners from different levels of skill and experience becomes immediately evident. Further development of this technology is underway, aiming at making its application more feasible and user-friendly in the ED setting (103). Automated saccade analysis may usefully complement video-oculography based HIT (104).

Whether or not the presence of a neurologist is necessary for reducing the rate of diagnostic error on PCS is equivocal: The presence of in-house neurology residents was associated with a lower risk of missed stroke in young patients but only after the exclusion of those patients who did not receive an emergency neurological consultation (105). However, even if a specialist assessment is obtained, the risk of missing the correct diagnosis is not fully abolished (72). In addition, community and academic hospitals, usually with easier access to neurological expertise in the latter, did not differ in the rate of missed strokes (37). Targeted education of neurology and ED physician trainees working in the ED concerning atypical stroke presentations may hence be an opportunity to further reduce diagnostic error in the ED. If direct neurological consultation is neither possible nor feasible, technology enables the remote assessment of patients with suspected stroke (106) and a wide variety of neurological conditions. Dizziness and vertigo have also been targets of telemedical approaches (107). Connected technology for data acquisition in conjunction with information from the patient's history and imaging may feed into the development of machine learning-based decision support solutions (108). It finally bears mentioning that the ongoing COVID-19 pandemic has substantially boosted the need for efforts to improve remote assessment and management of patients with these complaints (109, 110).

Regarding the pitfalls associated with MRI imaging in case of suspected PCS, several strategies may be pursued, such as adjusting MRI sequences with regard to slice thickness and orientation (111), using higher b-values for better contrast (112), adding additional perfusion sequences (113), or performing MRI in a time window of 5–12 h after symptom onset for increased sensitivity (59). Many argue that despite higher diagnostic accuracy of MRI, it commonly involves complex workflows that could potentially cause treatment delays and that performing comprehensive CT at presentation is the most cost-effective initial imaging strategy at comprehensive stroke centers (114). Even in light of these important areas of limitations and discordance, increased use of DWI in patients with atypical or unspecific symptoms in the ED is an especially useful aid in diagnosing entities such as cerebellar stroke presenting with isolated vertigo (115) and in evaluating patients with symptoms suspected to be stroke mimics (116), or those with migrainous stroke (117). MRI, therefore, plays a pivotal role in guiding the correct diagnosis and treatment of patients with PCS. In this regard, the formulation of imaging guidelines for patients

presenting with atypical symptoms is an important area to focus on to further improve diagnostic accuracy and yield, particularly with respect to PCS (118)—all the more so since current recommendations emphasize symptom duration and patient selection for different therapeutic options—again with a focus on the anterior circulation (119, 120).

Figure 3 summarizes pitfalls and challenges and approaches to overcome them with respect to the early links in the chain of acute stroke care.

Challenges and Opportunities for PCS Diagnostic Accuracy in the Context of the Coronavirus Disease 2019 (COVID-19) Pandemic

The ongoing COVID-19 pandemic has been posing extraordinary challenges to medicine and healthcare. The surge of infections in particular during the first wave of the pandemic frequently necessitated the reorganization and restructuring of prehospital and emergency room pathways of stroke patients and the reallocation of resources, impacting access diagnostics and therapy (121). Moreover, even in regions that were not as severely affected or where resources for acute stroke care were not limited, hospital admissions for cerebrovascular events decreased, presumably reflecting the influence of social distancing measures (122, 123). Not only may these cause patients to not seek medical help in the first place but they may theoretically impede the clinical assessment (124). Hence, there has been growing need for efforts to improve remote evaluation and management of patients with neurologic complaints. The use and acceptance of teleneurological consultations have been increasing (125, 126), and it is encouraging that observable neurological signs, which are feasible for remote assessment, appear to have better inter-rater reliability than elicitable signs, which often require direct contact with the patient (127). Since virtual HINTS and the Dix-Hallpike maneuver have been demonstrated to be applicable via telemedicine (110), solutions for additional components of the oculomotor exam may be developed and implemented. It remains to be seen, first, if and how these approaches, which can theoretically be applied to synchronous as well as asynchronous assessments, supplement or replace on-site examination, and second, how their implementation impacts on the diagnostic accuracy of PCS.

DISCUSSION

Emergency department utilization in many countries has substantially increased in recent years. The treatment of patients with neurological emergencies such as acute ischemic stroke is time-sensitive and requires swift action. In addition, the medical management of stroke patients today is more complex and multifaceted than ever before. The diagnostic process—an essential component of patient care in emergency departments—highly relies on successful teamwork among health care professionals, like EMS staff and ED healthcare teams, including physicians of various disciplines and nurses. This concerted and collaborative effort of all those participating in the acute management of stroke patients is critical to successfully circumnavigate the challenges and pitfalls of PCS diagnosis.

AUTHOR CONTRIBUTIONS

CH: conducted literature search, conceptualized review, and wrote the first draft. KS: conducted literature search and revised the manuscript. Both authors contributed to the article and approved the submitted version.

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Mechanical Thrombectomy in Isolated Occlusion of the Proximal Posterior Cerebral Artery

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Introduction: Endovascular therapy (EVT) is established as first-line treatment for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) in the anterior circulation. For basilar artery occlusion, recent randomized clinical trials demonstrated not only equipoise but also advantages for EVT under particular circumstances. It remains unclear whether EVT offers an advantage over best medical management (BMM) including thrombolysis (IVT) in isolated occlusion of the proximal posterior cerebral artery (PCAO).

Methods: Patients with AIS due to PCAO proven by CT or MR angiography were retrospectively identified from local databases at four comprehensive stroke centers in Germany, USA, and Taiwan between 2012 and 2020. Demographic and clinical data were collected, and imaging characteristics including pretherapeutic, interventional, and follow-up imaging were reviewed locally at each center. Patients were grouped according to therapy, i.e., BMM including IVT alone vs. BMM and EVT. Efficacy endpoints were early neurological improvement (ENI) after 24 h or at discharge, good outcome (modified Rankin scale 0–2) after 3 months, as well as hemorrhagic complications and in-house deaths as safety endpoints.

Results: We included 130 patients of whom 23 (17.7%) received EVT. EVT patients had more proximal occlusions (69.9 vs. 43%, $p = 0.023$) and had a better premorbid function [premorbid mRS, 0 (0–4) vs. 1 (0–3), $p < 0.01$] when compared to BMM patients. IVT showed a trend toward being less performed in the EVT group (21.7 vs. 41.1%, $p = 0.1$), while other baseline parameters were balanced. Successful reperfusion was achieved in 52% of EVT patients. ENI was more frequent in the EVT group (61 vs. 35.5%, $p = 0.034$). Good outcome at 90 days and safety endpoints did not differ. In a bivariate analysis, ENI was independently predicted by the use of EVT (OR, 2.76; CI, 1.055–7.04) and the baseline National Institutes of Health Stroke Scale (NIHSS) (OR, 1.082; CI, 1.027–1.141 per point increase).

Discussion: EVT in isolated PCAO appears safe and feasible. Positive effects on clinical outcome are primarily on ENI but also depend on the initial stroke severity. Further prospective or randomized studies are needed to better describe the potential long-term clinical benefits of EVT for PCAO as compared with best medical management.

Keywords: posterior circulation stroke, posterior cerebral artery, endovascular therapy, mechanical thrombectomy, best medical management

INTRODUCTION

Endovascular therapy (EVT) is a standard of care for patients with acute ischemic stroke (AIS) due to large vessel occlusions (LVO) in the anterior circulation. Although EVT was pioneered in basilar artery (BA) occlusion (1), evidence for the benefit of EVT in BA occlusion (BAO) could not be concluded, yet. Recent randomized clinical trials (RCTs) failed to meet the primary endpoint of good outcome after 90 days but demonstrated benefit in a subgroup of severely affected patients or in the as-treated population (2, 3). There is a profound difference between the anterior and posterior circulation in functional vascular anatomy, topography, and pathophysiology of stroke. Ischemic damage in vascular territories of proximal perforating arteries in the posterior circulation, i.e., brainstem and diencephalon, has a greater influence on neurological function and the National Institutes of Health Stroke Scale (NIHSS) compared to infarction in the rostral basal ganglia, i.e., caudate nucleus and putamen. Here, infarction occurs regularly even after clinically successful EVT (4, 5) because these areas are particularly vulnerable due to reduced collateral blood supply (6). At the same time, cortical areas supplied by the anterior circulation, e.g., the central region, impact the NIHSS much more than those supplied by the posterior circulation, i.e., in the occipital lobe. This topology also applies to the posterior cerebral artery. Here, perforating arteries originating proximally provide supply to the cerebral peduncle and dorsolateral thalamus. Nevertheless, motor deficits are reported only in about 30% of acute, isolated posterior cerebral artery (PCA) occlusion (7–9).

Therefore, we investigated whether EVT can have beneficial effects on immediate and long-term functional outcome in patients with AIS caused by primary, isolated occlusion of the PCA in comparison to best medical management (BMM), with or without concomitant thrombolysis.

PATIENTS AND METHODS

In four centers, two in Germany, one in the USA, and one in Taiwan, respectively, patients consecutively treated between 2012 and 2020 for acute ischemic stroke (AIS) with isolated occlusion of the posterior cerebral artery were retrospectively identified from prospectively maintained stroke databases. Inclusion criteria were (1) occlusion of the proximal posterior cerebral artery in the P1 segment, at the P1/P2 junction or in the P2 segment proven by either CT angiography (CTA) or magnetic resonance angiography (MRA), and (2) causing acute focal neurological symptoms (NIHSS >0). Exclusion criteria were (1) severe preexisting disability defined as modified Rankin scale (mRS) >4 prior to index stroke; (2) secondary PCA occlusion after reperfusion of BAO, spontaneously or after therapy; (3) bilateral occlusion of the PCA or its branches; (4) peripheral PCA occlusions, i.e., beyond the P2 segment; and (5) concomitant occlusion in the anterior circulation, i.e., internal carotid artery (ICA), middle cerebral artery (MCA), or anterior cerebral artery (ACA) or their branches. Imaging protocols [computed tomography (CT) or magnetic resonance imaging (MRI) and perfusion imaging] and treatment decision followed local standard operation procedures (SOPs) at each center. Demographic data, comorbidities (including diabetes mellitus, previous stroke, smoking, and atrial fibrillation), previous anticoagulation or antiplatelet therapy, initial National Institute of Health Stroke Scale (NIHSS), prestroke mRS, time intervals to stroke therapy, intravenous thrombolysis therapy (IVT) using recombinant tissue plasminogen activator (rtPA), location of vessel occlusion, and presence of intracerebral hemorrhage (ICH) defined according to the Heidelberg Bleeding Classification (HBC) (10) were collected. ICH was rated as symptomatic if there was a clinical deterioration resulting in an NIHSS increase, which was accountable to the bleeding. All clinical scores were obtained by NIHSS/mRS-certified neurologists. The clinical outcome as per mRS 90 days after stroke onset was obtained by a standardized interview (unblinded investigator per phone call or a personal letter to the patient) or patient assessment during follow-up in clinic. Reperfusion was described according to the modified thrombolysis in cerebral infarction (mTICI) scale and grouped in a simplified scheme, i.e., complete (3 and 2b) or no reperfusion (0–2a) in the territory of the posterior cerebral artery (11). Mismatch on perfusion imaging between time to peak (TTP) and cerebral blood volume (CBV) maps or diffusion weighted imaging (DWI) was only semiquantitatively assessed and defined as described in the European Cooperative Acute Stroke Study (ECASS) IV trial protocol with a TTP to infarct core (DWI, CBV) ratio of 1.2 (>20 mL) (12).

The primary efficacy endpoint was early neurological improvement (ENI) defined as a decrease in four or more points compared to baseline NIHSS or zero points on the earliest NIHSS score after 24 h but before discharge in accordance with a recently published study (13). The secondary endpoint was good outcome, defined as mRS 0–2 after 90 days. Safety endpoints were in-house deaths, fatal ICH, and asymptomatic ICH. Ethical approval was obtained at the local centers' institutional review boards that contributed the patients to the pooled analysis with anonymized data.

Statistical Analysis

The statistical analysis followed an exploratory design, and the patient cohort was described using summary measures of the empirical distribution. Continuous variables are given as means (SD) and/or median [interquartile range (IQR) and range, as appropriate]. Nominal variables are described as absolute and relative frequencies. Patients were first grouped according to the mode of therapy, i.e., BMM or BMM incl. EVT, and parameters were compared between groups. In general, continuous variables were tested using a *t*-test for independent groups, and ordinal variables were compared with the Mann–Whitney test, whereas categorical variables were compared using the chi^2 test. Since this was a retrospective data analysis, all *p*-values are to be interpreted in a descriptive sense; $p < 0.05$ were denoted as significant. To identify factors that were associated with the primary outcome endpoint, patients were also compared according to ENI. After univariate analysis, selected variables with $p \leq 0.1$ were included in a logistic regression model with a stepwise forward approach for independent predictors of ENI. All statistical analyses were performed using SPSS27®.

Anonymized data are available by reasonable request to the corresponding author.

RESULTS

We included 130 patients with a median age of 77.5 years (IQR, 66–82) who presented 137 (median; IQR, 73.5–268.5) min after symptom onset, which was unwitnessed in 38 (29.2%) of patients. Sixty patients (46.2%) were female, 62 (47.7%) had proximal occlusions (i.e., in the P1 segment), while the remaining occlusions were distal to P1. All PCAs originated from the basilar tip. Most patients (117/90%) were admitted directly and had a median NIHSS of 7 (IQR, 3–12). Premorbid disability (mRS > 2) was present in 22 (16.9%) of patients, and the median premorbid mRS was 1 (range, 0–4). There was a weak but significant correlation between the premorbid mRS and the NIHSS on admission ($r = 0.2$; $p = 0.02$; Spearman rank). Imaging was primarily performed with computed tomography (CT) in 118 (91%) and CT angiography in 106 (81.5%) of the patients, while 32 (24.6%) had an MRI (21 patients had both consecutively, i.e., CT and MRI). Perfusion imaging with either MRI or CT was performed in 31 (23.8%) of the patients, and 23 (74%) of them had a visual mismatch, either on MRI (6) or on CT (14).

Twenty-three patients received EVT (17.7%) with a mean door-to-groin time of 122 ± 100 min of whom five patients also received IVT. Overall, IVT was performed in 49 (37.7%) of the patients with a mean door-to-needle time of 49 (25–78.5) min. BMM without any acute reperfusion therapy was utilized in 63 (48.5%) of patients.

In the BMM group, significantly more patients had typical vascular risk factors, i.e., hypertension, diabetes, and hypercholesterolemia (see **Table 1**). The prestroke Rankin scale was significantly higher in the conservative group. Patients in the EVT group had more proximal occlusions, had less CT imaging, and had more perfusion imaging, irrespective of the imaging modality. Although there was a non-significant trend for EVT patients to arrive later in the hospital, subsequently, they received IVT faster than those who did not undergo EVT. Other parameters were balanced between both groups. Of 23 patients who received EVT, 13 (54%) experienced complete or near-complete reperfusion (TICI 2b−3) with 2 (16%) of them exhibiting a residual stenosis of the target vessel of more than 50%, while five patients had only partial recanalization with the majority (4/5) harboring a residual stenosis (see **Table 2**). In the remaining six patients, no successful recanalization could be achieved.

The primary endpoint ENI was significantly more frequent in EVT patients. The NIHSS dropped in median by four points (IQR, 1–7) in the EVT group and by two points (IQR, 0–4) in the BMM group ($p = 0.29$). Long-term outcome parameters, however, did not differ; the median mRS at 90 days was 3 (0–6; $p = 0.57$) in both groups, and the proportion of patients with good outcome (mRS 0–2) was 43.5% in the EVT and 42.1% ($p = 1.0$) in the BMM group, which increased to 51.4% in the BMM group but was unchanged in the EVT group when patients who returned to their prestroke mRS level ($p = 0.65$) were included (see **Table 2**). Moreover, more patients with ENI tended to have a good outcome. In the EVT group, 6 (26%) patients had any ICH, while this occurred in 14 (13%) in the conservative group ($p = 0.12$). There was one mildly symptomatic parenchymal hemorrhage

TABLE 1 | Baseline clinical and imaging characteristics.

Baseline clinical data	BMM + EVT *n* = 23	BMM *n* = 107	*p*-value
Sex (female)	9 (39.1%)	51 (47.7%)	0.49$^{\chi}$
Age, mean ± SD	70 ± 13.3	74 ± 13.1	0.19^{t-test}
Mothership (vs. "drip & ship")	21 (91.3%)	96 (89.7%)	1.0$^{\chi}$
Wake-up stroke	7 (30.7%)	31 (29%)	1.0$^{\chi}$
Premorbid mRS, median (range)	0 (0–4)	1 (0–3)	<0.01^{MWU}
Premorbid disability (mRS > 2)	1 (4.3%)	21 (19.6%)	0.12 $^{\chi}$
NIHSS on admission, median (range)	9 (1–20)	7 (1–38)	0.15^{MWU}
Hypertension	16 (69.6%)	97 (90.7%)	0.013$^{\chi}$
Diabetes	4 (17.4%)	48 (44.9%)	0.018$^{\chi}$
Hypercholesterolemia	8 (36.4%)	72 (67.3%)	<0.01$^{\chi}$
Current smoking	5 (20%)	17 (15.9%)	0.54$^{\chi}$
Previous stroke	6 (26.1%)	29 (27.1%)	1.0$^{\chi}$
Coronary heart disease	8 (34.8%)	26 (24.3%)	0.31$^{\chi}$
Atrial fibrillation	6 (26.1%)	41 (38.7%)	0.34$^{\chi}$
Oral anticoagulation	4 (17.5%)	24 (22.6%)	0.78$^{\chi}$
Mean arterial pressure	110 ± 22	112 ± 17	0.74^{t-test}
Baseline radiological findings			
Occlusion location, proximal	16 (69.9%)	46 (43%)	0.023$^{\chi}$
CT performed	18 (78.3%)	100 (93.5%)	0.038 $^{\chi}$
MRI performed	5 (21.7%)	27 (25.2%)	1.0$^{\chi}$
Perfusion imaging performed (CTP or MRP)	10 (43.5%)	21 (19.6%)	0.03$^{\chi}$
MRP/CTP mismatch > 20%	9/10 (90%)	14/21 (70%)	0.37$^{\chi}$

$^{\chi}$, *chi-square test; MWU, Mann–Whitney test.*

TABLE 2 | Procedural and outcome parameters.

Procedural parameters	BMM + EVT (23)	BMM (107)	*p*-value
intravenous thrombolysis	5 (21.7%)	44 (41.1%)	0.1$^{\chi}$
Time-to-treatment (time from symptoms onset to IVT or to Groin Puncture) in min, mean ± SD	353 ± 263	246 ± 210	0.13^{t-test}
Onset to door (EVT center) in min, mean ± SD	281 ± 223	159 ± 115	0.061^{t-test}
Door to needle time in min, mean ± SD	20 ± 13	61 ± 35	<0.01^{t-test}
Door to groin time in min, mean ± SD	122 ± 100	n.a.	n.a.
Outcome parameters			
Recanalization complete or near complete (TICI 2b-3)	13/23 (56%)	n.a.	n.a.
Residual artery stenosis	4/23 (17%)	n.a.	n.a.
NIHSS drop, median (IQR)	4 (−1–7)	2 (0–4)	0.29^{MWU}
ENI	14 (61%)	38 (35.5%)	0.034$^{\chi}$
mRS at day 90, median (range)	3 (0–6)	3 (0–6)	0.57^{MWU}
Good outcome	10 (43.5%)	45 (42.1%)	1.0$^{\chi}$
Good outcome incl. return to baseline mRS	10 (43.5%)	55 (51.4%)	0.65$^{\chi}$
Excellent outcome (mRS 0–1 at 90 days)	4 (17.4%)	23 (21.5%)	0.78$^{\chi}$
Symptomatic ICH	1 (4%)	3 (3%)	0.55$^{\chi}$
Fatal ICH	0%	1 (0.9%)	1.0$^{\chi}$
In-house deaths	1 (4.3%)	5 (4.7%)	1.0$^{\chi}$
Death at day 90	3 (13%)	8 (7.5%)	0.41$^{\chi}$

BMM, best medical management; EVT, endovascular therapy; ENI, early neurological improvement; ICH, intracranial hemorrhage; χ, chi-square test, MWU, Mann–Whitney test.

TABLE 3 | ICH distribution according to the Heidelberg Bleeding Classification.

		BMM + EVT ($n = 23$)	BMM ($n = 107$)
Heidelberg Bleeding Classification	1a	1	5
	1b	2	5
	1c	1	0
	2	1	1
	3	0	1
	3a	0	1
	3c	1	0

1, hemorrhagic transformation of infarcted brain tissue; 1a, HI1 scattered small petechiae, no mass effect; 1b, HI2 confluent petechiae, no mass effect; 1c, PH1 hematoma within infarcted tissue, occupying <30%, no substantive mass effect; 2, intracerebral hemorrhage within and beyond infarcted brain tissue; PH2, hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect; 3, intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage; 3a, parenchymal hematoma remote from infarcted brain tissue; 3b, intraventricular hemorrhage; 3c, subarachnoid hemorrhage; 3d, subdural hemorrhage; HI, hemorrhagic infarction; PH, parenchymatous hematoma. Only categories found in the study cohort are listed.

i.e., resulting in a drop of two points on the NIHSS in the EVT group. In the conservative group, there were two cases of symptomatic intracranial hemorrhage, one parenchymal and one subarachnoid resulting in an NIHSS increase of 9 and 6 points, respectively, and one case of fatal ICH. All patients had received thrombolysis. There were no angiographic signs of vessel perforation and one asymptomatic subarachnoid bleeding on follow-up CT in the EVT group but none in the conservative group (for details, refer to **Table 3**). There was no difference between therapy groups in fatality rates neither for in-house deaths (4.3 vs. 4.7%; $p = 1.0$) nor after 90 days (13 vs. 7.5%; $p = 0.41$).

As an additional analysis, we compared patients treated with EVT either with or without IVT with those 44 patients treated with IVT only (see **Supplemental Table**). In this comparison, IVT patients again had a higher premorbid Rankin scale, and premorbid disability was more frequent and so was diabetes. EVT patients again were treated later after onset but received thrombolysis earlier than IVT patients. Other baseline parameters did not differ significantly. Regarding ENI or any other outcome parameter, there was no significant difference between these groups.

In univariate analysis, patients with ENI had more often EVT and had higher initial NIHSS. Other parameters did not differ. The above-mentioned two parameters were included as covariates in a binary logistic regression for ENI where both initial NIHSS (OR, 1.082; CI, 1.027–1.141; $p = 0.003$) and EVT (OR, 2.726; CI, 1.055–7.044; $p = 0.038$) predicted ENI independently (see **Table 4**). As a sensitivity analysis, we also performed a multivariate model including other factors with presumed association with ENI, like age, proximal occlusion location, IVT, and time to treatment, but again only EVT (OR, 5.0; CI, 1.2–20.6; $p = 0.03$) and baseline NIHSS (OR, 1.1; CI, 1.0–1.2; $p = 0.02$) remained predictive factors for ENI.

DISCUSSION

In this retrospective multicenter study comparing BMM and EVT with sole BMM in acute isolated unilateral occlusion of the posterior cerebral artery, EVT was safe and effective in terms of reperfusion and bleeding complications. Furthermore, an immediate clinical improvement could be observed more frequently after EVT, while long-term clinical outcome did not differ between groups. Both EVT and a higher NIHSS at baseline predicted ENI.

Occlusions of the posterior cerebral artery were excluded from recent randomized clinical trials on endovascular therapy to treat large vessel occlusion in acute ischemic stroke. Nevertheless, MT is increasingly performed in PCA occlusion (PCAO) as demonstrated by a growing number of retrospective studies (15–17). They consistently report high recanalization rates between 80 and 100% with low procedural complication rates between 4 and 7% and good clinical outcome at 90 days in 59–66%. In the present study, complete or near complete recanalization could be achieved in 54% of patients treated with EVT; 16% of these exhibited a residual stenosis, which was the underlying cause for incomplete recanalization in four of five patients, one of which

TABLE 4 | Univariate and bivariate analysis for the primary endpoint ENI (delta NIHSS ≥ 4 or post-NIHSS = 0.

Parameter	Univariate analysis			Bivariate analysis		
	OR	Lower CI	Upper CI	OR	Lower CI	Upper CI
EVT	2.83	1.12	7.13	2.76	1.055	7.04
NIHSS on admission	1.085	1.02	1.144	1.082	1.027	1.141

EVT, endovascular therapy; OR, odds ratio; CI, 95% confidence interval.

had an Asian ethnicity while the others were Western European. Interestingly, none of the studies reporting MT in PCAO found local PCA stenosis as underlying cause, although the prevalence in AIS patients is reported with 10–16% (9). The relatively high prevalence of stenosis in the present study might be attributable to the fact that we did not exclude patients on the basis of their age. Furthermore, vessel changes due to EVT, i.e., dissection or severe vasospasm cannot be ruled out completely.

There was a non-significant trend for a higher frequency of any intracranial bleeding in the EVT group, while there was only one fatal parenchymal hemorrhage that occurred in the BMM group after thrombolysis. There were no angiographic signs of vessel perforation. There was one (4%) subarachnoid hemorrhage in the EVT group as a complication attributable to endovascular treatment. This is in keeping with previous studies of which two report no procedural complications (15, 17), Meyer et al. reported two dissections in 43 cases (13), and Lee et al. reported 1 in 15 cases where recanalization failed due to local complications (16).

In the present study, there was no difference between these groups with regard to good clinical outcome defined as a score between 0 and 2 on the modified Rankin scale after 90 days. There is only one other study so far comparing clinical outcome between these groups in patients with acute occlusions of the proximal PCA, i.e., in the P1 and P2 segment. The patient cohort in this retrospective study by Strambo et al. (14) is similar to the present one in terms of patient numbers and demographic parameters. The initial symptom severity was equivalent, and there was a similar proportion of patients with premorbid disability, i.e., a mRS >2. The authors did not find a significant difference in clinical outcome after 90 days between treatment groups, which is consistent with the present results. Moreover, they only report a trend for an increase in ENI defined as a drop of four points or more on the NIHSS after EVT compared to BMM, while this difference was significant in the present study. In addition to ENI and mRS at 90 days, Strambo et al. also report results of a differentiated neuropsychological assessment with evaluation of visual deficits, apraxia, neglect, memory, executive functions, and attention. Especially in PCAO, this is a sophisticated approach since these features are proprietary to the PCA territory and underrecognized by the NIHSS and even more by the mRS at the same time. Importantly, Strambo et al. observed better visual outcomes after EVT only (14). Unfortunately, the local databases that were accessed for our analysis were lacking these specific neurological outcome features, and hence, we were not able to reproduce the above finding. Moreover, we could not determine whether PCA strokes led to loss of the driving license, which has an enormous effect on activities of daily living but again is not reflected in outcome scores.

Most recently, a retrospective multicenter study reported findings comparing EVT and BMM with or without thrombolysis in patients with peripheral PCAO, i.e., P2–P4 segments, hence after exclusion of P1 occlusions (13). Consistent with the more peripheral location, the median NIHSS of five was even lower than in the present study and the aforementioned by Strambo et al. (14). Of note, in this largest PCAO-EVT cohort published so far, procedural complications were similarly low despite the more peripheral occlusion locations. Again, the proportion of patients with good clinical outcome did not differ between groups after 90 days. ENI was more frequent in EVT patients but only in the subgroup presenting with an NIHSS >10. This is in accordance with the results from the present multivariate regression analysis where the use of EVT predicted ENI, but the effect on ENI was also dependent on the level of the baseline NIHSS. This means that ENI is more likely to be present in patients with higher baseline NIHSS. The fact that this does not translate into good clinical outcome after 90 days likely indicates that the improvement is in a range that is only detected by the NIHSS but not the mRS as to be expected for deficits of cortical functions of the PCA territory.

Limitations

This study has several limitations, with its retrospective uncontrolled and non-randomized design being the most prominent one. We can also not exclude a bias by indication, since treatment allocation in the participating centers was based on local SOPs and individual decisions of the treating physicians. Hence, treatment groups were not balanced, but the restricted number of patients did not allow for matching or propensity-score-based analysis. Furthermore, we stress in the present study and in that from Strambo et al. that there was a considerable proportion of patients with premorbid disability. We found a significant correlation between the premorbid mRS and the initial NIHSS, which might imply that the initial NIHSS in PCAO might also be, at least in part, attributable to premorbid disability.

CONCLUSIONS

In conclusion, our study adds to the current evidence that EVT in isolated PCAO seems to be safe with regard to procedure-related complications and that EVT is associated with ENI, but ENI is influenced or dependent on the baseline NIHSS score. Furthermore, EVT does not seem to be associated with higher rates of long-term good outcome compared to the best

medical management group. However, other features than the NIHSS and mRS, such as detailed visual and neuropsychological functions, for example, may need to be measured and evaluated as necessary in future studies to more reliably assess patient's benefits after PCAO.

DATA AVAILABILITY STATEMENT

The anonymized raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Heidelberg University Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CH and SN performed statistical analyses and drafted the manuscript. All authors retrieved and reviewed local data, reviewed and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.697348/full#supplementary-material

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Tenecteplase Thrombolysis in Posterior Circulation Stroke

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One in five ischaemic strokes affects the posterior circulation. Basilar artery occlusion is a type of posterior circulation stroke associated with a high risk of disability and mortality. Despite its proven efficacy in ischaemic stroke more generally, alteplase only achieves rapid reperfusion in ∼4% of basilar artery occlusion patients. Tenecteplase is a genetically modified variant of alteplase with greater fibrin specificity and longer half-life than alteplase, which can be administered by intravenous bolus. The single-bolus administration of tenecteplase vs. an hour-long alteplase infusion is a major practical advantage, particularly in "drip and ship" patients with basilar artery occlusion who are being transported between hospitals. Other practical advantages include its reduced cost compared to alteplase. The EXTEND-IA TNK trial demonstrated that tenecteplase led to higher reperfusion rates prior to endovascular therapy (22 vs. 10%, non-inferiority $p = 0.002$, superiority $p = 0.03$) and improved functional outcomes (ordinal analysis of the modified Rankin Scale, common odds ratio 1.7, 95% CI 1.0–2.8, $p = 0.04$) compared with alteplase in large-vessel occlusion ischaemic strokes. We recently demonstrated in observational data that tenecteplase was associated with increased reperfusion rates compared to alteplase prior to endovascular therapy in basilar artery occlusion [26% ($n = 5/19$) of patients thrombolysed with TNK vs. 7% ($n = 6/91$) thrombolysed with alteplase (RR 4.0 95% CI 1.3–12; $p = 0.02$)]. Although randomized controlled trials are needed to confirm these results, tenecteplase can be considered as an alternative to alteplase in patients with basilar artery occlusion, particularly in "drip and ship" patients.

Keywords: tenecteplase, basilar artery occlusion, alteplase, posterior circulation stroke, thrombolytic agent

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INTRODUCTION

One in five ischaemic strokes affects the posterior circulation (1). This type of stroke is associated with a high risk of recurrence, disability, and mortality (2). It has been over 25 years since the publication of the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial (3), the first large positive clinical trial of recombinant tissue plasminogen activator (tPA or alteplase) in ischaemic stroke patients. Despite accounting for 20% of all strokes (1), only 5% of patients from the NINDS study (3) had a posterior circulation stroke and these patients were underrepresented in most of the positive clinical trials of alteplase (4–7). However, several observational studies have demonstrated comparable efficacy and safety profiles in patients with anterior and posterior circulation stroke treated with alteplase. Several studies have also suggested a lower risk of haemorrhagic complications in posterior circulation compared to anterior circulation strokes (8–13). The lower risk of haemorrhagic transformation in posterior circulation stroke may be explained by a stronger tolerance to the ischaemic insult in the posterior circulation territory,

likely due to its greater proportion of white matter and collateral pathways, particularly in the brainstem (14). Furthermore, the lower infarct volume in posterior circulation stroke compared to anterior circulation stroke may result in lower bleeding risk in these patients (15). Basilar artery occlusion is a type of posterior circulation stroke associated with a high risk of disability and mortality (16, 17). However, clinical outcomes in basilar artery occlusion improve if reperfusion is achieved. Despite its proven efficacy in ischaemic stroke more generally, alteplase only achieves rapid reperfusion in ∼4% of basilar artery occlusion patients (18).

TENECTEPLASE IN ISCHAEMIC STROKE

Tenecteplase is a genetically modified variant of alteplase with greater fibrin specificity and longer half-life than alteplase (22 min for tenecteplase compared to 3–5 min for alteplase) (19), which can be administered by intravenous bolus without the need for the 1-h infusion of alteplase. Tenecteplase has been approved for acute myocardial infarction and was demonstrated to be superior to alteplase (20, 21). The first trial testing tenecteplase in stroke was an open-label, dose-escalation safety study comparing 0.1, 0.2, 0.4, and 0.5 mg/kg in $n = 88$ ischaemic stroke patients within 3 h (22). Although enrolment into the dose used for myocardial infarction (0.5 mg/kg) was closed prematurely due to the high risk of symptomatic intracranial hemorrhage, the doses of 0.1 to 0.4 mg/kg appeared safe in ischaemic stroke (22). Nonetheless, the 0.4-mg/kg dose tier in a subsequent phase 2b study was terminated due to safety concerns (23). In 2012, Parsons et al. completed a randomized phase IIb study in which they compared tenecteplase 0.1 mg/kg ($n = 25$ patients) and 0.25 mg/kg ($n = 25$ patients) to alteplase 0.9 mg/kg (n = 25 patients) in a cohort of ischaemic stroke patients with large-vessel occlusion and visually assessed salvageable tissue on CT perfusion, within 6 h of symptom onset (24). In this trial, which preceded the use of endovascular thrombectomy, the pooled tenecteplase groups had greater reperfusion ($p = 0.004$) and better outcomes (modified Rankin Score 0–2, 72 vs. 44%, p = 0.02) than the alteplase group. Tenecteplase was associated with increased reperfusion, early neurological improvement, and improved 3-month functional outcome with a strong dose-dependent relationship, with the 0.25-mg/kg dose achieving better efficacy outcomes compared to 0.1 mg/kg, and no increase in symptomatic intracerebral hemorrhage (24). A subsequent phase II trial compared tenecteplase 0.25 mg/kg to alteplase 0.9 mg/kg in n = 104 ischaemic stroke patients within 4.5 h of symptom onset. No significant differences were found for the primary endpoint of percentage of penumbra salvaged (68% [SD 28] in the tenecteplase group vs. 68% [SD 23] in the alteplase group; mean difference 1.3% [95% CI −9.6 to 12.1]; $p = 0{\cdot}81$) (25). However, a subsequent pooled analysis of these two trials demonstrated that treatment with tenecteplase was associated with greater early clinical improvement (median National Institutes of Health Stroke Scale score change: tenecteplase, 6; alteplase, 1; $p < 0.001$) and better functional outcomes (modified Rankin scale score 0–1: odds ratio, 2.33; 95% CI, 1.13–5.94; $p = 0.032$) than those treated with alteplase, with the greatest benefit seen in patients with a CT perfusion-defined target mismatch (26). Furthermore, patients with anterior circulation large-vessel occlusion treated with tenecteplase had higher recanalization rates at 24 h (71% for tenecteplase vs. 43% for alteplase, $p = 0.001$) and significantly better functional outcomes (modified Rankin scale score 0–1: odds ratio 4.82, 95% confidence interval 1.02–7.84, $p = 0.05$) than patients treated with alteplase (27). Patients with basilar artery occlusion were not included in these trials.

The Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial compared tenecteplase 0.25 mg/kg to alteplase prior to endovascular therapy in n = 202 patients with large-vessel occlusion (28). In this trial, tenecteplase led to higher reperfusion rates prior to endovascular therapy (22 vs. 10%, non-inferiority $p = 0.002$, superiority $p = 0.03$) and improved functional outcomes (ordinal analysis of the modified Rankin Scale, common odds ratio 1.7, 95% CI 1.0–2.8, $p = 0.04$) compared with alteplase in large-vessel occlusion ischaemic strokes. Subsequently, the EXTEND-IA TNK part 2 trial compared tenecteplase 0.25 mg/kg with 0.4 mg/kg and did not find any further benefit with the higher dose for vessel recanalization or improved outcomes (29). These results clarified that the optimal dose of tenecteplase for large-vessel occlusion stroke is 0.25 mg/kg. This came after the large phase III Norwegian Tenecteplase Stroke Trial (NOR-TEST) trial, comparing tenecteplase 0.4 mg/kg to alteplase in $n = 1{,}107$ stroke patients recruited within 4.5 h of onset or of awakening from sleep with symptoms (30). In this trial, tenecteplase did not show superiority in improving excellent outcome (modified Rankin Scale 0–1, 64 vs. 63%, odds ratio 1.08 [95% CI 0.84–1.38, $p = 0.52$]). The dose of tenecteplase 0.4 mg/kg was considered safe as the rate of symptomatic haemorrhagic transformation was not increased ($p = 0.70$). However, this cohort of patients had a very low median baseline severity (National Institutes of Health Stroke Scale score of 4) with a high number of stroke mimics (17%), which significantly reduced the power to detect a meaningful difference between the two thrombolytic agents for both efficacy and safety (30). A subsequent meta-analysis of non-inferiority including five trials of tenecteplase vs. alteplase (31) found that tenecteplase was non-inferior to alteplase for all clinical efficacy measures (modified Rankin Scale 0–1, 0–2, and ordinal analysis) as well as symptomatic haemorrhagic transformation, regardless of the dose being 0.25 mg/kg or 0.4 mg/kg or the need for endovascular therapy for large-vessel occlusion (31). No randomized controlled trial has ever investigated the effect of tenecteplase in a cohort of patients with posterior circulation stroke (with or without large-vessel occlusion). Zhong et al. recently demonstrated that the routine use of tenecteplase for stroke thrombolysis in New Zealand was feasible and had comparable safety profile and outcome to alteplase. This real-world observational study has found that tenecteplase was also safely implemented in two small regional stroke centers less experienced in stroke reperfusion treatment (32). However, the number of posterior circulation stroke patients treated with tenecteplase was not reported in this study. The 2019 American Heart Association/American Stroke Association guidelines endorsed class IIB recommendations for

tenecteplase for patients with large-vessel occlusion (33). The Australian Stroke guidelines support tenecteplase as a reasonable alternative to alteplase in patients with large-vessel occlusion (strong recommendation) and non-large-vessel occlusion (weak recommendation) ischaemic stroke who meet specific clinical and brain imaging eligibility criteria (34). Ongoing phase 3 trials comparing 0.25 mg/kg tenecteplase vs. alteplase include Tenecteplase vs. Alteplase for Stroke Thrombolysis Evaluation (TASTE) in stroke patients eligible for intravenous thrombolysis with target mismatch on computed tomography perfusion imaging, the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2) trial, and the Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT) trial enrolling patients based on non-contrast CT alone (**Table 1**). In Scandinavia, The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST 2) is enrolling patients 0–4.5 h on the basis of non-contrast CT using 0.40 mg/kg tenecteplase. These studies will provide Level 1 evidence on the use of tenecteplase in stroke patients within 4.5 h. Although only a small proportion of patients with posterior circulation stroke may be enrolled in these studies, the results of these trials will likely be applied to all stroke patients, regardless of infarct topography (as occurred with previous alteplase trials). Nonetheless, further studies to investigate the safety and efficacy of tenecteplase in posterior circulation stroke patients (with and without large-vessel occlusions) are warranted. Further tenecteplase randomized-controlled trials are ongoing (**Table 1**).

TENECTEPLASE IN BASILAR ARTERY OCCLUSION

The use of tenecteplase in basilar artery occlusion has been mostly described in case reports (35, 36). The EXTEND-IA TNK trial (28, 29) was the only tenecteplase trial including patients with basilar artery occlusion. However, it was unclear whether its findings can be extrapolated to basilar artery occlusion as only six patients were included with no difference in the primary outcome (one-third had reperfusion at initial angiography in each treatment arm).

We recently presented the first series of patients with basilar artery occlusion treated with tenecteplase (37). Our findings suggest that tenecteplase may be associated with increased reperfusion rates in comparison with alteplase in patients with basilar artery occlusion, with rates of reperfusion similar to the 22% with tenecteplase and 10% with alteplase reported in the EXTEND-IA TNK trial (28). In our study including $n = 110$ patients with basilar artery occlusion, reperfusion occurred in 26% ($n = 5/19$) of patients treated with tenecteplase vs. 7% (n = 6/91) treated with alteplase (RR 4.0, 95% CI 1.3–12; $p = 0.02$), obviating the need for endovascular therapy. This occurred despite shorter thrombolysis-to-arterial-puncture time in the tenecteplase-treated patients (48[IQR 40–71] min) vs. alteplase-treated patients (110[IQR 51–185]min, p = 0.004). No difference in symptomatic intracranial hemorrhage was observed (0/19(0%) TNK, 1/91(1%) alteplase, $p = 0.9$). In contrast to EXTEND-IA TNK (28), functional outcomes were similar in the two treatment groups but our study was underpowered to detect such differences. Nonetheless, there was a non-significant trend toward higher 3-month excellent outcomes in patients treated with tenecteplase (modified Rankin Scale 0–1 47 vs. 37%, p = 0.09) compared to alteplase, which did not translate into better outcomes after multivariable analysis adjusted for age and NIHSS (adjusted risk ratio 1.6, 95% CI 0.9–2.7; $p = 0.1$). However, patients treated with tenecteplase were older than those treated with alteplase, likely due to more recent broader age selection criteria for reperfusion therapies, and tended to have higher baseline NIHSS scores (20 (IQR 5–32) for tenecteplase-treated patients vs. 15 (IQR 7–32) for alteplase-treated patients, $p = 0.9$). These differences in baseline characteristics would favor improved functional outcomes in the alteplase group. Therefore, our findings may represent a conservative estimate of the clinical benefits associated with tenecteplase. Interestingly, in a recent meta-analysis including five tenecteplase trials ($n = 1,585$), a greater effect of tenecteplase was detected when excellent outcomes were used as primary endpoint [(modified Rankin scale 0–1, crude cumulative rates of disability-free 57.9% tenecteplase vs. 55.4% alteplase; risk difference 4% (95% CI, −1% to 8%)] compared to good outcomes (modified Rankin Scale score, 0–2, crude cumulative rates of functional independence, 71.9% tenecteplase vs. 70.5% alteplase, risk difference 2% (95% CI, −3 to 6%)] (31). Although no definitive conclusions about the clinical benefit of tenecteplase can be drawn from our findings, the well-established strong relationship between earlier reperfusion and better functional outcomes (28, 32) suggests that tenecteplase could improve outcomes. Nonetheless, larger studies are needed to detect treatment effect differences between the two thrombolytic agents, given the likely larger effect of endovascular therapy. Despite this, our findings corroborate the accumulating evidence that suggests the superiority of tenecteplase compared to alteplase in large-vessel occlusion strokes. Although the alteplase data were extracted from our prospective Basilar Artery Treatment and Management (BATMAN) registry (38) and the use of early-generation thrombectomy devices and learning curve of interventionalists may have influenced our secondary outcomes (e.g., 90 days modified Rankin scale score), these factors should not influence the primary outcome of reperfusion on the initial angiogram prior to endovascular therapy. Other factors such as time from thrombolysis to reperfusion assessment, which in our study was in favor of the alteplase group, thrombus location, and permeability appear to be independently associated with reperfusion (39). A recently published meta-analysis including only patients with large-vessel occlusions (four studies, $n = 433$ patients) (40) showed that patients receiving tenecteplase had higher successful recanalization (odds ratio, 3.05 [95% CI, 1.73–5.40]), higher odds of good outcomes (modified Rankin Scale scores of 0 to 2, odds ratio, 2.06 [95% CI, 1.15–3.69]), and functional improvement defined as a one-point decrease across all modified Rankin Scale (common odds ratio, 1.84 [95% CI, 1.18–2.87]) at 3 months compared with patients receiving alteplase (40).

Importantly, recent randomized controlled trials failed to show the superiority of endovascular therapy compared to

TABLE 1 | Ongoing tenecteplase randomized controlled trials.

	Number of anticipated enrolled patients	Posterior circulation stroke patients	Primary outcome	Primary hypothesis	Clinicaltrials.gov registration (or Australian New Zealand registration) number
TASTE	$n = 1{,}024$	YES	mRS 0–1 (no disability) at 90 days	Tenecteplase 0.25 mg/kg is superior to alteplase 0.9 mg/kg within 4.5 h after symptom onset in patients with acute ischaemic stroke eligible for intravenous thrombolysis and with target mismatch on computed tomography perfusion imaging	ACTRN12613000243718
ATTEST-2	$n = 1{,}870$	YES	Ordinal mRS analysis at 90 days	Tenecteplase 0.25 mg/kg is superior to alteplase 0.9 mg/kg within 4.5 h after symptom onset in patients with acute ischaemic stroke eligible for intravenous thrombolysis	NCT02814409
AcT	$n = 1{,}600$	YES	mRS 0–1 (no disability) at 90 days	Tenecteplase 0.25 mg/kg is non-inferior to alteplase 0.9 mg/kg within 4.5 h after symptom onset in patients with acute ischaemic stroke eligible for intravenous thrombolysis	NCT03889249
NOR-TEST2	$n = 1{,}342$	YES	mRS 0–1 (no disability) at 90 days	Tenecteplase 0.4 mg/kg is superior to alteplase 0.9 mg/kg in patients with acute ischaemic stroke treated within 4.5 h after symptom onset (or after awakening with stroke symptoms)	NCT03854500
TEMPO-2	$n = 1{,}274$	YES	Return to baseline mRS at 90 days	Tenecteplase 0.25 mg/kg is superior to standard of care in minor ischaemic stroke patients with proven acute symptomatic intracranial occlusion within 12 h after symptom onset	NCT02398656
ETERNAL-LVO	$n = 740$	NO	mRS 0–1 (no disability) or return to baseline mRS at 90 days	Tenecteplase 0.25 mg/kg is superior to current best practice in acute ischaemic stroke patients with a large-vessel occlusion and penumbral tissue on multimodal CT or MRI within 24 h after symptom onset	NCT04454788
TIMELESS	$n = 456$	NO	Ordinal mRS analysis at 90 days	Tenecteplase 0.25 mg/kg is superior to placebo in patients with acute ischaemic stroke with a large-vessel occlusion and penumbral tissue between 4.5 and 24 h after symptom onset	NCT03785678
TWIST	$n = 600$	YES	Ordinal mRS analysis at 90 days	Tenecteplase 0.25 mg/kg is superior to best standard treatment in acute ischaemic stroke patients within 4.5 h of awakening with stroke symptoms,	NCT03181360
TASTE-A	$n = 80$	YES	Volume of lesion on CT Perfusion performed on arrival at the receiving hospital	Tenecteplase 0.25mg/kg is superior to alteplase 0.9mg/kg in acute ischaemic stroke patients eligible for intravenous thrombolysis and attended by a mobile stroke unit	NCT04071613

mRS, modified Rankin Scale score; TASTE, Tenecteplase vs. Alteplase for Stroke Thrombolysis Evaluation Trial; ATTEST-2, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis trial; AcT, Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke trial; NOR-TEST2, The Norwegian Tenecteplase Stroke Trial 2; TEMPO-2, TNK-tPA vs. Standard of Care for Minor Ischemic Stroke With Proven Occlusion Trial; ETERNAL-LVO, Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion Trial; TIMELESS, Tenecteplase in Stroke Patients Between 4.5 and 24 h Trial; TWIST, Tenecteplase in Wake-up Ischaemic Stroke Trial; TASTE-A, Tenecteplase vs. Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance.

standard medical therapy alone in patients with basilar artery occlusion (41, 42). In the recently completed BASilar artery International Cooperation Study (BASICS) trial, the benefit of endovascular therapy was demonstrated only in patients with moderate-severe clinical syndromes (NIHSS $\geq$ 10) (43). This suggested that thrombolysis might be the optimal treatment in those with milder deficits.

ADVANTAGES OF TENECTEPLASE OVER ALTEPLASE

The reduced cost and single-bolus administration of tenecteplase vs. an hour-long alteplase infusion in patients with basilar artery occlusion who are being transported between hospitals is a major practical advantage. Tenecteplase is given as a single, 5-s intravenous bolus that requires ∼2 min to prepare and administer, whereas alteplase requires preparation of both a bolus syringe containing 10% of the dose and an intravenous pump for infusion of the remaining 90% of the dose over 60 min. Moreover, the use of tenecteplase can minimize the risk of error in the preparation and delivery of the thrombolytic drug in the acute setting. Therefore, tenecteplase could be administered more efficiently in patients with basilar artery occlusion, permitting faster commencement of subsequent endovascular therapy, especially in patients treated with intravenous thrombolysis at primary stroke centers, and then transferred for endovascular

therapy ("drip and ship patients"). These patients may have tenecteplase administered at the primary hospital and then be immediately transferred by a standard ambulance without having to wait for critical care transport with staff expert in continuous infusion pump management and without risking interruption or discontinuation of the alteplase infusion during transit (31). Tenecteplase also only requires one drug vial compared to potentially multiple for alteplase (patients >55 kg need two vials of alteplase but only ever one vial of tenecteplase, regardless of patient weight) and is cheaper than alteplase in most countries. Economic analysis of the EXTEND-IA TNK trial indicated that tenecteplase was dominant (cost-saving) vs. alteplase in patients with large-vessel occlusion (44). Finally, tenecteplase has been reported as a more practical thrombolytic agent during the COVID-19 pandemic. Eliminating the alteplase 1-h infusion and the required dedicated second intravenous cannula may reduce staff time in proximity to the patient. Moreover, tenecteplase does not need the intravenous infusion pump that accompanies the patient through other hospital departments and wards, presenting an additional surface that could facilitate the transmission of the virus (45).

Endovascular therapy is highly effective but resource-intensive, and access is currently limited in most countries. Endovascular patients with basilar artery occlusion can be referred to a comprehensive stroke center, either from regional hospitals where there are significant barriers to treatment or from metropolitan hospitals that do not have endovascular therapy capacity. Therefore, there may be significant delays to the initiation of endovascular therapy due to inter-hospital transfer times, especially for patients with basilar artery occlusion who often require intubation before endovascular therapy can be performed. Given that each minute reduction in door-to-reperfusion time is associated with a saving of 4.4 disability-adjusted life days (46), tenecteplase may be a safe and effective treatment to "buy some time" until endovascular therapy can be performed in these patients, especially in those transferred from regional areas. The EXTEND-IA TNK (part II trial) (28) demonstrated that longer times between thrombolysis with tenecteplase and commencement of endovascular therapy in rural sites was associated with significantly higher reperfusion rates prior to endovascular therapy compared with metropolitan patients. Therefore, tenecteplase may allow treatment of a higher number of patients with a devastating form of stroke such as basilar artery occlusion in regional areas and obviate the need to transfer some patients if there is rapid recanalization with early clinical improvement. During inter-hospital transfers, tenecteplase will have time to act on the occlusion which may facilitate early recanalization and have beneficial effects during transfer to a comprehensive center for endovascular therapy.

CONCLUSIONS

Tenecteplase has several practical advantages compared to alteplase. Although randomized controlled trials are needed to detect treatment effect differences between the two thrombolytic agents in patients with basilar artery occlusion, evidence from observational data suggests that it may be associated with higher reperfusion rates prior to thrombectomy, analogous to anterior circulation large-vessel occlusion stroke. Tenecteplase can be considered as an alternative to alteplase in patients with basilar artery occlusion, particularly in "drip and ship" patients.

AUTHOR CONTRIBUTIONS

FA has drafted the manuscript and led submission process. BC revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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IV-Thrombolysis in Ischemic Stroke With Unknown Time of Onset—Safety and Outcomes in Posterior vs. Anterior Circulation Stroke

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Background: rt-PA for ischemic stroke in the unknown or extended time window beyond the first 4. 5 h after symptom onset is safe and effective for certain patients after selection by multimodal neuroimaging. However, the evidence for this approach comes mainly from patients with anterior circulation stroke (ACS), while the data on posterior circulation stroke (PCS) are scarce.

Methods: Ischemic stroke patients treated with IV-thrombolysis in the unknown or extended time window between January 2011 and May 2019 were identified from an institutional registry. The patients were categorized into PCS or ACS based on clinico-radiological findings. We analyzed the hemorrhagic complications, clinical and imaging efficacy outcomes, and mortality rates by comparing the PCS and ACS patient groups. Adjusted outcome analyses were performed after propensity score matching for the relevant factors.

Results: Of the 182 patients included, 38 (20.9%) had PCS and 144 (79.1%) had ACS. Symptomatic acute large vessel occlusion (LVO) was present in 123 patients on admission [27 (22.0%) PCS and 96 (78.0%) ACS]. The score on the National Institutes of Health Stroke Scale (NIHSS), the time from last seen normal, and the door-to-needle times were similar in PCS and ACS. In patients with LVO, the NIHSS score was lower [8 (5–15) vs. 14 (9–18), $p = 0.005$], and infarction visible on follow-up imaging was less common [70.4 vs. 87.5%; aRD, −18.9% (−39.8 to −2.2%)] in the PCS patient group. There was a trend toward a lower risk for intracranial hemorrhage (ICH) following intravenous thrombolysis in PCS vs. ACS, without reaching a statistical significance [5.3 vs. 16.9%; aRD, −10.4% (−20.4 to 4.0%)]. The incidence of symptomatic ICH [according to the ECASS III criteria: 2.6 vs. 3.5%; aRD, −2.9% (−10.3 to 9.2%)], efficacy outcomes, and mortality rates were similar in PCS and ACS patients.

Conclusions: In this real-world clinical cohort, the safety and the efficacy of rt-PA for ischemic stroke in the unknown or extended time window did not show relevant differences between PCS and ACS, with a trend toward less hemorrhagic complications in PCS. The findings reconfirm the clinician in the usage of rt-PA beyond the first 4.5 h also in selected patients with PCS.

Keywords: wake-up stroke, extended time window, IV-thrombolysis, posterior circulation stroke, anterior circulation stroke

INTRODUCTION

In up to 16% of acute ischemic strokes treated with IV-thrombolysis, the territories of the posterior circulation, including the vertebral, basilar, or posterior cerebral arteries, are affected (1–4). In the subgroup of patients with severe ischemic stroke, presenting with National Institutes of Health Stroke Scale (NIHSS) scores >25, the proportion of PCS is increasing up to 36% (5). IV-thrombolysis is the standard of care for acute ischemic stroke within 4.5 h from symptom onset irrespective of the vascular territory affected (6, 7). In addition, several studies could demonstrate the safety and the efficacy of IV-thrombolysis for selected patients in the unknown or extended time window beyond 4.5 h (8–10). Multimodal CT or MRI was used for patient selection in these studies, and some of these approaches were implemented in the latest international guidelines (6–10).

The proportion of PCS was low or not reported in most randomized rt-PA trials with treatment within 4.5 h from onset and with treatment in the unknown or extended time window (8, 9, 11–14). Therefore, the transfer of the results to patients with PCS might be inappropriate.

A meta-analysis including 10,313 patients (PCS 11.9%) demonstrated a lower risk for symptomatic rt-PA-associated intracranial hemorrhage and higher rates of good functional outcome at 3 months in posterior circulation than in anterior circulation stroke patients receiving treatment in the approved time window of 4.5 h from onset (15).

The main objective of our study was to investigate these differences in the risk of hemorrhagic complications between PCS and ACS patients in the unknown or extended time window. The secondary objectives were imaging and functional efficacy outcomes and mortality rates.

MATERIALS AND METHODS

Study Population, Procedures, and Analyzed Parameters

This retrospective cohort study is based on the data of consecutive acute ischemic stroke patients treated with IV-thrombolysis (rt-PA) in the unknown or extended time window >4.5 h in the period from January 2011 to May 2019 at our tertiary university stroke center. The patients were eligible for IV-thrombolysis using multimodal CT or MR imaging according to our institutional treatment algorithm for the management of ischemic stroke in the extended or unknown time window as described previously (16). Accordingly, IV-thrombolysis was performed after (1) the exclusion of intracranial hemorrhage and (2) the exclusion of major infarction on non-contrast CT or gradient echo and fluid-attenuated inversion recovery sequences using MRI and (3) evidence of salvageable tissue at risk on perfusion imaging (mismatch between hypoperfusion vs. infarcted core on perfusion CT or mismatch between perfusion-weighted and diffusion-weighted imaging using MRI; mismatch quotient >1.4 for both modalities) (**Figure 1**). Follow-up imaging was performed 24 h after IV-thrombolysis or earlier in the case of neurologic deterioration (NIHSS score increase of four points or more). The modality of follow-up imaging (CT or MRI) was to the discretion of the treating physician. We categorized all patients according to clinical and/or radiological findings as posterior circulation stroke or anterior circulation stroke patients (full patient cohort—clinico-radiological categorization); patients with simultaneous anterior and posterior circulation stroke were excluded. In addition, we conducted a subgroup analysis of patients with acute large vessel occlusion (LVO). Patients with occlusion of the internal carotid and middle or anterior cerebral artery were categorized as ACS patients, and patients with occlusion of the vertebral, basilar, or posterior cerebral artery were categorized as PCS patients. Patients with complete fetal posterior cerebral artery were excluded from the study.

We analyzed the clinical and imaging stroke characteristics, risk factors, procedure times for IV-thrombolysis and mechanical thrombectomy (if performed), clinical course including intracranial hemorrhagic complications, evidence of cerebral infarction on follow-up imaging, mortality rates, and 90-day outcome. Demographic, clinical, and radiologic data were collected during inpatient stay. The assessment of day 90 follow-up was conducted *via* telephone interview, outpatient visit, or medical reports by trained raters.

Study Outcomes

The primary outcome was the incidence of hemorrhagic complication [any intracranial hemorrhage (ICH), symptomatic ICH according to different definitions—European Cooperative Acute Stroke Study (ECASS) III criteria (13), ECASS II criteria (11), and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria (12)] on follow-up imaging at 24 h after IV-thrombolysis.

The secondary outcomes were the rate of early major neurologic improvement (defined as a reduction of the NIHSS

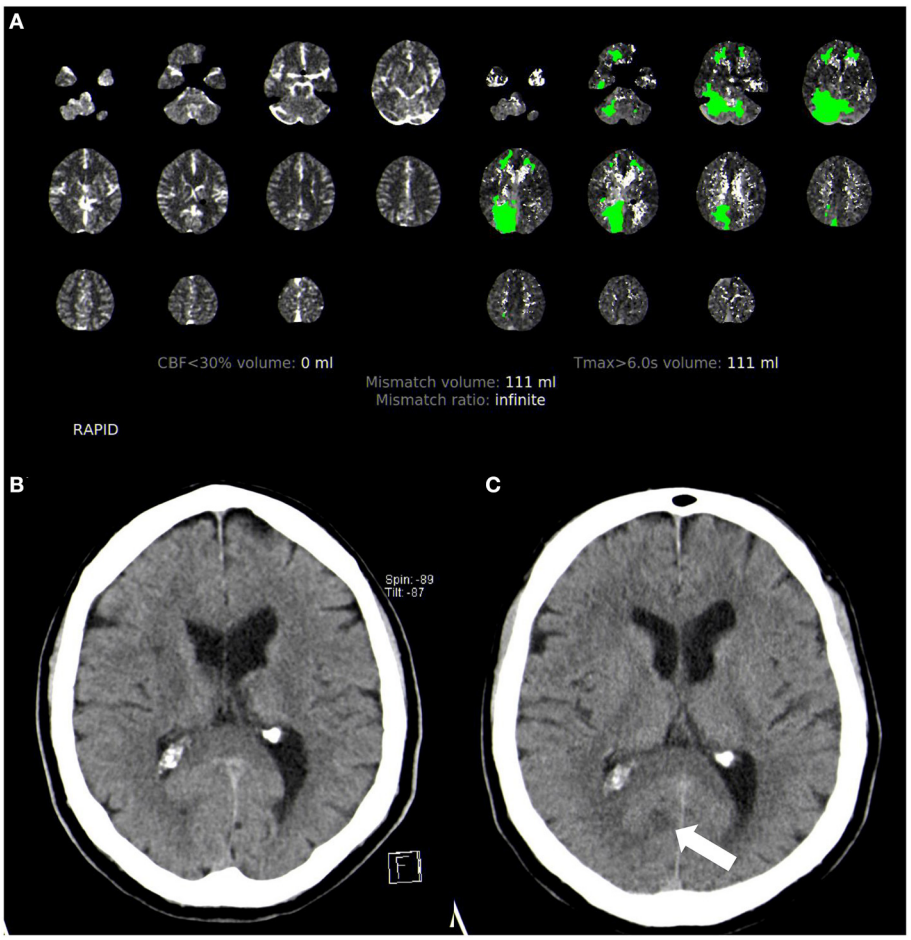

FIGURE 1 | Acute multimodal CT and follow-up non-contrast CT imaging in posterior circulation stroke. **(A)** Perfusion CT analyzed with Rapid CTP. **(B)** Initial non-contrast CT showing no infarction. **(C)** Follow-up non-contrast CT with a visible small infarction in the posterior cerebral artery territory (arrow).

score by at least eight points or a score of 0 or 1 after 24 h), evidence of cerebral infarction on follow-up imaging after 24 h, mortality, and favorable functional outcome at day 90 using the modified Rankin Scale (mRS). A favorable outcome was defined as either a score on the mRS 0–2 or an improvement to the level prior to stroke onset, respectively.

Statistics

Data were presented as absolute/relative numbers for categorical variables and median/interquartile range (IQR) for continuous variables. The significance of differences between patient groups (PCS and ACS) was calculated using the Mann–Whitney *U*-test, the χ^2 test, and the Fisher exact test as appropriate. Statistical significance was set *a priori* at *p*-value <0.05.

For the investigation of primary and secondary outcomes, adjusted analyses after propensity score matching (estimation algorithm: logistic regression, matching algorithm: nearest neighbor approach, caliper 0.2, match 1:3) were performed. The PCS and ACS patients were matched for age, female sex, arterial hypertension, diabetes mellitus, atrial fibrillation, NIHSS on admission, large vessel occlusion (in clinico-radiological cohort), and mechanical thrombectomy (**Supplementary Figures 1, 2**). We calculated absolute differences between PCS and ACS patients in percentage (absolute risk difference, aRD) with corresponding 95% confidence interval. Negative values indicate a decrease of measurement from ACS patients as reference.

Missing data of the 90-day follow-up were excluded from the outcome analyses. Statistical analyses were performed using IBM SPSS Statistics 21 software package (www.spss.com) and R 2.12.1 (www.r-project.org).

RESULTS

One hundred eighty-four acute ischemic stroke patients treated with IV-thrombolysis in the unknown or extended time window were identified. Two patients were excluded due to simultaneous anterior and posterior circulation stroke, resulting in the final

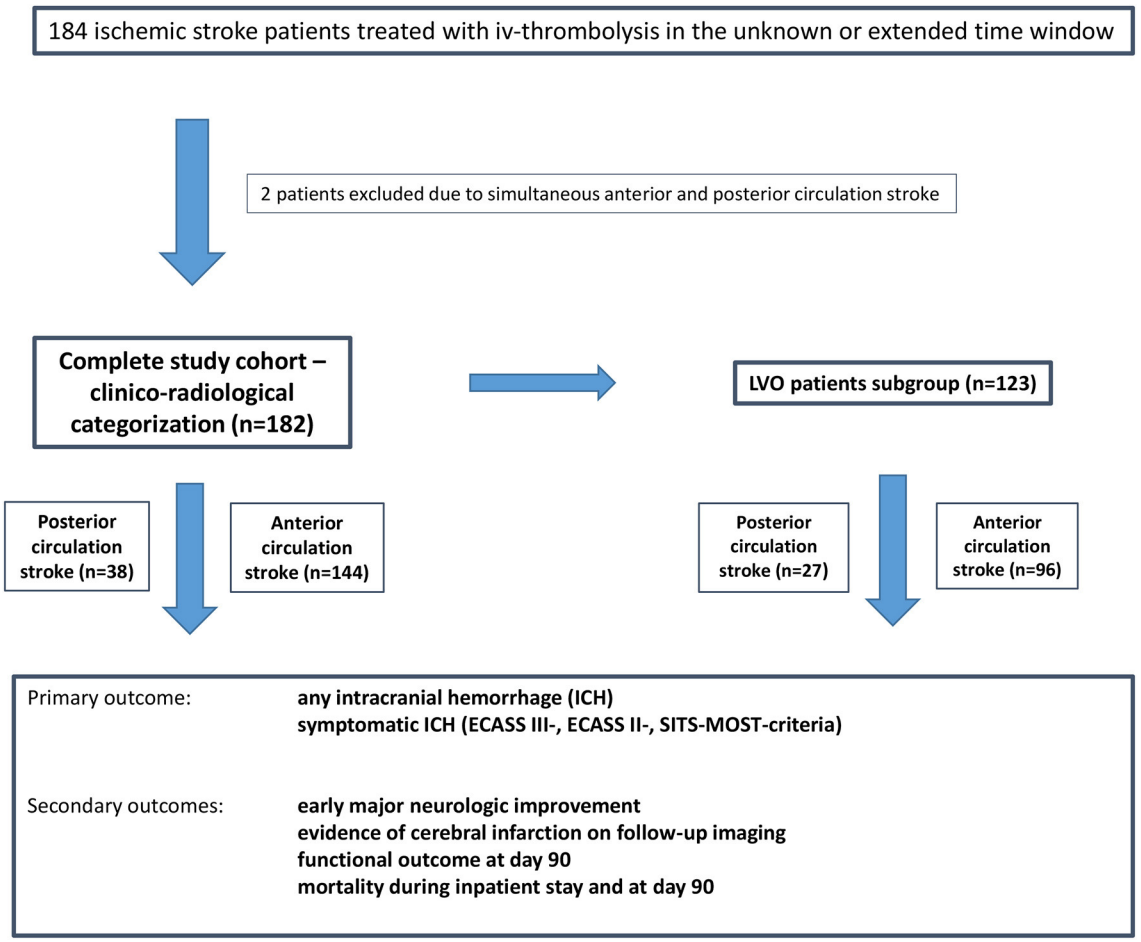

FIGURE 2 | Flow chart of the study cohort.

study cohort of 182 patients including 38 (20.9%) PCS and 144 (79.1%) ACS patients (**Figure 2**). Acute LVO was present in 123 patients (67.6%) and constituted the LVO patient subgroup.

Full Patient Cohort—Clinico-Radiological Categorization

Patients with PCS were less commonly female (28.9 vs. 56.9%, $p = 0.002$) but similar regarding comorbidities and concurrent medication (**Table 1**). The proportion of patients in the confirmed time window >4.5 h was higher in the PCS group (23.7 vs. 9.0%, $p = 0.023$), and the time from last seen normal to treatment was similar in PCS and ACS patients [450 min (362–719) vs. 558 min (354–819), $p = 0.148$]. Differences in NIHSS scores on admission between PCS and ACS patients [8 (5–14) vs. 11 (6–17), $p = 0.068$] did not reach statistical significance. Door-to-needle times were similar in PCS and ACS patients [56 min (42–91) vs. 59 min (41–76), $p = 0.510$]. Further clinical and imaging characteristics of stroke are shown in **Table 2**.

There was a statistical trend for a lower incidence of any intracranial hemorrhage post IV-thrombolysis in PCS than in ACS patients (5.3 vs. 16.9%, $p = 0.075$). The proportion of patients with symptomatic ICH following different definitions (ECASS III criteria: 2.6 vs. 3.5%, $p = 1.000$) and fatal ICH (0.0 vs. 1.4%, $p = 1.000$) was similar in PCS and ACS patients. There was no significant difference in the rate of infarction visible on follow-up imaging (65.8 vs. 77.5%, $p = 0.140$), early neurologic improvement (15.8 vs. 18.1%, $p = 1.000$), or functional outcome at day 90 (pre-mRS or mRS score 0–2: 33.3 vs. 39.3%, $p = 0.532$). The mortality rates during inpatient stay and at day 90 were similar in PCS and ACS patients (13.2 vs. 11.8%, $p = 0.784$ and 23.5 vs. 26.8%, $p = 0.827$) (**Figure 3**). Two patients in the ACS group died prior to follow-up imaging (the suspected cause of death was lung embolism and circulatory failure, respectively).

The analyses after propensity score matching included 124 patients (PCS, $n = 35$; ACS, $n = 89$) and did not lead to statistical differences in the incidence of any ICH [aRD −10.4% (−20.4 to 4.0%)], symptomatic ICH, evidence of infarction on follow-up

TABLE 1 | Baseline characteristics in the clinico-radiological patient cohort.

	Posterior circulation stroke ($n = 38$)	Anterior circulation stroke ($n = 144$)	p-value
Female sex, *n* (%)	11 (28.9)	82 (56.9)	0.002
Age in years, median (IQR)	77.5 (67.0–84.0)	80.0 (69.0–86.0)	0.268
Arterial hypertension, *n* (%)	32 (84.2)	124 (86.1)	0.796
Hyperlipidemia, *n* (%)	22 (57.9)	68 (47.2)	0.242
Diabetes mellitus, *n* (%)	12 (31.6)	37 (25.7)	0.467
History of stroke, *n* (%)	10 (26.3)	28 (19.4)	0.354
Atrial fibrillation, *n* (%)	12 (31.6)	64 (44.4)	0.153
Antiplatelets, *n* (%)	15 (39.5)	49 (34.0)	0.532
Oral anticoagulants, *n* (%)	1 (2.6)	15 (10.4)	0.199
Vitamin K antagonists, *n* (%)	1 (2.6)	6 (4.2)	1.000
Direct oral anticoagulants, *n* (%)	0 (0.0)	9 (6.3)	0.207
Pre-mRS score, median (IQR)	1 (0–3)	1 (0–3)	0.859

pre-mRS, pre-stroke modified Rankin scale.

TABLE 2 | Clinical and imaging characteristics of stroke in the clinico-radiological patient cohort.

	Posterior circulation stroke ($n = 38$)	Anterior circulation stroke ($n = 144$)	p-value
Last seen normal to door—min, median (IQR)	382 (283–681)	479 (301–746)	0.098
Symptom recognition to door—min, median (IQR)	74 (64–128)	74 (51–140)	0.511
Confirmed extended time window, *n* (%)	9 (23.7)	13 (9.0)	0.023
Symptom onset to door in patients in the extended time window—min, median (IQR)	284 (245–382)	309 (265–495)	0.262
Patients transferred from external hospital for treatment, *n* (%)	2 (5.3)	9 (6.3)	1.000
Multimodal CT imaging for thrombolysis, *n* (%)	23 (60.5)	76 (52.8)	0.394
NIHSS score on admission, median (IQR)	8 (5–14)	11 (6–17)	0.068
NIHSS score >25 on admission, *n* (%)	3 (7.9)	3 (2.1)	0.106
Intubated on admission, *n* (%)	2 (5.3)	5 (3.5)	0.637
Wake-up stroke, *n* (%)	23 (60.5)	101 (70.1)	0.258
Infra- and supratentorial stroke, *n* (%)	13 (34.2)		
Large vessel occlusion, *n* (%)	27 (71.1)	96 (66.7)	0.607
Volume of irreversibly injured ischemic core tissue at initial imaging[a,b]–ml, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–10.5)	0.001
Perfusion lesion volume at initial imaging[b,c]–ml, median (IQR)	36.0 (11.0–129.0)	45.0 (10.0–109.5)	0.916
Mechanical thrombectomy, *n* (%)	13 (34.2)	49 (34.0)	0.983
Additional intra-arterial thrombolysis, *n* (%)	3 (7.9)	3 (2.1)	0.106
Door to needle—min, median (IQR)	56 (42–91)	59 (41–76)	0.510
Last seen normal to needle—min, median (IQR)	450 (362–719)	558 (354–819)	0.148
Symptom recognition to needle—min, median (IQR)	143 (112–177)	145 (110–211)	0.675
Follow-up imaging MRI, *n* (%)	2 (5.3)	11 (7.7)	1.000

NIHSS, NIH Stroke Scale; rtPa, recombinant tissue plasminogen activator. Two anterior circulation stroke patients died prior to follow-up imaging.

[a] *The volume of irreversibly injured ischemic core tissue was calculated with the use of a threshold for relative cerebral blood flow of less than 30% of that in normal brain tissue or with the use of diffusion-weighted MRI (apparent diffusion coefficient).*

[b] *The volumetric assessment of perfusion imaging was available in 27 posterior circulation stroke and 101 anterior circulation stroke patients.*

[c] *To define the critically hypoperfused tissue, the perfusion lesion volume was calculated as the volume of tissue in which there had been a delayed arrival of an injected tracer agent exceeding 6 s.*

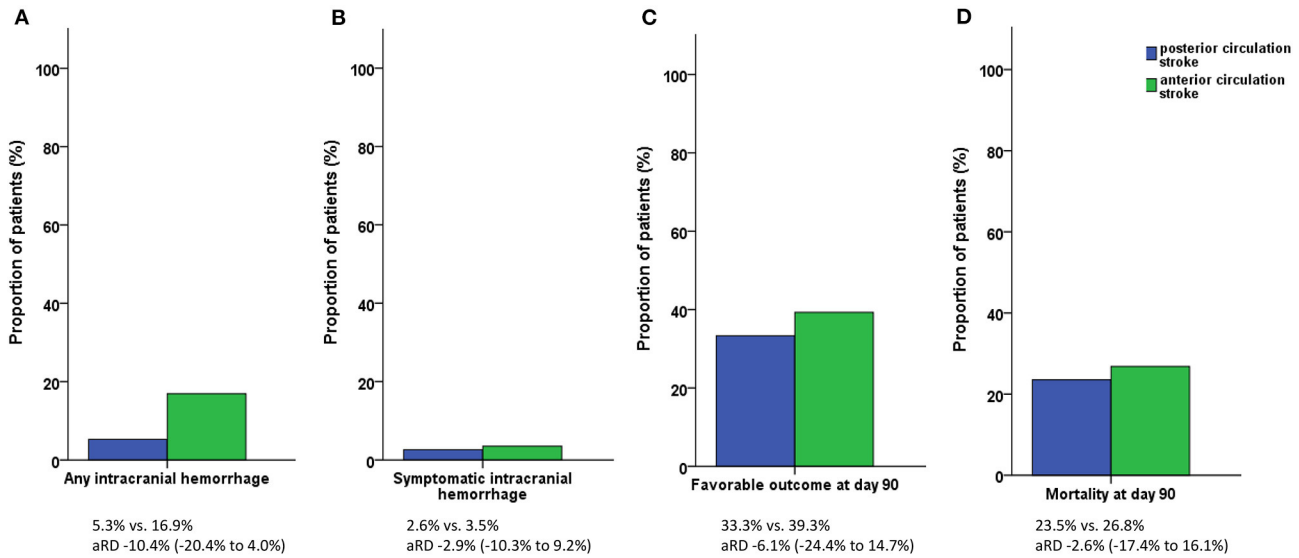

FIGURE 3 | Study outcomes. **(A)** Incidence of any intracranial hemorrhage. **(B)** Incidence of symptomatic intracranial hemorrhage. **(C)** Functional outcome at day 90. **(D)** Mortality at day 90. Symptomatic intracranial hemorrhage according to the ECASS III criteria. Favorable outcome defined as pre-modified Rankin Scale (mRS) or mRS score 0–2.

TABLE 3 | Outcomes in the clinico-radiological patient cohort.

	Posterior circulation stroke (*n* = 38)	Anterior circulation stroke (*n* = 144)	*p*-value	aRD[a]	95% CI
Any ICH, *n* (%)	2 (5.3)	24 (16.9)	0.075	−10.4%	−20.4 to 4.0%
Symptomatic ICH according to ECASS III criteria[b], *n* (%)	1 (2.6)	5 (3.5)	1.000	−2.9%	−10.3 to 9.2%
Symptomatic ICH according to ECASS II criteria[c], *n* (%)	1 (2.6)	6 (4.2)	1.000	−2.9%	−10.3 to 9.2%
Symptomatic ICH according to SITS-MOST criteria[d], *n* (%)	0 (0.0)	3 (2.1)	1.000	−3.4%	−9.7 to 6.7%
Fatal ICH, *n* (%)	0 (0.0)	2 (1.4)	1.000	−2.3%	−8.0 to 7.7%
ICH location remote[e], *n* (%)	2 (5.3)	7 (4.9)	1.000	–	–
Infarction on follow-up imaging, *n* (%)	25 (65.8)	110 (77.5)	0.140	−9.6%	−27.7 to 6.6%
Early major neurologic improvement[f], *n* (%)	6 (15.8)	26 (18.1)	1.000	1.4%	−11.3 to 18.1%
Mortality during inpatient stay, *n* (%)	5 (13.2)	17 (11.8)	0.784	3.6%	−6.6 to 18.6%
Favorable outcome at day 90 (pre-mRS or mRS score: 0–2)[g], *n* (%)	11 (33.3)	46 (39.3)	0.532	−6.1%	−24.4 to 14.7%
90-day mortality[h], *n* (%)	8 (23.5)	33 (26.8)	0.827	−2.6%	−17.4 to 16.1%

aRD, adjusted risk difference; ICH, intracranial hemorrhage; mRS, modified Rankin scale; pre-mRS, pre-stroke modified Rankin scale. Two anterior circulation stroke patients died prior to follow-up imaging.

[a]*Adjusted for age, female sex, arterial hypertension, diabetes mellitus, atrial fibrillation, NIHSS on admission, large vessel occlusion, and mechanical thrombectomy using propensity score matching; posterior circulation stroke (PCS), n = 35; anterior circulation stroke (ACS), n = 89.*

[b]*Any intracranial hemorrhage identified as a predominant cause of neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or any hemorrhage leading to death.*

[c]*Any intracranial hemorrhage with neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or any hemorrhage leading to death.*

[d]*Local or remote parenchymal hematoma type 2 and neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or hemorrhage leading to death.*

[e]*Two patients with remote ICH had an additional peri-ischemic hemorrhage (one PCS patient and one ACS patient).*

[f]*Early major neurologic improvement defined as a reduction of NIHSS score of at least eight points or a score of 0 or 1 at 24 h.*

[g]*The 90-day mRS was available in 150 patients (82.4%; 33 posterior circulation stroke patients and 117 anterior circulation stroke patients).*

[h]*Vital status at day 90 was available in 157 patients (86.3%; 34 posterior circulation stroke patients and 123 anterior circulation stroke patients).*

TABLE 4 | Distribution of large vessel occlusion (LVO) in the LVO patient cohort.

Occlusion site	PCS ($n = 27$)	ACS ($n = 96$)
Internal carotid artery (ICA)	–	14 (14.6%)[b]
Carotid-T	–	7 (7.3%)[b]
M1 segment of middle cerebral artery (MCA)	–	48 (50.0%)[b]
M2/M3 segment of MCA	–	28 (29.2%)[b]
Anterior cerebral artery (ACA)	–	2 (2.1%)[b]
Vertebral artery (VA)	8 (29.6%)[a]	–
Basilar artery (BA)	11 (40.7%)[a]	–
Posterior cerebral artery (PCA)	12 (44.4%)[a]	—

[a] *The PCA group included one patient with combined VA/PCA occlusion, two patients with combined BA/PCA occlusion, and one patient with combined VA/BA occlusion.*
[b] *The ACS group included two patients with combined ICA/M1 occlusion and one patient with combined M1/M2 occlusion.*

imaging, early neurologic improvement, functional outcome, or mortality (**Table 3**).

LVO Patient Subgroup

Among a total of 123 patients with acute large vessel occlusion, 27 (22.0%) were PCS patients and 96 (78.0%) were ACS patients. The distribution of occlusion sites in PCS and ACS patients is given in **Table 4**. The PCS patients were less commonly female (29.6 vs. 59.4%, $p = 0.008$). There were no significant differences in comorbidities and concurrent medication (**Table 5**). The proportion of patients in the confirmed extended time window beyond 4.5 h was higher in PCS patients (22.2 vs. 6.3%, $p = 0.023$), and the time from symptom recognition to admission was shorter in ACS patients [68 min (50–123) vs. 89 min (67–153), $p = 0.049$]. The NIHSS scores on admission were higher in ACS patients [14 (9–18) vs. 8 (5–15), $p = 0.005$]. The time from last seen normal to the start of IV-thrombolysis did not differ significantly between the PCS and ACS patients [457 min (368–745) vs. 613 (385–843), $p = 0.141$]; mechanical thrombectomy was equally performed in the PCS and ACS patient groups (48.1 vs. 51.0%, $p = 0.790$). The door-to-needle times [55 min (42–91) vs. 61 min (42–78), $p = 0.886$] and the door-to-groin times [97 min (78–121) vs. 94 min (77–111), $p = 0.621$] were similar in PCS and ACS patients. Further clinical and imaging characteristics of stroke are shown in **Table 6**. The incidence of any ICH (7.4 vs. 18.9%, $p = 0.239$), symptomatic ICH (ECASS III criteria: 3.7 vs. 2.1%, $p = 0.531$), and fatal ICH (0.0 vs. 1.0%, $p = 1.000$) was similar in PCS and ACS patients. Infarction on follow-up imaging was significantly more often evident in ACS patients than in PCS patients (87.5 vs. 70.4%, $p = 0.034$). Early neurologic improvement (18.5 vs. 16.7%, $p = 0.779$), functional outcome at day 90 (pre-mRS or mRS score 0–2: 21.7 vs. 28.9%, $p = 0.603$), and mortality rates (inpatient stay: 18.5 vs. 14.6%, $p = 0.563$; day 90: 29.2 vs. 30.7%, $p = 1.000$) were similar in PCS and ACS patients. One ACS patient died prior to follow-up imaging (the suspected cause of death was lung embolism).

In the analyses after propensity score matching (the total included 80 patients: PCS, $n = 23$; ACS, $n = 57$), the lower rate of infarction on follow-up imaging in PCS patients remained statistically significant [aRD −18.9% (−39.5 to −2.2%)]. No significant differences were detected regarding any ICH [aRD −7.4% (−20.7 to 12.2%)], symptomatic ICH, fatal ICH, and early or late neurologic/functional outcome or mortality rates (**Table 7**).

DISCUSSION

The major findings of our real-world clinical cohort study investigating the treatment of acute ischemic stroke with IV-thrombolysis in the unknown or extended time window are as follows: (1) the rates of symptomatic ICH were low, without a significant difference between PCS and ACS patients, (2) there was a trend toward more hemorrhages among ACS patients than in PCS patients, and (3) the functional outcome and mortality rates at day 90 did not differ.

The rates of symptomatic ICH in our study were similar to the ones reported in the literature, without a difference between PCS and ACS patients (2, 3). Controversially, a large meta-analysis including 10,313 patients (1,224 PCS) reported the risk for sICH in PCS as half of that in ACS (15). However, while the rate of symptomatic hemorrhages did not differ in our cohort, the incidence of any ICH (including asymptomatic ones) seemed slightly higher in ACS, without reaching statistical significance. The higher volumes of ischemic core on initial multimodal imaging may have contributed to the higher risk for hemorrhagic complications in ACS patients, as infarct size is an established risk factor for hemorrhagic transformation (17, 18). These differences in ischemic core on initial imaging might be responsible for the higher rates of cerebral infarction visible on follow-up imaging in ACS patients of our LVO cohort. In addition, cerebral infarction in the posterior circulation including the brainstem might be more difficult to detect compared to anterior circulation stroke infarction on follow-up imaging (19). The rates of MRI for follow-up imaging, improving the detection of infarction especially in the posterior cranial fossa, were low and did not differ between PCS and ACS patients.

The differences in infarction on follow-up imaging did not translate into a functional outcome in PCS and ACS patients in our LVO patient cohort. The absence of correlation between the volume of infarcted tissue and the functional outcome was reported earlier for LVO patients receiving recanalization therapy (20).

Several studies demonstrated similar functional outcomes in PCS and ACS patients (1–3, 15, 21). Consistently, we did not find differences in outcome between patient groups in the analysis of the full patient cohort.

The mortality rates in PCS and ACS are reported inconsistently in the literature (2, 3, 15). This heterogeneity may be attributed to differences in the proportion of severe stroke patients between study cohorts in ACS and PCS patients. In our study, the proportion of severe stroke patients presenting with NIHSS score >25 on admission seemed higher in PCS patients, without reaching statistical significance. Nevertheless,

TABLE 5 | Baseline characteristics in the large vessel occlusion patient cohort.

	Posterior circulation stroke ($n = 27$)	Anterior circulation stroke ($n = 96$)	p-value
Female sex, *n* (%)	8 (29.6)	57 (59.4)	0.008
Age in years, median (IQR)	77.0 (69.0–82.0)	80.0 (71.0–87.0)	0.179
Arterial hypertension, *n* (%)	23 (85.2)	85 (88.5)	0.739
Hyperlipidemia, *n* (%)	17 (63.0)	43 (44.8)	0.095
Diabetes mellitus, *n* (%)	12 (44.4)	26 (27.1)	0.085
History of stroke, *n* (%)	7 (25.9)	18 (18.8)	0.425
Atrial fibrillation, *n* (%)	9 (33.3)	52 (54.2)	0.081
Antiplatelets, *n* (%)	10 (37.0)	31 (32.3)	0.644
Oral anticoagulants, *n* (%)	1 (3.7)	12 (12.5)	0.294
Vitamin K antagonists, *n* (%)	1 (3.7)	5 (5.2)	1.000
Direct oral anticoagulants, *n* (%)	0 (0.0)	7 (7.3)	0.346
Pre-mRS score, median (IQR)	1 (0–2)	1 (0–3)	0.547

pre-mRS, pre-stroke modified Rankin scale.

TABLE 6 | Clinical and imaging characteristics of stroke in the large vessel occlusion patient cohort.

	Posterior circulation stroke ($n = 27$)	Anterior circulation stroke ($n = 96$)	p-value
Last seen normal to door—min, median (IQR)	396 (318–693)	533 (320–804)	0.127
Symptom recognition to door—min, median (IQR)	89 (67–153)	68 (50–123)	0.049
Confirmed extended time window, *n* (%)	6 (22.2)	6 (6.3)	0.023
Symptom onset to door in patients in the extended time window—min, median (IQR)	349 (256–491)	398 (299–636)	0.485
Patients transferred from external hospital for treatment, *n* (%)	1 (3.7)	7 (7.3)	0.684
Multimodal CT imaging for thrombolysis, *n* (%)	17 (63.0)	47 (49.0)	0.198
NIHSS score on admission, median (IQR)	8 (5–15)	14 (9–18)	0.005
NIHSS score >25 on admission, *n* (%)	3 (11.1)	3 (3.1)	0.119
Intubated on admission, *n* (%)	2 (7.4)	5 (5.2)	0.648
Wake-up stroke, *n* (%)	16 (59.3)	72 (75.0)	0.109
Infra- and supratentorial stroke, *n* (%)	11 (40.7)		
Volume of irreversibly injured ischemic core tissue at initial imaging[a,b]–ml, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–18.0)	0.001
Perfusion lesion volume at initial imaging[b,c]–ml, median (IQR)	46.0 (19.0–125.0)	87.0 (38.0–153.0)	0.132
Mechanical thrombectomy, *n* (%)	13 (48.1)	49 (51.0)	0.790
Additional intra-arterial thrombolysis, *n* (%)	3 (11.1)	3 (3.1)	0.119
Recanalization TICI 2b/3 in EVT patients	12/13 (92.3)	44/49 (89.8)	1.000
Recanalization after IVT prior to EVT	1/13 (2.0)	2/49 (15.4)	0.109
Door to needle—min, median (IQR)	55 (42–91)	61 (42–78)	0.886
Last seen normal to needle—min, median (IQR)	457 (368–745)	613 (385–843)	0.141
Symptom recognition to needle—min, median (IQR)	145 (115–237)	133 (107–194)	0.264
Door to groin[d]–min, median (IQR)	97 (78–121)	94 (77–111)	0.621
Last seen normal to recanalization[e]–min, median (IQR)	575 (521–958)	805 (525–970)	0.427
Symptom recognition to recanalization[e]–min, median (IQR)	260 (205–360)	265 (195–335)	0.929
Follow-up imaging MRI, *n* (%)	1 (3.7)	4 (4.2)	1.000

NIHSS, NIH Stroke Scale; rtPa, recombinant tissue plasminogen activator. One anterior circulation stroke patient died prior to follow-up imaging.

[a] *The volume of irreversibly injured ischemic core tissue was calculated with the use of a threshold for relative cerebral blood flow of less than 30% of that in normal brain tissue or with the use of diffusion-weighted MRI (apparent diffusion coefficient).*

[b] *The volumetric assessment of perfusion imaging was available in 20 posterior circulation stroke and 65 anterior circulation stroke patients.*

[c] *To define the critically hypoperfused tissue, perfusion lesion volume was calculated as the volume of tissue in which there had been a delayed arrival of an injected tracer agent exceeding 6 s.*

[d] *The time of groin puncture was available in 11 posterior circulation stroke (PCS) and 44 anterior circulation stroke (ACS) patients treated with additional mechanical thrombectomy.*

[e] *The time of recanalization was available in eight PCS patients and 39 ACS patients treated with additional mechanical thrombectomy.*

TABLE 7 | Outcomes in the large vessel occlusion patient cohort.

	Posterior circulation stroke ($n = 27$)	Anterior circulation stroke ($n = 96$)	*p*-value	aRD[a]	95% CI
Any ICH, *n* (%)	2 (7.4)	18 (18.9)	0.239	−7.4%	−20.7 to 12.2%
Symptomatic ICH according to ECASS III criteria[b], *n* (%)	1 (3.7)	2 (2.1)	0.531	0.8%	−8.5 to 17.6%
Symptomatic ICH according to ECASS II criteria[c], *n* (%)	1 (3.7)	3 (3.2)	1.000	0.8%	−8.5 to 17.6%
Symptomatic ICH according to SITS-MOST criteria[d], *n* (%)	0 (0.0)	2 (2.1)	1.000	−3.6%	−12.1 to 11.0%
Fatal ICH, *n* (%)	0 (0.0)	1 (1.0)	1.000	−1.8%	−9.4 to 12.6%
ICH location remote[e], *n* (%)	2 (7.4)	5 (5.3)	0.650	–	–
Infarction on follow-up imaging, *n* (%)	19 (70.4)	84 (87.5)	0.034	−18.9%	−39.8 to −2.2%
Early major neurologic improvement[f], *n* (%)	5 (18.5)	16 (16.7)	0.779	5.9%	−10.8 to 27.4%
Mortality during inpatient stay, *n* (%)	5 (18.5)	14 (14.6)	0.563	5.1%	−10.0 to 25.8%
Favorable outcome at day 90 (pre-mRS or mRS score 0–2)[g], *n* (%)	5 (21.7)	24 (28.9)	0.603	−15.5%	−34.0 to 9.7%
90-day mortality[h], *n* (%)	7 (29.2)	27 (30.7)	1.000	−1.9%	−21.1 to 22.2%

aRD, adjusted risk difference; ICH, intracranial hemorrhage; mRS, modified Rankin scale; pre-mRS, pre-stroke modified Rankin scale. One anterior circulation stroke patient died prior to follow-up imaging.

[a]Adjusted for age, female sex, arterial hypertension, diabetes mellitus, atrial fibrillation, NIHSS on admission, and mechanical thrombectomy using propensity score matching; posterior circulation stroke (PCS) n = 23, anterior circulation stroke (ACS) n = 57.

[b]Any intracranial hemorrhage identified as a predominant cause of neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or any hemorrhage leading to death.

[c]Any intracranial hemorrhage with neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or any hemorrhage leading to death.

[d]Local or remote parenchymal hematoma type 2 and neurologic deterioration as indicated by a NIHSS score increase of four or more points from baseline or the lowest score or hemorrhage leading to death.

[e]Two patients with remote ICH had an additional peri-ischemic hemorrhage (one PCS patient and one ACS patient).

[f]Early major neurologic improvement defined as a reduction of NIHSS score of at least eight points or a score of 0 or 1 at 24 h.

[g]The 90-day mRS was available in 106 patients (86.2%; 23 posterior circulation stroke patients and 83 anterior circulation stroke patients).

[h]Vital status at day 90 was available in 112 patients (91.1%; 24 posterior circulation stroke patients and 88 anterior circulation stroke patients).

we found no difference in mortality rates at day 90 between PCS and ACS patients in our study.

The proportion of patients with PCS in our study was slightly higher than the one reported in previous cohorts, including patients within 4.5 h from symptom onset (1–4, 15). Considering the poor prognosis of severe posterior circulation stroke without recanalizing therapies, the higher proportion of PCS in our cohort might refer to the aggressive treatment also beyond the first 4.5 h after onset (5, 22). Furthermore, a higher proportion of patients treated in the confirmed extended time window >4.5 h in PCS might have contributed to this finding and leads to the higher proportion of PCS patients in our cohort.

The higher proportion of female sex in ACS patients in our study was consistent to previous findings, demonstrating female sex as a known risk factor of ACS (15, 23). The PCS patients presented with lower median NIHSS scores on admission statistically significant in LVO patients confirming a known underrepresentation of PCS symptoms in the NIHSS (15, 21, 24).

As the symptoms of PCS can be clinically less noticeable, this may have led to longer times from symptom recognition to door in LVO patients of our study. Less noticeable symptoms may have led to longer door-to-needle times reported for PCS patients compared to ACS previously (25). In our study, the procedure times did not differ significantly between PCS and ACS patients despite the lower NIHSS scores on admission in PCS patients. Similar procedure times in ACS and PCS patients might be another evidence for an aggressive treatment of PCS patients in our cohort. Overall, the times from last seen normal to treatment were similar in PCS and ACS patients in our study.

Our study has relevant limitations, mainly its small patient number and monocentric design. The limited sample size might be causal for missing statistical significance in the difference of any ICH in our study. Furthermore, the classification as posterior or anterior circulation stroke based on clinical symptoms can be challenging in some patients presenting without LVO and with no infarction visible on follow-up imaging. This may have led to wrongly classifying some patients in the clinico-radiological cohort. However, no clear contradictory results between our clinico-radiological and LVO patient cohorts regarding primary and secondary outcomes were detected.

To conclude the main result of our study, the rates of hemorrhagic complications were low in PCS patients treated with IV-thrombolysis in the unknown or extended time window. This will reaffirm the clinician in the use of rt-PA for selected PCS patients beyond the established 4.5-h time window.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared on request to any qualified investigator.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Board, Medical Faculty, University of Erlangen-Nuremberg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KM contributed to the design and conceptualization of the study, acquisition and analysis of data, and drafting of the manuscript for intellectual content. PH, GS, RW, MK, and SS contributed to the acquisition of data and revision of the manuscript for intellectual content. TE, AD, and SS contributed to the design and conceptualization of the study and revision of the manuscript for intellectual content. IM contributed to the design and conceptualization of the study, analysis of data, and revision of the manuscript for intellectual content. BK contributed to the design and conceptualization of the study, analysis of data, and drafting of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.692067/full#supplementary-material

Supplemental Figure 1 | Standardized differences in variables included in the propensity score before and after matching in the clinico-radiologic patient cohort.

Supplemental Figure 2 | Standardized differences in variables included in the propensity score before and after matching in the large vessel occlusion patient cohort.

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Intraplaque Enhancement Is Associated With Artery-to-Artery Embolism in Symptomatic Vertebrobasilar Atherosclerotic Diseases

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Objective: There are limited data regarding the characteristics of intracranial plaques according to stroke mechanism in the posterior circulation. This study aims to compare whether the plaque characteristics and baseline features are different in patients with artery-to-artery (A-to-A) embolism and those with parent artery disease in the intracranial vertebrobasilar atherosclerotic disease.

Methods: From September 2014 to January 2017, patients with recent posterior circulation stroke due to intracranial vertebrobasilar atherosclerotic disease were retrospectively analyzed. Patients with the following eligibility criteria were included: (1) age ≥18 years old, (2) ischemic stroke in the vertebrobasilar territory, (3) 70–99% stenosis of the intracranial vertebral artery or basilar artery, and (4) two or more atherosclerotic risk factors. Patients with concomitant ipsilateral or bilateral extracranial vertebral artery >50% stenosis, cardio-embolism, or non-atherosclerotic stenosis were excluded. The plaque characteristics, including intraplaque compositions (intraplaque hemorrhage and intraplaque calcification), intraplaque enhancement, and remodeling index, were evaluated by using 3T high-resolution magnetic resonance imaging (HRMRI). The baseline features including vascular risk factors and the involved artery were collected. Patients were divided into A-to-A embolism and parent artery disease groups based on the diffusion-weighted images, T2-weighted images, or computed tomography. The plaque characteristics and baseline features were compared between the two groups.

Results: Among consecutive 298 patients, 51 patients were included. Twenty-nine patients had A-to-A embolism and 22 patients had parent artery disease. Compared with parent artery disease, the occurrence rates of intraplaque enhancement and intracranial vertebral involvement were higher in the A-to-A embolism group (79.3 vs. 36.4%;

$p = 0.002$ and 62.1 vs. 18.2%; $p = 0.002$, respectively). Multivariable logistic regression analysis showed that intraplaque enhancement and intracranial vertebral artery plaques were also associated with A-to-A embolism (adjusted OR, 7.31; 95% CI 1.58–33.77; $p = 0.011$ and adjusted OR, 9.42; 95% CI 1.91–46.50; $p = 0.006$, respectively).

Conclusion: Intraplaque enhancement and intracranial vertebral artery plaques seem to be more closely associated with A-to-A embolism than parent artery disease in patients with symptomatic intracranial vertebrobasilar disease.

Clinical Trial Registration: http://www.clinicaltrials.gov, identifier: NCT02705599.

Keywords: atherosclerosis, intracranial stenosis, vertebrobasilar disease, ischemic stroke, magnetic resonance imaging

INTRODUCTION

Posterior circulation stroke accounts for about 20–25% of ischemic stroke (1, 2), 9.9–16.3% of which is due to intracranial vertebrobasilar stenosis (3, 4). Patients with the symptomatic vertebrobasilar disease with evidence of impaired distal perfusion or blood flow due to severe stenosis are at a higher risk of recurrence with medical treatment (4–6). In these patients, the stroke mechanisms are usually impaired distal perfusion combined with A-to-A embolization or parent artery disease (7). Previous studies have shown that A-to-A embolism or multiple infarcts may be associated with vulnerable plaque, which has a higher risk of stroke recurrence (8–10). So far, studies on that whether the crucial plaque characteristics are different in patients with A-to-A embolism and those with parent artery disease due to severe intracranial vertebrobasilar stenosis are scarce.

Recently, HRMRI is increasingly used to understand the stroke mechanisms in patients with intracranial atherosclerotic stenosis. With the application of HRMRI, intracranial vessel wall affected by atherosclerosis can be imaged to display plaque components (11–13), plaque distribution (14, 15), and the degrees of enhancement after injection of Gadolinium-DTPA (16, 17). A few studies are unraveling the differences of the plaque features by using HRMRI between different stroke mechanisms in patients with anterior circulation stroke (18, 19), but is rarely studied in the posterior circulation.

Previous studies have shown that stroke mechanisms may differ in different intracranial artery territories (5, 20). The Warfarin–Aspirin Symptomatic Intracranial Disease study also showed that there was more parent artery disease in patients with posterior circulation stroke (35.9 vs. 15.3%) and less border-zone infarction (44.4 vs. 57.8%) than those in anterior circulation stroke (21). Furthermore, there are major differences in the mechanisms of stroke between the carotid and the middle cerebral arteries (5). However, a few studies focused on the difference between the intracranial vertebral and the basilar arteries.

The purpose of this study was aimed to explore the baseline features and the crucial plaque characteristics detected by HRMRI in severe intracranial vertebrobasilar stenosis and evaluate whether the plaque characteristics and the baseline features are different in patients with A-to-A embolism and those with parent artery disease.

MATERIALS AND METHODS

Study Design and Subjects

This was a prospective, observational study approved by the ethics committees of Beijing Tiantan Hospital and Chinese PLA General Hospital. Written informed consent was obtained from the patients or their legal guardians.

From September 2014 to January 2017, we prospectively recruited ischemic stroke patients due to intracranial atherosclerotic stenosis. All patients received thorough evaluations to determine the ischemic stroke etiology, including computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA), carotid Doppler ultrasonography, transcranial Doppler, echocardiography, electrocardiogram, etc. Patients with the following inclusion criteria were included: (1) age $\geq$18 years old, (2) ischemic stroke in the vertebrobasilar territory as identified by diffusion-weighted imaging (DWI)/T2-weighted imaging (T2WI)/CT, (3) 70–99% stenosis of the intracranial vertebral artery or basilar artery as confirmed by MRA, CTA, or DSA, and (4) two or more atherosclerotic risk factors including hypertension, hyperlipidemia, diabetes mellitus, obesity, and cigarette smoking. The definition of risk factor was the same as the previous protocol (22). Exclusion criteria were (1) coexistent >50% stenosis of the ipsilateral or bilateral extracranial vertebral artery; (2) evidence of cardio-embolism, such as atrial fibrillation, recent myocardial infarct within 4 weeks, mitral stenosis or prosthetic valve, etc.; (3) non-atherosclerotic vasculopathy that may result in ischemic stroke (e.g., vasculitis, moyamoya disease, or dissection).

Baseline features, including sex, age, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, obesity, and cigarette smoking), previous stroke history, antithrombotic medication, and statin medication were recorded for each patient.

Stroke Mechanisms Based on Routine Diffusion-Weighted Imaging/T2-Weighted Imaging/Computed Tomography and Magnetic Resonance Angiography/Computed Tomography Angiography/Digital Subtraction Angiography

All DWI/T2WI/CT and MRA/CTA/DSA images of patients were reviewed independently by two neurologists (MN and HZK) to determine the stroke mechanisms. In situations of disagreement, a third assessor adjudicated (XZQ). We classified the stroke mechanisms in the included patients as (1) parent artery atherosclerosis occluding penetrating artery (henceforth referred to as parent artery disease) is defined as isolated pons or medullary infarct on brain images, which localized in the territory of perforating arteries that arise at the site of the diseased basilar artery or vertebral artery. The parent artery was severe stenosed due to atherosclerosis. (2) A-to-A embolism is defined as single or multiple scattered cerebral or cerebellar cortical infarct(s) with or without subcortical infarcts (including the bilateral occipital lobe, medial temporal lobes, corpus callosum, midbrain, cerebellar hemisphere, and cerebellar vermis), which located in the branch territory of diseased intracranial vertebral artery or basilar artery. (23, 24).

Plaque Features Identified by High-Resolution Magnetic Resonance Imaging

Details of the parameters of the HRMRI multiple sequences were the same as the previous studies (22, 25). The images were acquired by a coronal or axial view, which covered the intracranial vertebral artery and basilar artery. T1-weighted vessel wall images of responsible lesions were reconstructed into cross-sectional areas (perpendicular to the vessel longitudinal axis) at the image workstation. The evaluation was subsequently performed on the reformatted images using freely available software ImageJ (Rasband, National Institute of Mental Health, Bethesda, MD, USA) (22). All images were analyzed by two experienced neuroradiologists (LX and LJH) who were blinded to the clinical data of the patients. An image-quality rating (poor, adequate, and good) was given to each image by the two neuroradiologists. Poor-quality images with severe motion artifacts or low signal intensity-to-noise ratio were excluded. The present study did not display intra- and interobserver variabilities with the same or different scanners in light of previous research showing that these variabilities are small (25).

All atherosclerotic plaques that were involved in the intracranial vertebral artery or basilar artery on HRMRI were defined as eccentric wall thickening with or without luminal stenosis identified on the reconstructed precontrast HRMR images (26). A responsible vessel was the artery that supplied the infarcted tissues. A culprit plaque within the responsible vessel was the plaque if it was the only lesion within the culprit vascular territory of the stroke or the most stenotic lesion when multiple plaques were present (26). The plaque characteristics, including intraplaque compositions (intraplaque hemorrhage and intraplaque calcification), intraplaque enhancement, and remodeling index were assessed. Intraplaque hemorrhage was defined as the brightest plaque signal intensity >150% of that of the adjacent gray matter on T1 sequences (12). Intra-plaque calcification was defined as a low-signal intensity spot in the plaque on all pulse sequences (27). The mean signal intensity values of culprit plaques and the normal adjacent vessel wall were measured on precontrast and postcontrast HRMR images. Intraplaque enhancement was defined as the enhancement degree of the culprit plaque higher than that of the normal adjacent vessel wall (26). The vessel areas at the maximal lumen narrowing site and reference site were automatically calculated after the manual vessel contour tracing in the software ImageJ (Rasband, National Institute of Mental Health, Bethesda, MD, USA). The remodeling index was defined and calculated as the ratio of the vessel area at the maximal lumen narrowing site to that at the reference site. The reference site was selected based on the WASID (Warfarin–Aspirin Symptomatic Intracranial Disease) method (28). Remodeling index $\geq$1.05 was defined as positive remodeling, 0.95 and 1.05 as intermediate remodeling, and $\leq$0.95 as negative remodeling (29).

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD) or median with interquartile range (IQR); categorical variables are presented as percentages. Categorical variables were analyzed using a $\chi 2$ test or Fisher's exact test. Continuous variables were compared using Student's *t*-test between the two groups. The associations between plaque characteristics and stroke mechanisms were further assessed by using multivariable logistic regression models. Variables were included for multivariate analysis if they were $p \leq 0.2$ in the univariate analysis. The adjusted odds ratio (OR) and their 95% confidence intervals (CI) were calculated. A two-sided *p*-value of <0.05 indicated statistical significance. All statistical analyzes were performed using commercial software (SPSS).

RESULTS

The Baseline Features of the Patients

The flow chart of the study is presented in **Figure 1**. Among 298 consecutive patients, 51 patients fulfilled the inclusion criteria. Of the 51 patients, 29 (56.9%) were determined as A-to-A embolism and 22 (43.1%) as parent artery disease. Detailed infarct distributions and MRA/CTA/DSA of included patients are presented in **Supplementary Figure 1**. Patient demographics, atherosclerotic risk factors, and the culprit plaque characteristics on HRMRI are presented in **Table 1**. The median time from the qualifying event to HRMRI was 31 days (IQR, 14–48 days).

Comparisons of the Baseline and Plaque Features of the Two Groups

There were no significant differences found between the two groups in sex, age, atherosclerotic risk factors, or time from the qualifying event to HRMRI. Previous stroke history, antithrombotic medication, and statin medication had no

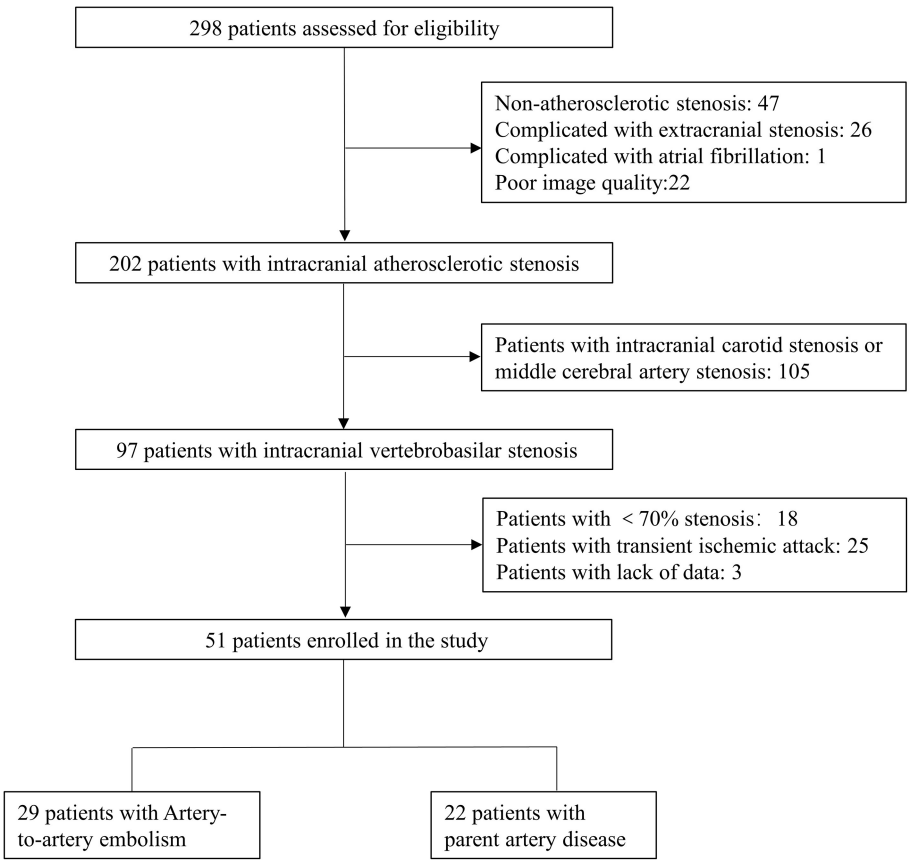

FIGURE 1 | Flow chart of the study.

significant difference between the A-to-A embolism group and the parent artery disease group (**Table 2**).

In the A-to-A embolism group, the occurrence rates of intracranial vertebral artery involvement and intraplaque enhancement were higher than those in the parent artery disease group (62.1 vs. 18.2%; $p = 0.002$ and 79.3 vs. 36.4%; $p = 0.002$) (**Table 3**; **Figures 2**, **3**). Culprit plaque was found in 81.8% of the basilar artery in the parent artery disease compared with 37.9% of the basilar artery in the A-to-A embolism group ($p = 0.002$). No significant difference was found between the two groups in plaque compositions and remodeling index.

Location of culprit plaque, intraplaque hemorrhage, and enhancement degree were used as input variables for the multivariable logistic regression analysis. After adjusting for confounding factors, intraplaque enhancement was associated with A-to-A embolism (adjusted OR, 7.31; 95% CI 1.58–33.77; $p = 0.011$). The intracranial VA of culprit plaque was also associated with A-to-A embolism (adjusted OR, 9.42; 95% CI 1.91–46.50; $p = 0.006$) (**Table 3**).

DISCUSSION

In patients with symptomatic severe intracranial vertebrobasilar atherosclerosis, we found that the patients with A-to-A embolism were more likely to have a higher occurrence of intraplaque enhancement and a higher rate of intracranial vertebral artery involvement than those with parent artery disease. The findings of our study have not previously been well-established in the literature.

Previous studies have indicated that there was an association between intraplaque enhancement and symptomatic intracranial atherosclerotic diseases. These studies found that plaque enhancement is more commonly observed in symptomatic intracranial artery stenosis (17, 30). Qiao et al. found that contrast enhancement of an intracranial plaque is associated with its likelihood to have caused a recent ischemic event, regardless of the plaque thickness (26). A previous study showed that intraplaque enhancement was independently associated with stroke recurrence (hazard ratio: 7.42, 95% CI: 1.74–31.75, $p = 0.007$) (16). However, a few studies of intracranial vessel wall imaging have concentrated on the relationship between stroke mechanisms and intraplaque enhancement. The result of our study showed that intraplaque enhancement was higher in the A-to-A embolism than in the parent artery disease. A similar finding was reported in a previous study focusing on evaluating the relationship between the middle cerebral artery plaque features on HRMRI and the stroke mechanism (19). In this study, patients with A-to-A embolism were more likely to have a high occurrence

TABLE 1 | Baseline and plaque characteristics.

Characteristics	Values
Age (mean ± SD, years)	58.0 ± 8.82
Male sex, *n* (%)	44/51 (86.3%)
Risk factors	
Hypertension, *n* (%)	44/51 (86.3%)
Diabetes mellitus, *n* (%)	22/51 (43.1%)
Hyperlipidemia, *n* (%)	21/51 (41.2%)
Obesity, *n* (%)	19/51 (37.3%)
Cigarette smoking, *n* (%)	35/51 (68.6%)
Ischemic stroke history, *n* (%)	12/51 (23.5%)
Antithrombotic medication, *n* (%)	6/51 (11.8%)
Statin medication, *n* (%)	10/51 (19.6%)
Time from qualifying event to HRMRI, median (IQR), days	31 (14–48)
Stroke mechanisms	
Parent artery disease, *n* (%)	22/51 (43.1%)
A-to-A embolism, *n* (%)	29/51 (56.9%)
Location of culprit plaque	
BA, *n* (%)	29/51 (56.9%)
Intracranial VA, *n* (%)	22/51 (43.1%)
Plaque compositions	
Intraplaque hemorrhage, *n* (%)	12/51 (23.5%)
Intraplaque calcification, *n* (%)	4/51 (7.8%)
Plaque enhancement degree	
Non-enhancement, *n* (%)	20/51 (39.2%)
Intraplaque enhancement, *n* (%)	31/51 (60.8%)
Remodeling index (mean ± SD)	1.10 ± 0.332

HRMRI, high-resolution magnetic resonance imaging; A-to-A embolism, artery-to-artery embolism; BA, basilar artery; VA, vertebral artery.

TABLE 2 | Patient baseline characteristics between the parent artery disease group and A-to-A embolism group.

Clinical characteristics	Parent artery disease ($n = 22$)	A-to-A embolism ($n = 29$)	*p*-value
Age (mean ± SD, years)	56.2 ± 8.33	59.3 ± 9.09	0.208
Male sex, *n* (%)	17/22 (77.3%)	27/29 (93.1%)	0.216
Risk factors			
Hypertension, *n* (%)	20/22 (90.9%)	24/29 (82.8%)	0.684
Diabetes mellitus, *n* (%)	10/22 (45.5%)	12/29 (41.4%)	0.771
Hyperlipidemia, *n* (%)	10/22 (45.5%)	11/29 (37.9%)	0.589
Obesity, *n* (%)	9/22 (40.9%)	10/29 (34.5%)	0.638
Cigarette smoking, *n* (%)	14/22 (63.6%)	21/29 (72.4%)	0.503
Ischemic stroke history, *n* (%)	7/22 (31.8%)	5/29 (17.2%)	0.224
Antithrombotic medication, *n* (%)	4/22 (18.2%)	2/29 (6.9%)	0.383
Statin medication, *n* (%)	5/22 (22.7%)	5/29 (17.2%)	0.894
Time from qualifying event to HRMRI, median (IQR), days	30.5 (14.8–35.5)	31 (13–50)	0.700

HRMRI, high-resolution magnetic resonance imaging; A-to-A embolism, artery-to-artery embolism.

of plaque enhancement than non-A-to-A embolism (75.0 vs. 21.4%, $p = 0.02$) (19). We think the plaque enhancement may be more related to the A-to-A embolism than the other stroke mechanisms in symptomatic intracranial atherosclerosis.

Plaque enhancement related to plaque vulnerability has been reported in several previous studies on coronary and carotid artery atherosclerosis (31–33). Studies on HRMRI findings of the internal carotid artery and its pathologic specimen from endarterectomy showed that enhanced plaque is associated with abundant active inflammatory cells, neo-vessel formation, and fibrous cap thinning (34). The exact mechanism of intracranial plaque enhancement remains unclear due to the relative inaccessibility of specimens. An analogous process may occur in the intracranial vasculature in the setting of ICAD. The instability of ICAD plaques secondary to neovascularization and inflammation can present with thromboembolism events, leading to multiple cerebral infarcts. When the fibrous cap of vulnerable plaque ruptures, plaque content and mural thrombus drop into the distal territory of the downstream vessel and result in A-to-A embolism. Focal plaque or thrombus occluding the perforator ostium caused parent artery disease. Considering the patients with A-to-A embolism have a higher recurrent stroke rate than stroke of other mechanisms (10), the plaques causing A-to-A embolism may be more vulnerable than the plaques causing parent artery disease. The intraplaque enhancement may be used as an imaging biomarker to predict the risk of recurrent stroke. This needs to be confirmed in future studies.

Furthermore, we have found that intracranial atherosclerotic stroke mechanisms differed between the intracranial vertebral artery and the basilar artery. The A-to-A embolism was higher in the intracranial vertebral artery stenosis than that in basilar artery stenosis, whereas parent artery disease was higher in basilar artery stenosis than in the intracranial vertebral stenosis. This difference may be attributable to more perforating vessels arising from the basilar artery that may be more vulnerable to occlusion in the presence of parental artery plaque. There are multiple groups of perforating vessels arising from the basilar artery, such as paramedian arteries, short lateral circumferential arteries, and long lateral circumferential arteries. In the New England Medical Center Posterior Circulation Registry, distal territory embolism accounts for 32.0% among patients with the symptomatic intracranial vertebral disease (35). A Korea prospective multicenter study also reported that A-to-A embolism was most frequent in the intracranial vertebral artery (53%), whereas parent artery disease was most frequently associated with the basilar artery (64%) (5). Our findings were similar to those published in previous studies.

In our study, there was no significant difference in the occurrence of intraplaque hemorrhage between A-to-A embolism and parent artery disease. As far as intraplaque hemorrhage, a previous study reported that hyperintense plaques on T1-weighted images were more closely associated with A-to-A embolism than non-A-to-A embolism (75.0 vs. 21.1%, $p < 0.001$) in the anterior circulation (18). This finding was not found in the present study. The occurrence rate of intraplaque hemorrhage was higher in this study than in our study [47.3%

TABLE 3 | Comparison of culprit plaque characteristics between the parent artery disease group and the A-to-A embolism group.

HRMRI characteristics	Univariable			Multivariable	
	Parent artery disease ($n = 22$)	A-to-A embolism ($n = 29$)	*p*-value	Adjusted OR (95% CI)	*p*-value
Location of culprit plaque			0.002	–	–
BA, *n* (%)	18/22 (81.8%)	11/29 (37.9%)	–	Ref	–
Intracranial VA, *n* (%)	4/22 (18.2%)	18/29 (62.1%)	–	9.42 (1.91–46.50)	0.006
Plaque compositions					
Intraplaque hemorrhage, *n* (%)	3/22 (13.6%)	9/29 (31.0%)	0.147	–	–
Intraplaque calcification, *n* (%)	1/22 (4.5%)	3/29 (10.3%)	0.625	–	–
Enhancement degree			0.002	–	–
Non-enhancement, *n* (%)	14/22 (63.6%)	6/29 (20.7%)	–	Ref	–
Intraplaque enhancement, *n* (%)	8/22 (36.4%)	23/29 (79.3%)	–	7.31 (1.58–33.77)	0.011
Remodeling index (mean ± SD)	1.08 ± 0.373	1.12 ± 0.304	0.672	–	–

HRMRI, high-resolution magnetic resonance imaging; A-to-A embolism, artery-to-artery embolism; BA, basilar artery; VA, vertebral artery.

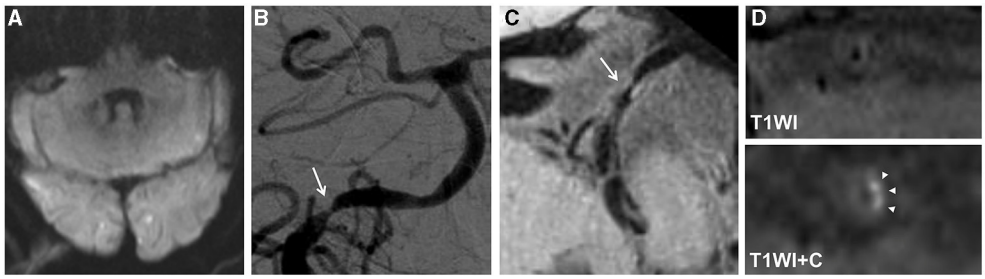

FIGURE 2 | An 80-year-old man presented with dizziness for 15 days. The diffusion-weighted imaging (DWI) showed infarcts of bilateral occipital lobes and left cerebellum **(A)**. The digital subtraction angiography (DSA) showed severe stenosis at the V4 segment of the right vertebral artery (arrow) **(B)**. The high-resolution magnetic resonance imaging (HRMRI) demonstrated a diffuse distributive plaque (arrow) **(C)** with an eccentric enhancement (arrowheads) on T1-weighted image after gadolinium–DTPA injection **(D)**.

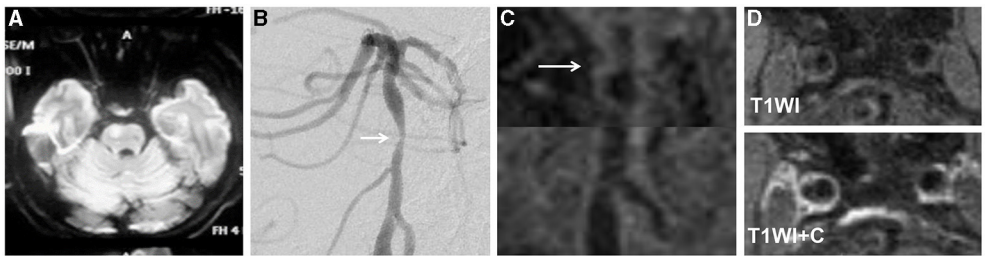

FIGURE 3 | A 68-year-old man presented with dysarthria for 20 days. The DWI showed an infarct located at the right pons **(A)**. The DSA showed severe stenosis in the middle segment of the basilar artery (arrow) **(B)**. The HRMRI demonstrated a diffuse distributive plaque (arrow) **(C)**. There was no plaque enhancement on T1-weighted image after gadolinium–DTPA injection **(D)**.

(35/74) vs. 23.5% (12/51)]. The following two factors may explain the difference. The first was the intrinsic difference between the anterior circulation and posterior circulation. The second was the changes in the signal of intraplaque hemorrhage over time. The duration of intraplaque hemorrhage signal on HRMRI in the cerebral arteries has not been established. Longer time from symptom onset to HRMRI scanning in our study (median time 31 days) was observed compared with that in the previous study (mean time 8.3 days).

In our study, no significant differences in other plaque features including intraplaque calcification and remodeling index were found between A-to-A embolism and parent artery disease. Intraplaque calcification and remodeling patterns (positive remodeling) reflected the features of advanced plaque, but there were no differences found between the A-to-A embolism and parent artery disease in posterior circulation stroke. These findings need to be confirmed in future studies.

There are several limitations to this study. First, the sample size was small, and it may lead to type II errors. Only patients with severe vertebrobasilar stenosis were included, and this may cause inclusion criteria bias. In addition, there are three patients with basilar artery stenosis with pontine infarction and more than two embolic infarctions in the posterior cerebral artery territory in this study. The stroke mechanism is usually regarded as the combined mechanism. Considering the small sample size, we divided them into the A-to-A embolism group. Large sample size studies are needed to compare the plaque characteristic among the combined mechanism, A-to-A embolism, and parent artery disease. Second, the previous study showed that the intracranial plaque may be enhanced within weeks to months of cerebral infarction (36), but the median time from qualifying event to HRMRI was 31 (IQR, 14–48) days in this study. Intracranial plaque enhancement might be attenuated as the interval from qualifying event to HRMRI scan prolonged. This may result in biased results. The relationship between intraplaque enhancement and interval between qualifying event to image scan should be explored in the future study. Third, all patients are Chinese, and the result may not generalize the other ethnic population. Fourth, the majority of patients with A-to-A embolism underwent intracranial angioplasty and stenting, so it was impossible to compare the long-term outcome in variable stroke mechanisms groups.

CONCLUSION

In patients with symptomatic intracranial vertebrobasilar stenosis, A-to-A embolism seems to be more closely associated with intraplaque enhancement and intracranial vertebral artery plaques than parent artery disease. Further studies are needed to confirm these findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tantian Hospital and Chinese PLA General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZH and NM: study concept and design, data analysis, drafting the manuscript, and full responsibility of data. ML, YL, and JH: data collection. JL, ZX, JJ, and XL: imaging data analysis. RW, YW, XL, and ZM: study concept and design of the work. All authors approved the final version to be published and they agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.680827/full#supplementary-material

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Association of Regular Thrombus Surface Phenotype With Complete Recanalization in First-Line Contact Aspiration Thrombectomy for Basilar Artery Occlusion

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Objective: To assess whether angiographic thrombus surface phenotype has an impact on efficacy of contact aspiration (CA) thrombectomy in patients with basilar artery occlusion (BAO).

Methods: From January 2016 to December 2019, consecutive stroke patients with a BAO and first-line CA were analyzed in this retrospective study. We assessed baseline and imaging characteristics and treatment and clinical outcomes. We rated thrombus surface phenotype on pre-treatment digital subtraction angiography in a three-reader-consensus setting. Primary outcome was complete recanalization (modified treatment in cerebral ischemia [mTICI] 3 and arterial occlusive lesion [AOL] 3) after first-line CA without additionally stent retriever passes. Data analysis was stratified according to thrombus surface phenotype and complete first-line recanalization.

Results: Seventy-eight patients met the inclusion criteria. Median age was 74 years (IQR 64–80), 64% were male, and median baseline NIHSS score was 24 (IQR 7–32). Thirty patients had a regular and 16 patients had an irregular thrombus phenotype. Thrombus surface was not assessable in 32 patients. In patients with a regular phenotype, complete recanalization was more often achieved compared to irregular and non-ratable phenotypes (50 vs. 18.8% and 21.9%; $p = 0.027$). Patients with a regular phenotype [odds ratio [OR] 8.3; 95% confidence interval [CI]: 1.9–35.8; $p = 0.005$], cardioembolic stroke (OR 12.1, 95% CI: 2.0–72.8; $p = 0.007$), and proximal end of the thrombus in the middle basilar artery segment (OR 5.2, 95% CI: 1.0–26.6; $p = 0.046$) were more likely to achieve complete recanalization after first-line CA without rescue therapy.

Conclusion: The efficacy of CA may differ according to the angiographic thrombus surface phenotype in patients with BAO. A regular phenotype is associated with higher rates of complete recanalization in first-line CA. However, assessment of thrombus phenotype is frequently not feasible in BAO.

Keywords: basilar artery occlusion (BAO), endovascualar treatment, contact aspiration thrombectomy, complete recanalization, thrombus characteristics

INTRODUCTION

Without successful recanalization, basilar artery occlusion (BAO) is associated with high morbidity and mortality (1). Endovascular thrombectomy (EVT) is the standard of care for anterior circulation large vessel occlusion (acLVO) demonstrating high rates of recanalization and favorable outcome (2). In contrast, randomized controlled trials have not confirmed a benefit of EVT and best medical management (BMM) compared with BMM alone for patients with BAO (3, 4).

Early and complete recanalization seems to be a major factor for a favorable clinical outcome in BAO patients (5–7). First-line contact aspiration (CA) thrombectomy may be associated with higher rates of complete recanalization and a shorter procedure time in BAO compared to stent retriever (SR) (7, 8). In patients with an acLVO, the presence of a regular thrombus surface on pre-treatment digital subtraction angiography (DSA) seems to be associated with higher recanalization rates if treated by first-line CA (9, 10). This association has not been shown for BAO. However, a recent study has demonstrated that meniscoid-like thrombus surface is associated with higher recanalization rates if treated with CA (11).

We aimed to evaluate factors associated with complete recanalization using CA for BAO. We hypothesized that a regular thrombus surface in pre-treatment DSA is positively associated with complete recanalization in first-line CA without additional SR passes.

MATERIALS AND METHODS

Patients and Study Design

We included consecutive patients with acute BAO undergoing first-line CA thrombectomy within 24 h from symptom onset who presented to our center between January 2016 and December 2019.

We prospectively recorded patients' baseline and clinical characteristics (sex, age, comorbidities, vascular risk factors, onset, and severity of stroke: National Institutes of Health Stroke Scale [NIHSS] and intravenous thrombolysis [IVT]) in our institutional stroke register. Stroke etiology was assessed according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (12): (1) cardioembolic, large vessel atherosclerosis of (2) vertebral artery (VA) with arterio-arterial embolism or (3) BA with local atherosclerotic occlusion and (4) other or undetermined etiology. We included patients with a pre-hospital mRS 0–2. We excluded patients with revascularization of BA in pre-treatment DSA and in whom no access to the target occlusion could be gained.

This study has institutional ethics committee approval (Ethikkommission TU Dresden; EK272072017) with waiver of informed consent and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (13).

Procedural Data

We prospectively collected procedure times, endovascular devices used, number of device passes, and periprocedural complications. Primary CA was the preferred first-line treatment modality in our center for patients with BAO. We used different aspiration catheters (ACE 60, 64 or 68, Penumbra Inc., Alameda, CA, USA) that were combined with stent retrievers (SR) (EMBOTRAP II, Cerenovus, Johnson and Johnson, Raynham, MA, USA; pREset, phenox GmbH, Bochum, Germany; Separator 3D, Penumbra Inc., Alameda, CA, USA) if a rescue strategy was necessary. In case an underlying high-grade stenosis of the vertebral or basilar artery had to be treated, we used balloon-mounted or self-expanding stents (Coroflex Blue, B. Braun Melsungen AG, Berlin, Germany; PRO-Kinetic Energy Explorer, Biotronik AG, Bülach, Switzerland; Neuroform Atlas, Stryker Neurovascular, Fremont, CA, USA; Enterprise, Codman Neuro, Johnson and Johnson, Raynham, MA, USA) combined with balloon angioplasty, if needed. We selected the type of anesthesia (procedural sedation or general anesthesia) in cooperation with the anesthetist and stroke neurologist based on stroke severity, cardiopulmonary stability, and patient cooperation. The patients were treated on a biplane angiography system (AlluraXper FD20/15, Philips Medical Systems, Hamburg, Germany) and then transferred to the neurological intensive care unit or stroke unit.

Occlusion Characteristics and Recanalization Status

Three readers retrospectively analyzed pre-treatment occlusion characteristics on computed tomographic or magnetic resonance angiography. For localization of the occlusion, we divided the VA, BA, and the posterior cerebral arteries (PCA) into segments, as widely accepted (14). We assessed the location of the proximal thrombus end and the number of involved vessel segments. Anatomical variants of the V4-segment of vertebral arteries (VA) were scored as described before (15). The readers independently categorized the proximal surface of the thrombus on the pre-treatment DSA as "regular" if the profile was smoothly straight, convex, or concave (i.e., meniscoid-like) in the full vessel

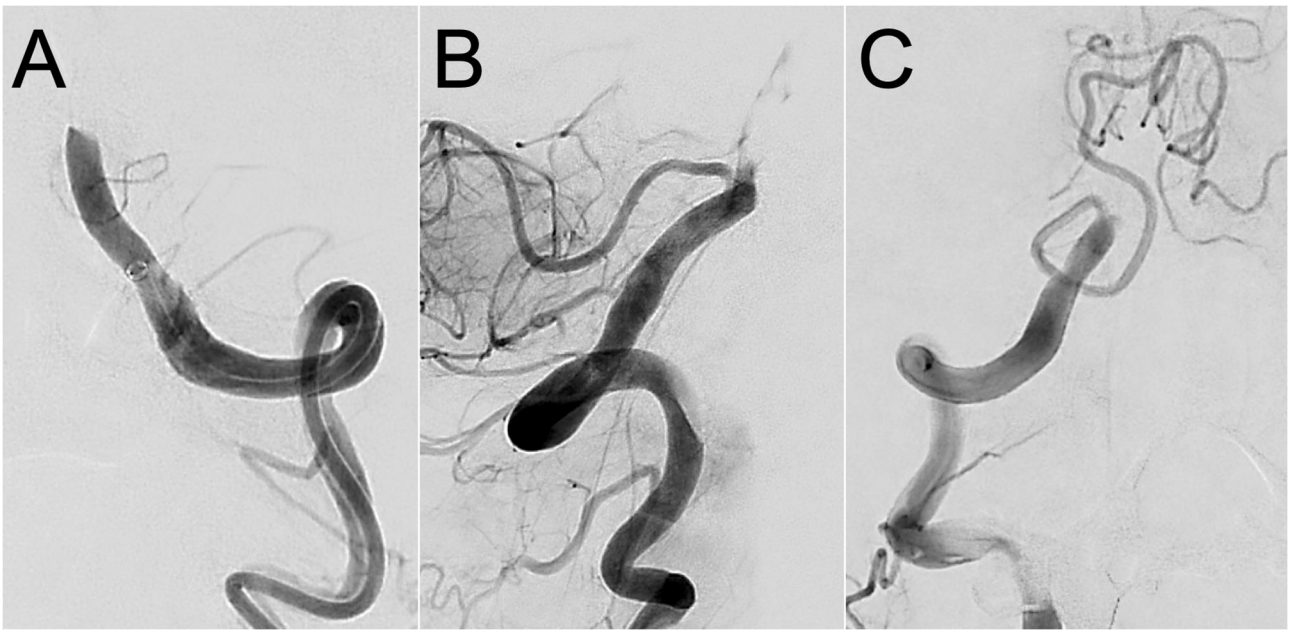

FIGURE 1 | Different gradings of thrombus surface phenotype in basilar artery occlusion. Pre-treatment digital subtraction angiography images of a basilar artery occlusion in a patient with a regular **(A)** and irregular **(B)** thrombus surface phenotype. Thrombus surface phenotype was non-ratable in panel **(C)** due to outflow in the ipsilateral posterior inferior cerebellar artery (PICA).

diameter, and "irregular" if these criteria were not met (**Figure 1**) (9). If readers were unable to determine the phenotype, we categorized the thrombus surface as not assessable and stated a reason. Status of recanalization (modified Treatment In Cerebral Ischemia [mTICI]) and (Arterial Occlusive Lesion [AOL]) was determined on the final angiogram of the procedure (16). Discrepant cases were resolved by consensus of the three readers.

Outcome Measures

The primary objective of our study was to evaluate the rate of complete recanalization (mTICI 3 and AOL 3) after first-line CA without additional SR passes depending on the phenotype of the thrombus surface. Apart from the occlusion phenotype, we analyzed the association of other variables (stroke etiology, thrombus location and extent, and anatomical variants of VA) with complete recanalization after first-line CA. Secondary outcome measures were favorable clinical outcome [modified Rankin Scale [mRS] 0–3] and death (mRS 6) after 90 days.

Statistical Analysis

The study population was stratified according to the phenotype of the thrombus surface and complete first-line recanalization. Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as absolute and relative frequencies. Distributions of continuous variables were tested for normality with the Kolmogorov–Smirnov test. We compared baseline characteristics, treatment and outcome variables between the groups using the chi-squared test and Fisher's exact test or an analysis of variance (ANOVA) and the Kruskal–Wallis test as appropriate. Logistic regression analyses were carried out on predictors identified by univariate analysis. The inter-rater reliability of grading the occlusion phenotype and recanalization status was assessed using Fleiss' Kappa (κ) with its 95% confidence interval (CI). Kappa values 0–0.2 indicate slight, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 substantial, and 0.81–1.00 almost perfect agreement (17). For all statistical analyses, a $p < 0.05$ or its Bonferroni correction was considered significant. We analyzed the data with SPSS Statistics (Version 25, IBM, Armonk, USA).

RESULTS

Patients

Of 135 patients with BAO, we excluded 34 patients who did not qualify for DSA due to large infarct size ($n = 2$), recanalization of BAO on CT-angiography in our hospital ($n = 28$), study randomization ($n = 1$), and neurological improvement to NIHSS 0 ($n = 3$). One patient was treated with a stent retriever first-line. Of 100 patients that received a digital subtraction angiography (DSA) with the intention to perform first-line CA, we subsequently excluded 11 patients with recanalized BA on pre-treatment DSA and 11 patients in whom we could not access the target arterial occlusion. Finally, we included 78 patients in the study (**Figure 2**). Median age was 74 years (IQR 64–80) and 64% were of male sex. The median NIHSS on admission was 24 (IQR 7–32). Overall, 40 (51.3%) patients received IVT before proceeding to endovascular treatment. The median time from

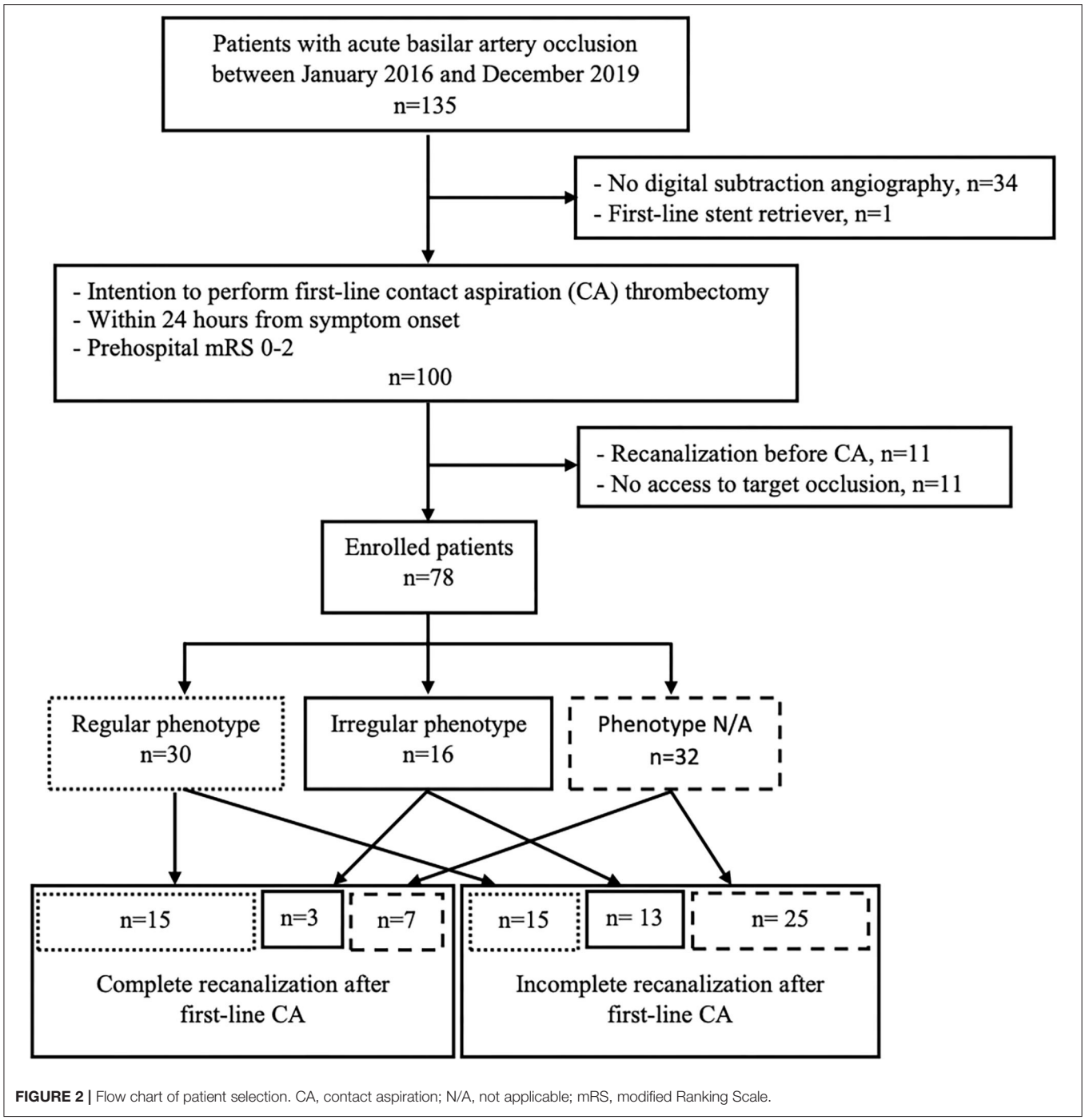

FIGURE 2 | Flow chart of patient selection. CA, contact aspiration; N/A, not applicable; mRS, modified Ranking Scale.

symptom onset to groin puncture was 295 min (IQR 185–365 min).

Thrombus Surface Phenotype

We rated 30 patients as having a regular and 16 patients as having an irregular phenotype. Phenotype grading was not possible in 32 patients due to poor delineation of the thrombus surface because of the inflow from the contralateral vertebral artery ($n = 19$), early outflow *via* cerebellar arteries ($n = 2$), or a stenosis of the intracranial VA or BA ($n = 11$). The inter-rater reliability of rating the phenotype of the occlusion was moderate with $\kappa = 0.46$ (95% CI: 0.36–0.55).

If the proximal end of the thrombus was located in the distal segment of the BA, we were able to rate its surface significantly more often than in other occlusion locations (3.7% N/A ratings in distal vs. 40.7% in middle, 22.9% in proximal segment of BA, and 33.3% in V4; $p < 0.05$). We found no association of stroke

TABLE 1 | Baseline and procedural characteristics, treatment results, and outcomes.

	Overall, $n = 78$	Phenotype			
		Regular, $n = 30$	Irregular, $n = 16$	N/A, $n = 32$	p-value
Baseline and clinical data					
Age, years, median (IQR)	74 (64–80)	73 (63–80)	76 (71–81)	74 (65–80)	0.483
Men, *n* (%)	50 (64)	22 (73)	9 (56)	19 (59)	0.570
Hypertension, $n = 72$ (%)	52 (72.2)	19 (65.5)	13 (81.3)	20 (74.1)	0.561
Diabetes mellitus, $n = 72$ (%)	33 (45.8)	11 (37.9)	7 (43.8)	15 (53.6)	0.313
Dyslipidemia, $n = 33$ (%)	6 (18.2)	1 (5.9)	3 (50)	2 (20)	0.108
Atrial fibrillation, $n = 73$	32 (43.8)	12 (41.4)	7 (43.8)	13 (46.2)	0.797
Previous stroke, $n = 73$ (%)	14 (19.2)	4 (13.8)	4 (25)	6 (21.4)	0.597
Coronary artery disease, $n = 33$ (%)	1 (3)	1 (5.9)	0	0	0.708
Antithrombotic treatment, *n* (%)	58 (74.4)	22 (73.3)	13 (81.3)	23 (71.9)	0.489
Drip and ship, *n* (%)	48 (61.5)	17 (55.7)	10 (62.5)	21 (65.6)	0.505
Baseline NIHSS, median (IQR)	24 (7–32)	26 (7–32)	19 (11–28)	26 (7–32)	0.815
Prehospital mRS 0–2, *n* (%)	78 (100)	30 (100)	16 (100)	32 (100)	–
IVT, *n* (%)	40 (51.3)	15 (50)	6 (37.5)	17 (53.1)	0.612
Onset to groin puncture, min, $n = 52$	295 (185–365)	251 (201–328)	280 (183–410)	287 (216–326.5)	0.248
Procedural data					
General anesthesia, *n* (%)	71 (91)	27 (90)	16 (100)	28 (87.5)	0.286
Duration of procedure, min, mean (IQR)	55 (37–93)	34 (52–76)	56 (36–94)	63 (35–103)	0.897
CA passes, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)	0.586
SR rescue, *n* (%)	10 (12.8)	1 (3.3)	5 (31.3)	4 (12.5)	0.323
Angioplasty extracranial, *n* (%)	10 (12.8)	3 (10)	2 (12.5)	5 (15.6)	0.363
Angioplasty intracranial, *n* (%)	7 (9)	4 (13.3)	0	3 (9.4)	0.430
Procedural complication, *n* (%)	3 (3.8)	0	2 (12.5)	1 (3.1)	0.092
Recanalization and outcome					
Complete recanalization, *n* (%)	25 (32.1)	15 (50)	3 (18.8)	7 (21.9)	**0.027**
Final substantial recanalization, *n* (%)	67 (85.9)	27 (90)	12 (75)	28 (87.5)	0.358
90-day mRS 0–3, $n = 72$ (%)	26 (36.1)	9 (32.1)	5 (33.3)	12 (41.4)	0.744
90-day mRS 6, $n = 72$ (%)	31 (43.1)	10 (35.7)	7 (46.7)	14 (48.3)	0.567

CA, contact aspiration; IVT, intravenous thrombolysis; IQR, interquartile range; min, minute; mRS, modified Ranking Scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; SR, stent retriever. Bold values are statistical significance.

etiology with thrombus surface phenotype ($p = 0.589$) but a non-significant trend to occlusion location ($p = 0.055$).

Procedural Data and Recanalization Results According to Thrombus Phenotype

Stratified according to the phenotype of the thrombus surface, patients were comparable regarding baseline characteristics, procedural data, and clinical outcome (**Table 1**). We used SR as a rescue strategy in one patient with regular, in five with irregular, and in four patients with undetermined phenotype. Stroke etiology, thrombus length, and rates of hypo-/aplastic V4-segments did not differ between the phenotypical groups.

A complete recanalization after first-line CA without additional SR passes was achieved in $n = 15/30$ (50%) of patients with a regular surface compared to $n = 3/16$ (18.8%) of patients with an irregular phenotype and $n = 7/32$ (21.9%) of patients where thrombus surface characteristics could not be determined ($p < 0.05$). In total, $n = 67$ (85.9%) of the patients had a substantial reperfusion (mTICI 2b-3) after all devices with no group differences according to the phenotype of the occlusion site. The inter-rater reliability for mTICI and AOL ratings were substantial with $\kappa = 0.67$ (95% CI: 0.57–0.77) and $\kappa = 0.77$ (95% CI: 0.69–0.85), respectively. Three patients experienced complications: two hemorrhages (one subarachnoid and one intracerebral hemorrhage) and one embolization to a new territory (PCA territory).

Predictors of Complete First-Line Recanalization

Patients with a complete recanalization (mTICI 3 and AOL 3) after first-line CA without additional SR passes more often had a regular thrombus phenotype and cardioembolic stroke and less frequently arterio-arterial embolism as stroke etiology. The location of the proximal thrombus end was less frequently in the V4-segment of the VA and more frequently in the middle segment of the BA compared to patients without complete recanalization (**Table 2**). The number of involved vessel segments was lower in successful recanalized patients.

TABLE 2 | Predictors of complete first-line recanalization.

	Complete first-line recanalization		
	Yes, $n = 25$	**No, $n = 53$**	***p*-value**
Phenotype, n (%)			
Regular	16 (60)	15 (28.3)	**0.012**
Irregular	3 (12)	13 (24.5)	0.164
N/A	7 (28)	25 (47.2)	0.108
Stroke etiology, n (%)			
VA arterio-arterial embolism	3 (12)	19 (35.8)	**0.024**
BA atherosclerosis	1 (4)	10 (18.9)	0.072
Cardioembolism	19 (76)	18 (34)	**0.001**
Undetermined or other	2 (8)	6 (11.3)	0.496
Clot location, n = 69 (%)			
V4	2 (8.3)	15 (33.3)	**0.021**
BA proximal	4 (16.7)	12 (26.7)	0.282
BA middle	13 (54.2)	11 (24.4)	**0.012**
BA distal	5 (20.8)	7 (15.6)	0.390
Involved segments, median (IQR)	2 (2–2)	2 (1–3)	**0.002**
VA contralateral hypo-/aplastic, *n* (%)	17 (68)	29 (60)	0.614
Outcome 90 days, n = 72 (%)			
mRS 0–3	47.8 (11)	30.6 (15)	0.192
mRS 6	5 (21.7)	26 (53.1)	**0.011**

BA, basilar artery; mRS, modified Ranking Scale; N/A, not applicable; VA, vertebral artery; V4, distal segment of vertebral artery. Bold values are statistical significance.

In logistic regression analysis, patients with a regular phenotype [odds ratio [OR] 8.3, 95% CI: 1.9–35.8; $p = 0.005$], cardioembolic stroke (OR 12.1, 95% CI: 2.0–72.8; $p = 0.007$), and proximal end of the thrombus in the middle BA segment (OR 5.2, 95% CI: 1.0–26.6; $p = 0.046$) were more likely to reach complete first-line CA recanalization. The logistic regression model was significant [chi-squared test (6) = 29.615; $p < 0.001$] and showed a large effect size ($f^2 = 0.93$).

Clinical Outcome

Clinical outcome at 90 days was available for 72 patients. In total, 26 (36.1%) patients had a favorable outcome and 31 (43.1%) died. Patients with complete recanalization after first-line CA had a non-significant trend to better outcomes ($n = 11/23$ vs. $n = 15/49$; n.s.) and a significantly lower mortality rate ($n = 5/23$ vs. $n = 26/49$; $p < 0.05$).

DISCUSSION

We found that a regular thrombus phenotype, cardioembolic stroke etiology, and occlusion in the middle segment of the BA might be predictors of complete recanalization if CA is chosen as the first-line thrombectomy method in BAO patients. However, phenotyping of the thrombus surface in BAO was technically less feasible compared to anterior circulation large vessel occlusions (acLVO) (9, 18).

Early complete recanalization seems to be a strong predictor for better clinical outcomes in BAO and is the primary goal of EVT regardless of the technique used (5–7). In BAO, first-line CA thrombectomy may be associated with higher rates of complete recanalization compared to SR (7, 8). The finding that a regular thrombus surface impacts on first-line CA recanalization success confirms our hypothesis and is in line with previous findings in acLVO (9, 10). However, we have no data on the impact of the thrombus surface phenotype on first-line SR effect as we used first-line SR only in one patient with BAO during the study period. Additionally, the rates of SR rescue strategy were too small for further subgroup analyses.

Recently, another study suggested the "meniscus sign" for the angiographic phenotype of the BAO site. In this study, patients were treated with both techniques, CA and SR (11). The meniscus sign, partly resembling our definition of a regular thrombus phenotype, was associated with higher complete recanalization rates in CA compared with SR after propensity score matching (11). These results underline our hypothesis that the efficacy of EVT technique may differ according to the angiographic phenotype in BAO. There are different definitions of the type of thrombus surface phenotype that best responds to CA (9–11). We would recommend our definition of a "regular" phenotype (i.e., smoothly straight, convex, or concave profile in the full vessel diameter) for clinical practice as it unifies the different classifications and a stricter definition could exclude patients who might benefit from a phenotype-based device selection.

Cardioembolic stroke and more distal thrombus location were associated with higher rates of complete revascularization. This is in line with previous studies but does not apply to CA only as it was described in patients treated by SR or IVT as well (8, 19, 20).

We found no association of the thrombus phenotype with stroke etiology. This is in contrast to a previous study showing an association of the positive clot meniscus sign with an embolic etiology (21). Hypothetically, the effectiveness of CA in recanalizing occlusions with a regular thrombus surface might depend on the consistency of the thrombus rather than the underlying stroke etiology. Histological thrombus composition seems to be a key factor in determining susceptibility to mechanical manipulation and the degree of successful reperfusion (22). Future studies are needed to assess the association of thrombus phenotype, composition, and stroke etiology.

The inter-rater reliability for mTICI and AOL scales in BAO were substantial. We used a combination of mTICI and AOL to assess complete revascularization as there is controversy as to which revascularization scale is the most suitable for posterior circulation stroke (23).

In line with previous studies (5–7), complete first-line revascularization was associated with better clinical outcomes; however, our study was not powered to draw any firm conclusion. Prospective studies are required to assess whether thrombus surface characteristics should influence the choice of the revascularization technique used in BAO to achieve best procedural and clinical outcomes. Choosing the most effective first-line thrombectomy device can also have economic benefits as it avoids the need for additional devices.

A limitation of thrombus surface phenotyping in BAO is the moderate inter-rater agreement compared to substantial agreement in acLVO (9, 10, 18). We introduced a third category

"not applicable" if the thrombus surface phenotype could not be determined. We outlined two main reasons for this difference between acLVO and BAO: First, the indirect delineation of the thrombus surface against the contrast medium was interfered by inflow from the contralateral vertebral artery or early outflow *via* cerebellar arteries. Second, intracranial vertebral or basilar artery stenosis disguised the thrombus surface. Interestingly, low flow conditions due to hypoplastic or aplastic contralateral VA or the absence of a local stenosis in BA were not associated with higher rates of successful phenotyping. Instead, phenotyping was most successful, if the occlusion occurred in the distal segment of the BA. Based on the study focus, we excluded BAO patients with no DSA or no access to target arterial lesion and patients with recanalized BA before EVT. This study design could affect the results of our analysis. However, thrombus surface analysis proved very difficult in CTA and MRA in preparatory studies.

This single-center study has all the limitations of a retrospective observational design. However, we prospectively recorded the data in our institutional stroke register and a single-center study offers homogeneity in (peri-) procedural patient care. Another limitation is the small number of patients and differing experience of the interventionalists that both might be unaccounted confounding variables.

CONCLUSION

The efficacy of CA thrombectomy may differ according to the angiographic phenotype of the thrombus surface at the target occlusion in patients with BAO. A regular phenotype may be an independent predictor for complete recanalization with first-line CA. Thrombus phenotyping in pretreatment DSA may be used to assist in choosing the first-line thrombectomy strategy. However, thrombus phenotyping was often not feasible in our cohort of BAO patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission TU Dresden. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

DK and JG contributed to conception and design of the study. MG, PK, JL, DK, JG, L-PP, and VP had a major role in data acquisition. KH and DK organized the database. KH, RW, PK, JG, VP, and DK contributed to the analysis of the data. DK performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Predictors of Early Neurological Deterioration in Stroke Due to Vertebrobasilar Occlusion

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Background and Aims: This study explores the predictors of early neurological deterioration (END) in patients with vertebrobasilar occlusion (VBO) in both primary endovascular therapy (EVT) and medical management (MM) groups.

Methods: Patients diagnosed with VBO from 2010 to 2018 were included. Comparative and multivariate analyses were used to identify predictors of all-cause END in the EVT group, and END due to ischemia progression (END-IP) in the MM group.

Results: In 174 patients with VBO, 43 had END. In the primary EVT group ($N = 66$), 17 all-cause END occurred. Distal basilar occlusion (odds ratio (OR), 14.5 [95% confidence interval (CI), 1.4–154.4]) and reperfusion failure (eTICI < 2b67 (OR, 5.0 [95% CI, 1.3–19.9]) were predictive of END in multivariable analysis. In the MM group (N=108), 17 END-IP occurred. Higher systolic blood pressure (SBP) at presentation (per 10 mmHg increase, OR, 1.5 [95% CI, 1.1–2.0]), stroke onset-to-door time <24 h (OR, 5.3 [95% CI, 1.1–2.0]), near-total occlusions (OR, 4.9 [95% CI, 1.2–19.6]), lower posterior circulation-Alberta Stroke Program Early CT scores (OR, 1.6 [95% CI, 1.0–2.5]), and lower BATMAN collateral scores (OR, 1.6 [95% CI, 1.1–2.2]) were predictive of END-IP.

Conclusions: In patients with stroke due to VBO, potential predictors of END can be identified. In the primary EVT group, failure to achieve reperfusion and distal basilar occlusion were associated with all-cause END. In the MM group, higher SBP at presentation, onset-to-door time less than 24 h, incomplete occlusions, larger infarct cores, and poorer collaterals were associated with END-IP.

Keywords: vertebrobasilar artery occlusion, early neurological deterioration, endovascular treatment, mechanical thrombectomy, posterior circulation stroke

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INTRODUCTION

Early neurological deterioration (END) occurs in up to one-third of patients with acute ischemic stroke and considerably affects outcome (1). With the advent of the stroke endovascular treatment (EVT) era, END is regaining focus for a few reasons. First, prediction of individual patient risk of END can identify candidates that can benefit from EVT, especially those with a lower National Institutes of Health Stroke Scale (NIHSS) score (2). Second, even with reperfusion therapy, END

may occur, both associated with incomplete reperfusion (3) and even after successful reperfusion (4); namely unexplained END. However, the aforementioned concerns regarding END have not been appropriately addressed in vertebrobasilar occlusion (VBO).

Identification of factors predictive of END in VBO patients treated with EVT is important in VBO for a few reasons. First, the brain tissue of posterior circulation is more eloquent, and the consequences of incomplete reperfusion can be more critical. Second, the collateral vasculature of the posterior circulation may be more likely to be effected by procedural complications, as the primary Willisian collateral is distally located in the vascular bed (basilar top) in contrast to the proximal location of the anterior circulation. Careful identification of END predictive factors is needed to maximize EVT treatment effect in VBO.

Identification of factors predictive of END in VBO patients with medical management may provide keys to expand the pool of patients that may benefit from EVT. Currently, there is no successful clinical trial that shows the superiority of EVT for VBO (5), but it is likely that through reasonable patient selection, EVT for VBO will result in good outcomes (6). However, patient selection by strict NIHSS scores and time parameters is more difficult to apply in VBO for a few reasons. First, the clinical severity of posterior circulation stroke may be underrated by NIHSS scores (7). Second, the frequency of atherosclerotic disease involving the vertebrobasilar artery is higher, resulting in fluctuating prodromal symptoms, unclear stroke onset, and neurological deterioration (8). Furthermore, in clinical practice, it may be important to identify more patients that may benefit from EVT, rather than to over-select (9). Patients that experience END during medical treatment may be potential candidates if their cause of END is ischemia progression (10) in specific.

As stated above, the general EVT criteria are guided by clinical severity, time metrics, identification of large vessel occlusion, and infarct volume. However, in clinical practice, the decision should be, and tends to be, individualized (9). There may be specific predilections stroke neurologists already have in this selection process in concern of END. In other words, their decision to perform or not to perform EVT may already be affected by their belief that some clinical and imaging findings may be associated with END.

Therefore, through a single-center registry, our goal was to explore potential predictors of END in patients with VBO. In the primary EVT population, we aimed to identify the clinical significance and predictors of all-cause END. In the medical management (MM) population, we identified the clinical significance and predictors of END specifically due to ischemia progression (END-IP). Finally, to clarify the predilections the clinicians already have in the selection of patients for EVT in VBO, we evaluated patients that deviated from the institutional EVT selection criteria.

MATERIALS AND METHODS

Patient Selection

From a university hospital ischemic stroke registry, patients with posterior circulation stroke were identified between 2010 and 2018 ($N = 1{,}710$). In this cohort, medical record search and analysis of baseline non-invasive angiography were performed to identify patients presenting with occlusion or near-total occlusion in the basilar artery (BA), bilateral vertebral arteries (VA), or dominant VA with contralateral flow absence. Patients in whom VBO occurred during hospitalization for ischemic stroke in another vascular territory were excluded.

The patients were classified into the primary EVT group if EVT decision was made at presentation in the emergency department by the attending stroke neurologist based on the institutional indication of EVT for VBO. The institutional EVT indications were as follows: occlusion of the basilar artery, bilateral V4, or unilateral V4 with contralateral hypoplasia, NIHSS $\geq$ 5 (if NIHSS $<$ 5, when clinical progression is highly expected), and onset-to-puncture $\leq$ 6 h (if 6–24 h, decision based on advanced imaging). In specific, EVT performed on the late time window (onset-to-puncture between 6 and 24 h) was also included in the primary EVT group if EVT decision was made at presentation to the emergency department. Otherwise, all patients who did not undergo EVT at presentation were classified into the MM group, in which the patients received standard antithrombotic treatments. Intravenous (IV) thrombolysis was performed when indicated, and IV thrombolysis did not affect patient grouping.

EVT was performed as a "rescue" therapy in some patients after the occurrence of END during the admission course. The decisions on the rescue EVT were made regardless of the initial intent for the treatment of the patients and did not affect patient grouping.

All EVT patients in this population were primarily treated with stent retriever thrombectomy or direct aspiration thrombectomy. The Ajou University Hospital Institutional Review Board approved this research (MED-MDB-20-268), and the board waived the need for patient consent.

Clinical Variables and Classification of END

The clinical severity was measured by serial NIHSS scores which were evaluated upon first evaluation by the neurologist, and routinely per 6 h after admission to stroke unit by professional stroke nurses. Presenting NIHSS scores were further trichotomized to $\leq$5, 6–20, and $>$20. Functional outcomes were measured by the modified Rankin scale (mRS) at 3 months.

END was defined as an increase in the NIHSS score compared with the best neurological status by more than four points during admission (1). The causes of END were separately classified in the primary EVT group and MM group.

In the primary EVT group, END caused by immediate and overt subarachnoid or intraventricular hemorrhages post-procedures were first classified as procedural complications. Next, reperfusion was graded based on the expanded treatment in cerebral ischemia (eTICI) scores (11), and successful reperfusion was classified as $\geq$eTICI2b67 (reperfusion of more than two-thirds of involved territory). In patients with reperfusion failure, all ENDs were considered as the result of reperfusion failure. In patients with successful reperfusion, causes of END were classified as cerebral edema, symptomatic hemorrhage, or reocclusion. Patients

with END due to unexpected, severe medical problems disproportionate to stroke treatment, such as acute kidney injury or cardiac arrest followed by resuscitation, were classified as medical.

In the MM group, the cause of END was classified as ischemia progression (END-IP), cerebral edema, symptomatic hemorrhage, or medical based on follow-up imaging and medical record review according to a previous study (10), with slight modification. Symptomatic hemorrhage was defined as an END due to hemorrhagic lesions with mass effects. Cerebral edema was defined as an END due to edema of initially infarcted tissue with mass effect without hemorrhagic transformation. Ischemia progression was defined as an END due to the expansion of infarction or the development of additional infarctions within the same vascular territory. If there were more than one cause of deterioration, the preceding insult was considered as the cause of END. Medical causes were defined as END due to unexpected, severe medical problems disproportionate to stroke treatment.

Image Analysis and Occlusion Etiology

Commercial image-viewing software (Picture Archiving and Communication System; Maroview 5.3 Infinitt Co., Seoul, Republic of Korea) was used for image analysis after blinding. The occlusion location was trichotomized to distal basilar, proximal to mid basilar, and vertebral arterial occlusions according to the initiation point of luminal filling defect. The posterior circulation Alberta Stroke Program Early CT score (PC-ASPECTS) was used to grade presenting infarct volume, which was evaluated predominantly on baseline diffusion-weighted images (12). Each assigned point was subtracted when there was more than 20% involvement of the relevant territory (13). Each specific infarct location according to the items on PC-ASPECTS was separately analyzed for its association with END. The Basilar Artery on Computed Tomography Angiography (BATMAN) score (14) and its specific anatomical composition of collateral vessels were utilized to measure baseline collateral status and incorporated into the analyses.

The etiology of VBO was classified as embolic, intracranial-atherosclerotic (15), arterial embolic (16), and dissecting occlusions through review of medical records and serial neuro-images. In the primary EVT group, the etiological classification was sequentially performed according to previous literature (15). For this study, the embolic group was subdivided as arterial embolism if significant culprit stenosis or occlusion was identified proximal to the occlusion of interest (16).

If EVT was not performed/reperfusion not achieved, the occlusion etiology was determined by integrating predictors previously reported, such as the presence of atrial fibrillation, truncal-type occlusions (intracranial atherosclerotic occlusions) vs. branching-site occlusions (embolic occlusions) (17, 18), and severe calcifications (19) at the occlusion site. Serial vessel imaging was also reviewed for recanalization revealing underlying focal stenosis vs. normal lumen (20). Dissections were classified by the identification of intimal flap, double lumen, and intramural hematoma. It was also supplemented by a string of pearls appearance and rapid changes in the vascular morphology.

Statistical Analysis

In the total VBO population, the patients were classified into the primary EVT group and MM group. Comparative analysis was performed between the two groups. Next, in the primary EVT group, clinical characteristics and pretreatment imaging findings were evaluated for predictors of all-cause END. In the MM population, clinical characteristics and pretreatment imaging findings were evaluated for predictors of END-IP. Next, outcomes of patients that performed rescue EVT due to END were graded. Finally, the patients with inconsistency between institutional EVT inclusion criteria and actual procedure were described. Continuous variables were compared using the Student *t*-test and Mann–Whitney *U*-test, and categorized variables using the chi-square test. Multiple logistic regression was performed for the identification of predictors of END including clinically relevant variables. Data are presented as the mean ± standard deviation, number (%), or median [interquartile range (IQR)] as appropriate. All statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

General Characteristics of the Primary EVT Group and MM Group

In total, 174 patients with VBO [age: 67 ± 13, male: 113 (64.9%)] were included in the study, and END occurred in 43 (24.7%) patients. Primary EVT was performed in 66 (37.9%) patients. Occlusion etiology was classified as embolisms in 41 (23.6%), intracranial atherosclerotic occlusions in 108 (62.1%), arterial embolisms in 12 (6.9%), and dissections in 13 (7.5%).

A between-group comparison of patients in the primary EVT group and MM group was performed (**Table 1**). In clinical parameters, history of hypertension (69.8 vs. 53.0%, $p = 0.04$) and diabetes mellitus (40.6 vs. 24.2%, $p = 0.043$) were more frequently found in the MM group. Stroke onset-to-door time was shorter (2 [1–3] vs. 10 [3–31.5], $p < 0.001$), and initial stroke severity by trichotomized NIHSS groups was higher in the primary EVT group.

Among imaging parameters, more truncal-type occlusions (77.8 vs. 47.0%, $p < 0.001$) and incomplete occlusions (33.3 vs. 10.6%, $p = 0.001$) were seen, with a higher proportion of intracranial atherosclerotic occlusions (71.3 vs. 47.0%, $p < 0.001$) in the MM group. Larger initial infarct volumes represented by PC-ASPECTS (8 [7–9] vs. 9 [8–10], $p < 0.001$), poorer collateral status represented by BATMAN collateral score (5 [3–6] vs. 6.5 [5–8], $p < 0.001$), and absent fetal-type posterior cerebral arteries (PCA) were observed in the primary EVT group.

The rate of ENDs that occurred in the two groups was similar (24.1 vs. 25.8%, $p = 0.945$). Functional outcome, represented by 3 months mRS, was poorer (5 [2–5] vs. 2 [1–5], $p < 0.001$) in the primary EVT group.

Distribution of END

In the primary EVT group ($N = 66$), END occurred in 17 patients (25.8%). Among them, the causes of END were reperfusion

TABLE 1 | General characteristics of patients in the primary EVT group and MM group.

	Total (*N* = 174)	Primary EVT (*N* = 66)	MM (*N* = 108)	*P*-value*
Clinical parameters				
Age	67.48 ± 13.03	67.01 ± 13.07	67.78 ± 13.06	0.706
Sex, male	113 (64.9%)	43 (65.2%)	70 (64.8%)	>0.99
Hypertension	109 (63.4%)	35 (53.0%)	74 (69.8%)	0.040
Diabetes mellitus	59 (34.3%)	16 (24.2%)	43 (40.6%)	0.043
Atrial fibrillation	31 (17.8%)	14 (21.2%)	17 (15.7%)	0.477
BMI (kg/m^2)	24.15 ± 3.42	24.66 ± 3.78	23.84 ± 3.17	0.178
Systolic blood pressure (mmHg)	141.78 ± 20.67	139.21 ± 20.71	143.35 ± 20.59	0.202
Stroke onset-to-door time (h)	4.5 [2–14.75]	2 [1–3]	10 [3–31.5]	<0.001
NIHSS				<0.001
≤5	71 (40.8%)	7 (10.6%)	64 (59.3%)	
≤20	63 (36.2%)	27 (40.9%)	36 (33.3%)	
>20	40 (23.0%)	32 (48.5%)	8 (7.4%)	
IV thrombolysis	45 (25.9%)	36 (54.6%)	9 (8.3%)	<0.001
Imaging parameters				
Occlusion site				0.040
Bilateral VA	65 (37.4%)	17 (25.8%)	48 (44.4%)	
Prox. to mid-basilar	91 (52.3%)	42 (63.6%)	49 (45.4%)	
Distal basilar	18 (10.3%)	7 (10.6%)	11 (10.2%)	
Truncal-type occlusion	115 (66.1%)	31 (47.0%)	84 (77.8%)	<0.001
Incomplete occlusion	43 (24.7%)	7 (10.6%)	36 (33.3%)	0.001
Occlusion etiology				<0.001
Embolism	41 (23.6%)	25 (37.9%)	16 (14.8%)	
Intracranial atherosclerotic	108 (62.1%)	31 (47.0%)	77 (71.3%)	
Arterial embolism	12 (6.9%)	8 (12.1%)	4 (3.7%)	
Dissection	13 (7.5%)	2 (3.0%)	11 (10.2%)	
PC-ASPECTS	8 [8–10]	8 [7–9]	9 [8–10]	<0.001
Thalamic involvement				0.004
Unilateral	17 (9.8%)	8 (12.1%)	9 (8.3%)	
Bilateral	11 (6.3%)	9 (13.6%)	2 (1.9%)	
Cerebellar involvement	53 (30.5%)	22 (33.3%)	31 (28.7%)	0.635
Occipital lobe involvement	18 (10.3%)	10 (15.2%)	8 (7.4%)	0.170
Midbrain involvement	21 (12.1%)	14 (21.2%)	7 (6.5%)	0.008
Pontine involvement	61 (35.1%)	28 (42.4%)	33 (30.6%)	0.153
BATMAN collateral score	6 [4–7.75]	5 [3–6]	6.5 [5–8]	<0.001
P-com subscore	2 [0–3]	1 [0–2]	2 [0–4]	0.067
PCA subscore	2 [1.25–2]	2 [0–2]	2 [2–2]	0.003
Basilar subscore	2 [1–2.75]	1 [1–2]	2 [1.75–3]	<0.001
VA subscore	1 [0–1]	1 [0–1]	1 [0–1]	0.230
Presence of fetal type PCA				0.039
None	126 (72.4%)	55 (83.3%)	71 (65.7%)	
Unilateral	33 (19.0%)	7 (10.6%)	26 (24.1%)	
Bilateral	15 (8.6%)	4 (6.1%)	11 (10.2%)	
Functional outcomes				
END	43 (24.7%)	17 (25.8%)	26 (24.1%)	0.945
Δ NIHSS ≥ 4	31 (17.8%)	11 (16.7%)	20 (18.5%)	0.916
3 months mRS	3 [1–5]	5 [2–5]	2 [1–5]	<0.001
Good outcomes	83 (47.7%)	23 (34.9%)	60 (55.6%)	0.013

**Primary EVT group vs. MM group.*

EVT, endovascular treatment; MM, medical management; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; Prox, proximal; VA, vertebral artery; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; P-com, posterior communicating artery; PCA, posterior cerebral artery; END, early neurological deterioration; eTICI, expanded treatment in cerebral ischemia; mRS, modified Rankin Score.

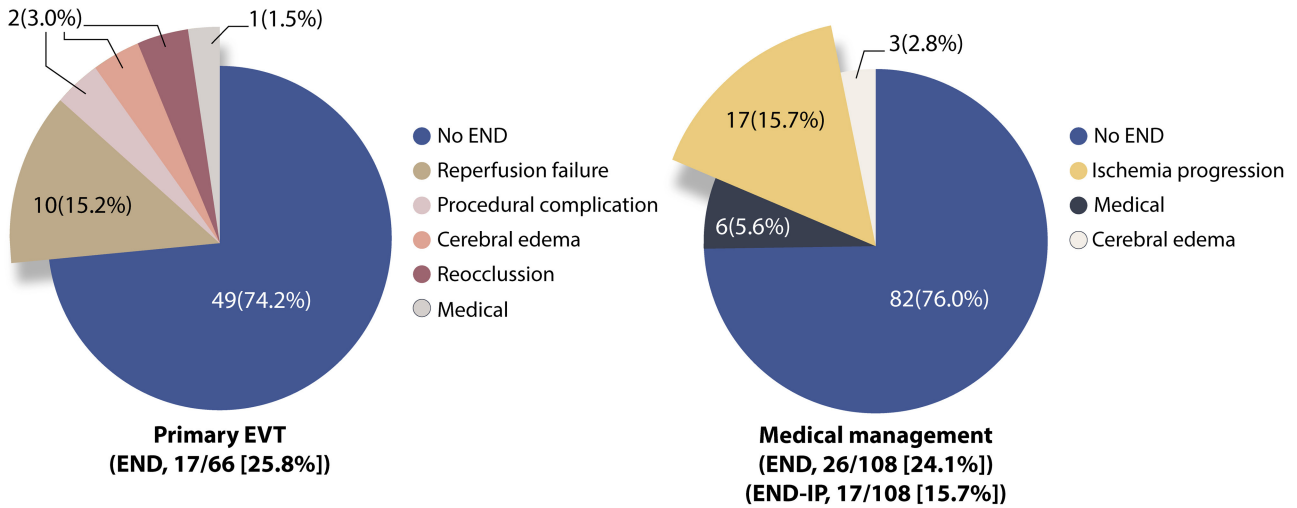

FIGURE 1 | The distribution of causes of early neurological deterioration in the primary endovascular treatment group and medical management group. END, early neurological deterioration; EVT, endovascular treatment; END-IP, early neurological deterioration-ischemia progression.

failure in 10 (15.2%), procedure-related in 2 (3.0%), cerebral edema in 2 (3.0%), re-occlusion in 2 (3.0%), and medical in 1 (1.5%). In the MM group ($N = 108$), END occurred in 26 patients (24.1%) and its causes were ischemia progression in 17 (15.7%), cerebral edema in 3 (2.8%), and medical in 6 (5.6%) (**Figure 1**).

Predictors of All-Cause END in VBO With Primary EVT

In total, 66 patients were treated with primary EVT. An eTICI ≥ 2b67 was achieved in 40/66 (60.6%) of the patients, and eTICI ≥ 2b50 was achieved in 47/66 (71.2%). END occurred in 17/66 (25.8%) and resulted in ΔNIHSS ≥ 4 in 11/17 (64.7%) at discharge, with a significantly poorer 3-month median mRS compared to the no-END group (5 [4.5–6] vs. 4 [1–5], $p < 0.001$). On comparison of the patients that experienced END and those who did not, there was a frequency of distal basilar occlusions compared to proximal to mid basilar and VA occlusions in the END group ($p = 0.013$) (**Table 2**). Specific locations of infarction according to the items on PC-ASPECTS and anatomical composition of collaterals by BATMAN collateral scores were not significantly different between the END and no-END groups. The rate of eTICI ≥ 2b67 was lower (35.3 vs. 69.4%, $p = 0.013$) in the END group, while the differences in patients that achieved eTICI ≥ 2b50 did not reach clinical significance.

In the multivariable analysis, a distal basilar occlusion location (bilateral VA as reference, OR, 14.5 [95% confidence interval (CI), 1.4–154.4], $p = 0.027$) and failure to achieve eTICI2b67 (OR, 4.9 [95% CI, 1.3–18.7], $p = 0.019$) was associated with END, when trichotomized NIHSS scores and BATMAN collaterals were incorporated as covariates. The occlusion etiology of seven distal basilar occlusion patients was embolic in five, and arterial embolism in two. All showed branching-site occlusion patterns of thrombus involving the basilar bifurcation. Among the five patients with distal basilar occlusion that experienced END, two were due to procedural hemorrhagic complications (subarachnoid hemorrhage and intraventricular hemorrhage), two due to reperfusion failure, and one due to cerebral edema.

Predictors of END Due to Ischemia Progression in Medically Managed VBO

In the MM group ($N = 108$), END-IP occurred in 17 patients (15.7%). The END-IP group showed higher systolic blood pressure (SBP) at presentation (155 ± 22 vs. 142 ± 20 mmHg, $p = 0.012$), and lower BATMAN collateral scores (5 [4–6.5] vs. 7 [5–9], $p = 0.030$). END-IP was highly associated with poorer mRS at 3 months (1 [1–4] vs. 4 [4–5], $p < 0.001$). When specific infarction locations were analyzed, more thalamic (23.1 vs. 6.1%, $p = 0.022$), cerebellar (46.2 vs. 23.2%, $p = 0.045$), and pontine (50.0 vs. 24.4%, $p = 0.026$) involvements were observed in the END-IP group. Lower posterior communicating artery (P-com) subscores in BATMAN collateral scores (0.5 [0–2] vs. 2 [1–4], $p = 0.001$) were also observed in the END-IP group. The absence of fetal-type PCA was slightly more frequent in the END-IP group (84.6 vs. 59.8%), although it did not reach statistical significance.

In the multivariable analysis, higher SBP at presentation (per 10 mm Hg increase, OR, 1.5 [95% CI, 1.1–2.1], $p = 0.012$), onset-to-door time less than 24 h (OR, 5.3 [95% CI, 1.1–2.0], $p = 0.049$), incomplete occlusions (OR, 4.9 [95% CI, 1.2–19.6], $p = 0.024$), larger infarct cores (per 1 point decrease in PC-ASPECTS, OR, 1.6 [95% CI, 1.0–2.5], $p = 0.042$), and poorer collaterals (per 1 point decrease in BATMAN scores, OR, 1.56 [95% CI, 1.1–2.2], $p = 0.018$) were associated with END-IP, along with trichotomized presenting NIHSS as covariable (**Table 3**).

Rescue EVT

Rescue EVTs were performed in seven patients after the occurrence of END during the admission course. Six patients

TABLE 2 | Prediction of END in vertebrobasilar artery occlusive stroke patients with primary EVT.

	Univariate analysis			Multivariate analysis	
	No-END (*N* = 49)	**END (*N* = 17)**	***P*-value**	**OR [95% CI]**	***P*-value**
Clinical parameters					
Age	67 ± 14	67 ± 12	0.883		
Sex, male	32 (65.3%)	11 (64.7%)	0.964		
Hypertension	28 (57.1%)	7 (41.2%)	0.256		
Diabetes mellitus	11 (22.4%)	5 (29.4%)	0.564		
Atrial fibrillation	11 (22.4%)	3 (17.6%)	0.676		
BMI (kg/m^2)	24.6 [22.1–26.2]	24.0 [20.1–28.7]	0.908		
Systolic blood pressure (mmHg)	137 ± 21	143 ± 16	0.368		
Stroke onset-to-door time (h)	2 [1.0–3.5]	2 [1.0–3.5]	0.478		
NIHSS			0.170		0.358
≤5	5 (10.2%)	2 (11.8%)		Reference	
≤20	17 (34.7%)	10 (58.8%)		1.8 [0.2–13.6]	0.568
>20	27 (55.1%)	5 (29.4%)		0.6 [0.1–13.6]	0.654
IV thrombolysis	25 (51.0%)	11 (64.7%)	0.488		
Imaging parameters					
Occlusion site			0.013		0.044
Bilateral VA	14 (28.6%)	3 (17.6%)		Reference	
Prox. to mid-basilar	33 (67.3%)	9 (52.9%)		0.6 [0.1–5.1]	0.881
Distal basilar	2 (4.1%)	5 (29.4%)		14.5 [1.4–154.4]	0.027
Truncal-type occlusion	22 (44.9%)	9 (52.9%)	0.567		
Incomplete occlusion	6 (12.2%)	1 (5.9%)	0.463		
Occlusion etiology			0.823		
Embolism	19 (38.8%)	6 (35.3%)			
Intracranial atherosclerotic	22 (44.9%)	9 (52.9%)			
Arterial embolism	6 (12.2%)	2 (11.8%)			
Dissection	2 (12.2%)	0 (0.0%)			
PC-ASPECTS	8 [7–10]	8.0 [5.5–9.0]	0.248		
Thalamic involvement			0.465		
Unilateral	5 (10.2%)	3 (17.6%)			
Bilateral	8 (16.3%)	1 (5.9%)			
Cerebellar involvement	14 (28.6%)	8 (47.1%)	0.233		
Occipital lobe involvement	7 (14.3%)	3 (17.7%)	0.709		
Midbrain involvement	8 (16.3%)	6 (35.3%)	0.165		
Pontine involvement	20 (40.8%)	8 (47.1%)	0.778		
BATMAN collateral score	5 [3–6]	5 [4.0–6.0]	0.085	0.8 [0.6–1.2]	0.249*
P-com subscore	1 [0–2]	2 [1–4]	0.257		
PCA subscore	2 [0–2]	1 [0–2]	0.297		
Basilar subscore	1 [1–2]	1 [1–2]	0.347		
VA subscore	1 [0–1]	1 [0–1]	0.827		
Presence of fetal type PCA			0.855		
None	40 (81.6%)	15 (88.2%)			
Unilateral	6 (12.2%)	1 (5.9%)			
Bilateral	3 (6.1%)	1 (5.9%)			
Procedural parameters					
Door-to-puncture time (min)	120 [104–148]	131.5 [116.5–178.75]	0.237		
Procedure type			0.083		
Diagnostic/approach failure	6 (12.2%)	6 (35.3%)			
Thrombectomy alone	21 (42.9%)	4 (23.5%)			
Angioplasty/IA tirofiban	22 (44.9%)	7 (41.2%)			
Total procedure time (min)	61 [38–98]	63.5 [35.5–94.25]	0.932		

(Continued)

TABLE 2 | Continued

	Univariate analysis			Multivariate analysis	
	No-END (*N* = 49)	**END (*N* = 17)**	***P*-value**	**OR [95% CI]**	***P*-value**
eTICI ≥ 2b50	38 (77.6%)	9 (52.9%)	0.053		
eTICI ≥ 2b67	34 (69.4%)	6 (35.3%)	0.013	5.0 [1.3–19.9]	0.023[†]
Functional outcomes					
Δ NIHSS ≥4	0 (0.0%)	11 (64.7%)	<0.001		
3 months mRS	4 [1.0–5.0]	5 [4.5–6]	<0.001		
Good outcomes	23 (42.6%)	0 (0.0%)	0.005		

**Per 1 score decrease. [†]For reperfusion failure.*
END, early neurological deterioration; OR, odds ratio; CI, confidence interval; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; VA, vertebral artery; Prox, proximal; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; P-com, posterior communicating artery; PCA, posterior cerebral artery; IA, intra-arterial; eTICI, expanded treatment in cerebral ischemia; mRS, modified Rankin Score.

TABLE 3 | Prediction of END due to ischemia progression in vertebrobasilar artery occlusive stroke patients managed medically.

	Univariate analysis			Multivariate analysis	
	No-END-IP (*N* = 91)	**END-IP (*N* = 17)**	***P*-value**	**OR [95% CI]**	***P*-value**
Clinical parameters					
Age (years)	68 ± 13	65 ± 14	0.277		
Sex, male	59 (64.8%)	11 (64.7%)	0.992		
Hypertension	63 (69.2%)	11 (64.7%)	0.728		
Diabetes mellitus	34 (37.4%)	9 (52.9%)	0.430		
Atrial fibrillation	16 (17.6%)	1 (5.9%)	0.224		
BMI (kg/m^2)	23.9 [24.1–25.7]	24.3 [22.5–26.9]	0.368		
Systolic blood pressure (mmHg)	142 ± 20	155 ± 22	0.018	1.5 [1.1–2.0]	0.012*
Stroke onset-to-door time	10 [3–37]	8 [3–22.5]	0.383		
Stroke onset-to-door time			0.394		0.049
<24 h	60 (65.9%)	13 (76.5%)		5.3 [1.1–2.0]	
≥24 h	31 (34.1%)	4 (23.5%)		Reference	
Trichotomized NIHSS			0.115		0.994
≤5	56 (61.5%)	8 (47.1%)			
≤20	27 (29.7%)	9 (52.9%)			
>20	8 (8.8%)	0 (0.0%)			
IV thrombolysis	5 (5.5%)	4 (23.5%)	0.033		
Imaging parameters					
Occlusion site			0.460		
Distal basilar	10 (11.0%)	1 (5.9%)			
Prox. to mid-basilar	39 (42.9%)	10 (58.8%)			
Bilateral VA	42 (46.2%)	6 (35.3%)			
Truncal-type occlusion	69 (75.8%)	15 (88.2%)	0.259		
Incomplete occlusion	27 (29.7%)	9 (52.9%)	0.062	4.9 [1.2–19.6]	0.024
Occlusion etiology			0.801		
Embolism	14 (15.4%)	2 (11.8%)			
Intracranial atherosclerotic	64 (70.3%)	13 (76.5%)			
Arterial embolism	4 (4.4%)	0 (0.0%)			
Dissection	9 (9.9%)	2 (11.8%)			
PC-ASPECTS	10 [8–10]	8 [7–9.5]	0.059	1.6 [1.0–2.5]	0.042[†]
Thalamic involvement			0.027		
Unilateral	4 (4.9%)	5 (19.2%)			

(Continued)

TABLE 3 | Continued

	Univariate analysis			Multivariate analysis	
	No-END-IP (*N* = 91)	**END-IP (*N* = 17)**	***P*-value**	**OR [95% CI]**	***P*-value**
Bilateral	1 (1.2%)	1 (3.9%)			
Cerebellar involvement	19 (23.2%)	12 (46.2%)	0.045		
Occipital involvement	6 (7.3%)	2 (7.7%)	>0.99		
Midbrain involvement	3 (3.7%)	4 (15.4%)	0.056		
Pontine involvement	20 (24.4%)	13 (50.0%)	0.026		
BATMAN collateral score	7 [5–9]	5 [4–6.5]	0.030	1.6 [1.1–2.2]	0.018[†]
P-com subscore	2 [1–4]	0.5 [0–2]	0.001		
PCA subscore	2 [2–2]	2 [1–2]	0.051		
Basilar subscore	2 [2–3]	2 [1–3]	0.479		
VA subscore	1 [0–1]	1 [0–1]	0.455		
Presence of fetal type PCA			0.077		
None	49 (59.8%)	22 (84.6%)			
Unilateral	23 (28.1%)	3 (11.5%)			
Bilateral	10 (12.2%)	1 (3.9%)			
Functional outcomes					
3 months mRS	1 [1–4]	4 [4–5]	<0.001		
Good outcome	58 (63.7%)	2 (11.8%)	<0.001		

[*]Per 10 mmHg increase. [†]Per 1 score decrease.

END, early neurological deterioration; END-IP, END due to ischemia progression; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; IV, intravenous; VA, vertebral artery; Prox, proximal; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; P-com, posterior communicating artery; PCA, posterior cerebral artery; mRS, modified Rankin Score.

were from the MM group, and one patient was from the primary EVT group. Among them, six of seven (85.7%) occlusions were presumed to be atherosclerotic in origin and required additional EVTs such as angioplasty and/or intra-arterial tirofiban, other than first-line mechanical thrombectomy. Even though eTICI $\geq$ 2b67 reperfusion was achieved in five of seven (71.5%), no patients achieved functional independence at 3 months, while 42.9% were bedridden or had died (**Table 4**).

Deviation Between Institutional EVT Criteria and Actual Implementation

Overall, five patients did not meet the institutional inclusion criteria for EVT due to low NIHSS, but received EVT (**Table 5**). In three (60.0%) patients, basilar top occlusions were observed which the clinician considered as a sign predictive of END, while in two (40.0%) other patients, younger age of onset led to a more aggressive treatment decision.

On the contrary, EVT was not performed on 21 patients despite fulfilling the clinical severity and time criteria (**Table 6**). Among them, four were socioeconomic decisions or related to poor baseline functional status. In the rest of the 17 patients, six (35.3%) were because the clinician had doubts about the benefits of EVT in obviously chronic occlusions. In four (23.5%) patients, suspicion for dissecting occlusion led to the deviation. In another four (23.5%) patients, there were clinical improvements before EVT.

DISCUSSION

This single-center retrospective study explores the potential predictors of END in stroke due to VBO, in regard to the different treatment populations, which are the primary EVT group and MM group. In this study, we found that in the primary EVT group, failure to achieve eTICI2b67 reperfusion and distal basilar occlusion were associated with all-cause END. In the MM group, higher SBP at presentation, onset-to-door time less than 24 h, incomplete occlusions, larger infarct cores, and poorer collaterals were associated with END-IP. There were also deviations between institutional EVT criteria (based on time and clinical severity) and actual implementation. In this study, the clinicians' decisions were biased toward implementation of EVT in patients with basilar top occlusions, and against EVT in patients with suspicious dissecting occlusions or chronic intracranial atherosclerotic occlusions.

A factor predictive of END in the primary EVT group was failure to achieve reperfusion of more than 66% of the involved territory (eTICI2b67). In contrast, more classical reperfusion of more than 50% of the involved territory (mTICI2b) failed to predict END. Compared to the anterior circulation, EVT for posterior circulation is prone to Willisian collateral failure by distal embolization (21). Thus, aiming for a higher reperfusion grade may be able to prevent END on VBO, and future advances in EVT may also need to focus on higher reperfusion grades, such as distal vessel thrombectomy (22). A selective reperfusion grading system for VBO may also maximize EVT treatment effect.

TABLE 4 | Clinical characteristics and outcome of patients who underwent rescue EVT therapy.

No	Sex/age	O-to-D time (h)	NIHSS	Occlusion type	Infarct location	Occlusion etiology	PC-ASPECTS	BATMAN	Cause of END and imaging findings	Onset to rescue EVT	Procedure type	eTICI	3-m mRS
Primary EVT group													
1	M/55	1	6	BSO	Bilateral cerebellum, thalamus	Arterial embolism	4	4	Reocclusion: arterial re-embolism	7 hours	Thrombectomy/ angioplasty	3	6
Medical management group													
2	M/72	16	4	TTO	Bilateral pons, Rt cerebellum	ICAS	7	9	END-IP, near-total occlusion to complete occlusion	4 days	Thrombectomy	2b67	6
3	M/59	1	7	TTO	Rt pons	ICAS	8	6	END-IP, near-total occlusion to complete occlusion	3 days	Angioplasty/ IA tirofiban	2a	6
4	F/81	3	0	TTO	Bilateral pons	ICAS	10	7	END-IP, no vessel change	5 days	IA tirofiban	2b50	4
5	F/76	11	4	TTO	Lt pons	ICAS	8	7	END-IP, near-total occlusion to complete occlusion	1 day	IA tirofiban	2b67	4
6	F/73	8	8	TTO	Rt cerebellum, Bilateral occipital	ICAS	9	5	END-IP, no vessel change	2 days	IA tirofiban	2b67	4
7	F/80	5	9	TTO	Rt pons	ICAS	8	2	END-IP, elongation of near-total occlusion length	1 day	Thrombectomy/ IA tirofiban	3	4

No, number; O-to-D, onset-to-door; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; END, early neurological deterioration; EVT, endovascular therapy; eTICI, expanded treatment in cerebral ischemia; mRS, modified Rankin Score, M, male; F, female; BSO, branching-site occlusion, TTO; truncal-type occlusion; Rt, right; Lt, left; ICAS; intracranial atherosclerosis; END-IP, END due to ischemia progression; IA, intra-arterial.

TABLE 5 | Brief description of patients who did not meet the institutional inclusion criteria for EVT, however did receive the EVT.

No	Year	Sex/ age	O-to-d time (h)	NIHSS	IV tPA	Infarct location	Occlusion etiology	PC-ASPECTS	BAT-MAN	Reason for deviation	END and cause	Procedure type	eTICI	3-m mRS
1	2011	M/40	3	3	Yes	Rt lat medullary, PICA scattered infarct	Arterial embolism	10	4	Basilar top occlusion		Diagnostic	2a	2
2	2012	M/74	1	4	Yes	Lt portion of the corpus callosum body	Embolism	10	5	Basilar top occlusion		Thrombectomy	3	0
3	2014	F/71	5	2	-	Lt paramedian pontine & Lt PCA scattered	Embolism	10	6	Basilar top occlusion		Diagnostic	0	0
4	2013	M/57	4	2	Yes	Lt cerebellar	Dissection	8	4	Young age midbasilar occlusion	Reperfusion failure	Thrombectomy, angioplasty, IA tirofiban	2b50	5
5	2013	M/61	1	4	Yes	Lt paramedian pons	ICAS	7	6	Young age neurological fluctuation		Thrombectomy, angioplasty	2b67	0

No, number; O-to-D, onset-to-door; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; END, early neurological deterioration; EVT, endovascular therapy; eTICI, expanded treatment in cerebral ischemia; mRS, modified Rankin Score, M, male; F, female; Rt, right; Lt, left; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; ICAS; intracranial atherosclerosis; IA, intra-arterial.

Distal basilar occlusions were also associated with END. The causes of END were reperfusion failure and procedural complications. A distal basilar occlusion is likely to be embolic, with the main thrombus burden in the basilar bifurcation, or the posterior cerebral artery. Considering this, technical difficulty may have been the reason for the association between END and distal basilar occlusions. For example, a saddle-shaped thrombus at the arterial bifurcation point may be more resistant to stent retrieval thrombectomy (23). Extended manipulation may also injure the perforators at the basilar tip. The only two cases of procedure-related hemorrhagic complications in this study occurred in this group. Hence, neuro-interventionalists should be wary of procedural complications to prevent END in distal basilar occlusions, and utilizing contact aspiration (24) or dual-stent retrievers (23) as the first-line thrombectomy method may be useful.

Previously known factors associated with the prognosis of VBO were also analyzed for its relation to END in our study. For example, factors such as bilateral thalamic involvement (25), presence of P-com collaterals (26), infarct burden (12), or total collaterals (14) were previously reported. In our study, within the MM group, total infarct burden and collaterals could predict END. In specific, lower P-com collateral subscores were associated with END, while a fetal type PCA tended to be reversely associated with END, but did not reach clinical significance. The protective effect of presence and caliber of P-com collaterals have been consistently reported (26, 27), while for fetal-type PCA, there are contradicting results, which are likely affected by recanalization or stroke mechanisms. In terms of infarct location and burden, lesions in the bilateral thalamus, pons, and cerebellum may be associated with critical perfusion failure of the posterior circulation; future research is warranted. Interestingly, such associations were not seen in the primary EVT group, suggesting that END after EVT may be largely dependent on the consequence of reperfusion.

While a wide definition of END (1) and differences between anterior and posterior circulation (7) bring confusion to the clinical significance of a given END definition, our results demonstrate that END, classified as an increase of 4 or more in the NIHSS score, during medical management is a critical event. Moreover, a large percentage of END was due to ischemia progression, while END due to symptomatic hemorrhage was less common compared with the anterior circulation (10, 28). In a previous study, we have evaluated predictors of neurological deterioration, classified as an increase in NIHSS of 4 or more at discharge, in a smaller number of patients with medically managed VBO (29). Even though the current study differs from the previous in that END was described as an increase in NIHSS of 4 or more during admission, and selectively identified END due to ischemia progression, the important predictors of END due to ischemia progression did not differ largely.

The outcomes of rescue EVT were unsatisfactory, showing median 3 months mRS of 5. The majority were due to intracranial atherosclerotic occlusions, and a likely explanation is that underlying intracranial atherosclerotic disease can cause END by various mechanisms (30). If the main mechanism

TABLE 6 | Brief description of patients who met the institutional indication for EVT decision, however did not receive EVT.

No	Year	Sex/age	O-to-d time (h)	NIHSS	IV tPA	Infarct location	Occlusion etiology	PC-ASPECTS	BAT-MAN	Reason for deviation	END and cause	3-m mRS
EVT not performed based on clinical factors												
1	2011	F/74	5	12	-	Bilateral pontine	ICAS	6	6	Chronic occlusion, long prodrome		4
2	2012	F/78	3	7	-	Bilateral paramedian pontine	ICAS	8	9	Chronic occlusion Clinically lacunar syndrome		4
3	2014	M/80	1	15	-	Rt pontine, Lt cerebellar, Lt MCA scattered	ICAS	8	3	Chronic occlusion, long prodrome	Medical	5
4	2015	M/72	1	9	-	Bilateral pontine, Rt lateral medullary	ICAS	8	9	Chronic occlusion, incomplete occlusion		5
5	2016	F/68	2	5	-	Rt medial medullary	ICAS	10	6	Chronic occlusion Stroke not due to perfusion failure		3
6	2017	M/64	1	14	-	Bilateral medial medullary, Lt cerebellar scattered	ICAS	10	5	Chronic occlusion, incomplete occlusion		2
7	2015	M/41	3	6	Yes	Rt lateral medullary	Dissection	10	10	Cannot rule out dissection Stroke not due to perfusion failure		1
8	2013	M/30	2	7	Yes	Bilateral paramedian pontine	Dissection	8	9	Cannot rule out dissection	END-IP	5
9	2014	M/55	0	19	-	Bilateral pontine	ICAS	10	9	Cannot rule out dissection		3
10	2014	M/54	1	8	Yes	Lt PICA, Rt posterior choroidal, Rt SCA scattered	Arterial embolism	9	8	Cannot rule out dissection		3
11	2012	M/62	2	16	Yes	Lt pontine	Embolism	10	6	Improving neurological state	END-IP	4
12	2013	M/72	1	13	-	Lt occipital	ICAS	10	9	Improving neurological state		5
13	2017	M/76	5	10	-	Bilateral pontine and cerebellar scattered	ICAS	8	7	Improving neurological state	Medical	5
14	2018	F/89	3	10	-	Rt hippocampal	Embolism	10	4	Improving neurological state		2
15	2011	M/67	3	18	-	Bilateral cerebellar scattered	Arterial embolism	7	7	Incomplete occlusion		3
16	2011	M/71	1	31	-	Bilateral pontine and cerebellar	Arterial embolism	6	5	Large infarct core, in-hospital delay		6
17	2011	F/82	4	19	-	Bilateral thalamus	Embolism	10	4	Cardiogenic shock		5

(Continued)

TABLE 6 | Continued

No	Year	Sex/age	O-to-d time (h)	NIHSS	IV tPA	Infarct location	Occlusion etiology	PC-ASPECTS	BAT-MAN	Reason for deviation	END and cause	3-m mRS
EVT not performed based on socioeconomic factors												
18	2011	F/86	1	30	Yes	Lt thalamus and cerebellar	Embolism	8	3	Caregiver refusal	Medical	5
19	2013	F/99	1	18	Yes	Lt PCA, Rt pontine, Rt cerebellar	Embolism	5	3	Caregiver refusal	Cerebral edema	5
20	2017	M/81	2	15	-	Lt PICA territory, Lt pontine, bilateral PCA territory	ICAS	7	3	Caregiver refusal	Medical	6
21	2018	F/91	1	31	-	Bilateral pontine, Lt AICA	Embolism	5	2	Caregiver refusal		6

No, number; O-to-D, onset-to-door; NIHSS, National Institutes of Health Stroke Scale; IV tPA, intravenous tissue plasminogen activator; PC-ASPECTS, posterior circulation Alberta Stroke Program Early CT score; BATMAN, The Basilar Artery on Computed Tomography Angiography score; END, early neurological deterioration; EVT, endovascular therapy; eTICI, expanded treatment in cerebral ischemia; mRS, modified Rankin Score, M, male; F, female; Rt, right; Lt, left; MCA, middle cerebral artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery; ICAS; intracranial atherosclerosis; END-IP, END due to ischemia progression.

is due to *in situ* occlusion and hemodynamic impairment, rescue EVT may result in neurological improvement, but if the main mechanism is due to arterial embolism or local branch occlusion, neurological improvement would be less likely. Considering the poor outcomes associated with END and unsatisfactory results of rescue EVT, a high-risk group for END in patients with VBO may benefit from preemptive EVT. This is supported by recent literature advocating for primary EVT in patients with anterior circulation large-vessel occlusions and low NIHSS scores (31). Considering a predominance of intracranial atherosclerotic occlusions in this group, a rational EVT plan would be to achieve luminal flow by atraumatic stent-retrieval thrombectomy, followed by intra-arterial antiplatelet agent injections to stabilize the endothelium (19).

There were deviations from institutional EVT criteria and actual implementation. While this may be a potential source of bias for the study analysis, it can also be valuable data showing that clinicians' concerns for END influences EVT decision. VBO with the involvement of the basilar top led the clinician to anticipate END without definitive reperfusion measures, which is justifiable considering the critical role of the basilar top in the Willisian collaterals. In such cases, manual aspiration thrombectomy may be chosen over stent retriever thrombectomy (24) to prevent END associated with vessel trauma. On the contrary, suspicion for dissecting occlusions led the clinician to worry about END associated with endovascular procedures. Subarachnoid hemorrhage due to vessel rupture during microcatheter navigation (32) and inadvertent stenting of pseudolumen are feared complications. Direct aspiration may be chosen first to theoretically avoid such complications (32). Chronic VBO may also deteriorate with EVT due to its reduced arterial caliber or difficulties in the lesion approach. However, when considering that rescue EVT outcomes were unsatisfactory, future studies are warranted regarding optimal treatment time and method in this population. While current evidence is limited, a recent literature regarding EVT for non-acute intracranial vertebral arterial occlusions reports acceptable outcomes with careful classification (33).

Several limitations exist for this study. First, the retrospective design and imaging-based inclusion criteria may include patients with heterogeneous stroke mechanisms, and mixed acute and chronic VBO. As our study goal was to find clues for maximizing EVT effect and expanding the pool of patients that will benefit from EVT in VBO, this heterogeneity was intended. However, this study was performed in a population with a higher proportion of intracranial atherosclerosis, and implementation of its results may vary according to ethnic differences. Second, in the primary EVT group, a more detailed analysis of collateral changes or distal embolizations and their consequences could not be performed. We hope to address such issues in a larger number of VBO patients undergoing reperfusion. Third, while we show predictors of END in VBO managed medically, and poor outcomes of rescue EVT, we could not provide evidence that a preemptive EVT may improve patient outcomes. Future prospective studies will be needed

to address this issue. Fourth, while all EVT patients were primarily treated with stent retriever thrombectomy or direct aspiration thrombectomy, there may be heterogeneity in EVT methods due to the rather long period of patient inclusion. The following may have influenced the EVT methods; in Korea, the Penumbra system was approved in November 2008 and reimbursed in August 2009 in Korea. The second-generation Penumbra system was approved in July 2014. Solitaire AB has been approved for stent-assisted coiling since May 2010 and was reimbursed in January 2011. The Solitaire FR was approved for mechanical thrombectomy in April 2013 and reimbursed in August 2014. Trevo was approved for mechanical thrombectomy in December 2012 and reimbursed in August 2014 (34).

In conclusion, in patients with stroke due to VBO, several potential predictors of END can be identified according to the different treatment statuses. In the primary EVT group, failure to achieve reperfusion and distal basilar occlusion were associated with all-cause END. In the MM group, higher SBP at presentation, onset-to-door time less than 24 h, incomplete occlusions, larger infarct cores, and poorer collaterals were associated with END-IP. Stroke neurologists considered basilar top occlusions to be liable to deteriorate without EVT while dissecting occlusions or chronic intracranial atherosclerotic occlusions to be associated with END related to EVT. Recognization of such variables and addressing these issues may improve overall patient selection and treatment outcomes in VBO.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ajou University Hospital Institutional review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SK: data interpretation, drafted the work, and approved the final version of the paper. SL, WJ, JC, JL, and JH: data interpretation, revised the draft critically for important intellectual content, and approved the final version of the paper. S-JL: conceptualization and supervision of the study, data interpretation, revised the draft critically for important intellectual content, and approved the final version of the paper. All authors have seen and approved the manuscript being submitted.

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frontiers in Neurology

CASE REPORT
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Case Report: Four Early Recurrent Basilar Artery Occlusions Successfully Treated With Mechanical Thrombectomy and Subsequent Vertebral Artery Coil Occlusion

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We present the case of a middle-aged patient who had four recurrent acute basilar artery occlusions over a period of 3 months, each time successfully treated with mechanical thrombectomy. Extensive stroke work-up showed no obvious stroke etiology aside from a dysplastic right vertebral artery with multifocal stenoses. Treatment with different antiplatelet and anticoagulant regimes did not prevent basilar artery occlusion recurrence. Therefore, transarterial coil occlusion of the V4-segment of the right vertebral artery was performed as ultima ratio without complications. At final discharge, the patient had no persistent neurological deficits. No further cerebrovascular events occurred over a 12-month follow-up period.

Keywords: thrombectomy, stroke, recurrent stroke, large vessel occlusion, basilar artery occlusion, endovascular treatment (EVT), ischemic stroke

INTRODUCTION

Basilar artery occlusion (BAO) entails a high risk for severe disability and mortality. The role of mechanical thrombectomy (MT) in large vessel obstruction of the posterior cerebral circulation has been discussed controversially (1). However, more recent data support an effective role of MT in BAO (2, 3). Especially data on treatment strategies of recurrent BAO are scarce, with only few cases published (4–8). A case of four recurrent BAOs refractory to various medical treatment regimens has not yet been described in the literature.

CASE DESCRIPTION

A 53-year-old man presented with acute onset of dizziness, left-sided hemiparesis and progressive loss of consciousness. CT angiography (CTA) revealed BAO and additionally showed a calcified dysplastic right vertebral artery (VA) with multifocal stenoses. One month earlier, the patient had suffered from a bithalamic infarct treated with intravenous thrombolysis (IVT). The patient recovered well and had been discharged with atorvastatin and dual antiplatelet therapy with aspirin

and clopidogrel, though aspirin had been discontinued few days before readmission. Vascular risk factors included dyslipidemia, coronary heart disease and peripheral artery disease.

IVT and MT achieved complete recanalization (**Figures 1A1,A2**) and an excellent neurological outcome with a modified Rankin Scale (mRS) of 0 and a National Institutes of Health Stroke Scale (NIHSS) of 0. Aspirin and subcutaneous enoxaparin were initiated during stroke work-up and early rehabilitation. Nine days post-thrombectomy, while still in hospital, the patient suddenly developed acute left-sided hemiparesis and dysarthria. MR angiography (MRA) showed distal BAO; subsequently direct MT was performed. Again, full recanalization was achieved and the patient remarkably improved (mRS 0/NIHSS 0) (**Figures 1B1,B2**). Two weeks later, the patient was discharged without any neurological deficits with a combination therapy of dabigatran, aspirin and atorvastatin due to the recurrent BAO. Notably, he did not take any additional drugs potentially interfering with blood clotting (such as nonsteroidal anti-inflammatory drugs).

Four days after discharge, the patient was readmitted with left-sided hemiparesis and dysarthria. CTA confirmed the third recurrent BAO, and the patient was again successfully recanalized with MT (**Figures 1C1,C2**). Follow-up MRI displayed new small infarcts in both occipital lobes and both cerebellar hemispheres, but again the patient had very good clinical outcome (mRS 0/NIHSS 0). Platelet aggregation testing showed a very good response to aspirin. After further stroke work-up and early rehabilitation, the patient was discharged with no persisting deficits and switched to a combination treatment of phenprocoumon and aspirin.

One week after discharge, the patient again presented with vertigo and left-sided sensory deficits. MRA again showed a

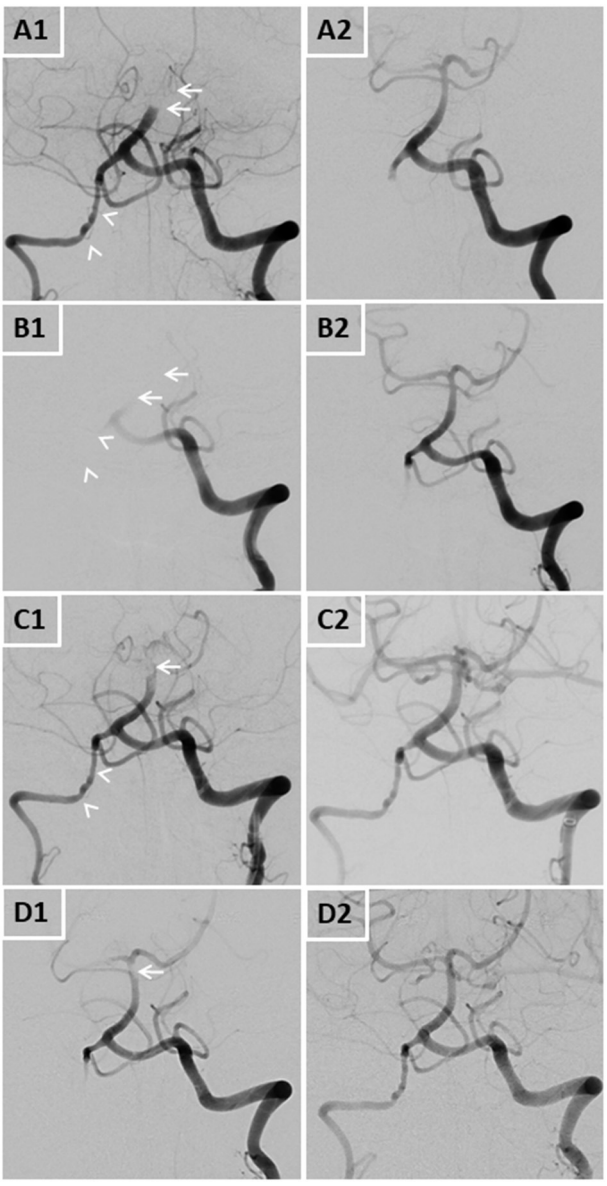

FIGURE 1 | DSA images of all four basilar artery occlusions pre- **(A1,B1,C1,D1)** and post-interventionally **(A2,B2,C2,D2)**. Arrows display arterial occlusions and/or thrombi, arrowheads display the dysplastic right vertebral artery.

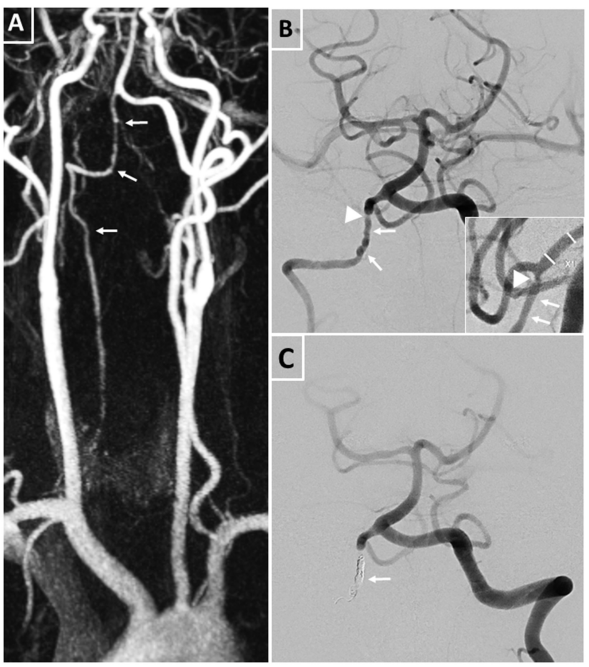

FIGURE 2 | Pre- and post-interventional images of the right dysplastic vertebral artery and its multifocal stenoses. **(A)** MRA displaying the right vertebral artery with multiple intra- and extracranial irregularities (tailed arrows) corresponding to the diagnosis of a dysplastic vertebral artery. **(B)** Pre-interventional digital subtraction angiography of the posterior circulation with irregularities (tailed arrows) and distal stenosis of the vertebral artery (arrow head) proximal to the outflow of the right posterior inferior cerebellar artery in two plains. **(C)** Post-interventional digital subtraction angiography of the posterior circulation after coil occlusion of the right V4 segment (tailed arrow) with preservation of the right posterior inferior cerebellar artery outflow.

FIGURE 3 | Timeline of stroke events.

thrombus in the distal basilar artery and the proximal left posterior cerebral artery, which were removed by endovascular therapy using an aspiration catheter (**Figures 1D1,D2**).

Extensive stroke work-up was performed. Transesophageal echocardiography excluded relevant structural cardiac abnormalities, ECG monitoring at the neurocritical care and stroke unit as well as repeated 24 h ECG did not reveal paroxysmal atrial fibrillation. Dyslipidemia was well-controlled with atorvastatin. Extensive laboratory tests, full-body PET and MRA, lumbar puncture and flow cytometry analysis excluded vasculitis, collagenosis, cancer and antiphospholipid antibody syndrome. However, MRA and CTA repeatedly showed a dysplastic right vertebral artery with multifocal stenoses. The family history of the patient was unremarkable.

After ruling out numerous etiologies for recurrent BAO and as all strokes occurred in the same arterial territory, arterio-arterial embolism originating from the dysplastic multifocally stenosed right VA was regarded as the presumed cause, with the most likely underlying process being either atherosclerosis or fibromuscular dysplasia (FMD).

As different aggressive antithrombotic medical treatments had failed to prevent recurrent BAO, we decided for a deconstructive interventional approach after careful consideration and elaborate discussion with the patient. Since blood supply by the left VA seemed sufficient for the posterior cerebral circulation, transarterial coil-occlusion of the right VA was performed. The proximal V4-segment was occluded in a cross-over technique with multiple platinum coils, whereas the right PICA and the distal V4-segment were preserved (**Figures 2A–C**).

A 6F sheath (Neuron Max 0.88, Penumbra, Inc., CA, USA) was placed in the left vertebral artery. Dual microcatheter technique was applied to exactly place the platinum coils. The first microcatheter (Excelsior SL10, Stryker, CA, USA) was exactly positioned proximal to the origin of the PICA, and a coil (Smart coil, Penumbra, Inc., CA, USA) was placed but not released. The second microcatheter (Excelsior SL10, Stryker, CA, USA) was placed proximal to the first, at the beginning of the V4 segment. Through this microcatheter, seven platinum coils were placed. Only after confirmation of the correct and safe positioning of the coils without compromising the origin of the PICA, the first coil was released.

The patient was ultimately discharged without focal neurological deficits/residual symptoms (mRS 0/NIHSS 0) and with dual antiplatelet therapy (aspirin and clopidogrel) in order to minimize risk of recurrent atherothrombotic events. Clopidogrel was discontinued after 6 months. No recurrent cerebrovascular events occurred during a 12-month follow-up period. **Figure 3** depicts a full timeline of the mentioned events.

DISCUSSION

We present a patient with four recurrent BAO that had occurred during a remarkably short time period and were all treated successfully with endovascular stroke therapy leading to excellent outcome. Notably, a multifocally stenosed right VA was identified as the most likely underlying cause. This apparently highly aggressive arterial embolic source could not be controlled with different medical strategies. Therefore, successful coil occlusion of the V4 segment of the VA was performed. During the follow-up period, no further cerebrovascular events occurred.

Recurrent BAO was reported in the context of VA dissection (3), neoplasia (5), antiphospholipid syndrome (6) and VA stenosis (5). A recent case series on recurrent cerebral large vessel occlusion suggested that periinterventional endothelial lesions might contribute to recurrent large vessel occlusions (4). Notably, we did not detect such lesions in any angiographic series and no other intervention-associated complications such as dissections or vasospasms had occurred in our patient.

Therapeutic VA occlusion has been described in the context of ruptured dissecting aneurysms, external VA compression or pre-operative intervention in cervical spine trauma (9–11). Our case is the first report of recurrent BAO with VA occlusion as final therapy. Successful recanalization

by MT in every instance, good collateralization, a short symptom to recanalization time as well as site and size of thrombi contributed to the favorable outcome of our patient (3).

Regarding the stenosed right VA, our patient's history of coronary heart and peripheral artery disease suggest an atherosclerotic cause as source of recurrent embolism. However, the inefficacy of aggressive antiplatelet and anticoagulation therapy points toward an alternative non-atherosclerotic mechanism, such as focal FMD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SL, SF-H, and TG were involved in the conception of this case report. SL wrote the manuscript draft. SF-H supervised the study. All authors were involved in the treatment of the patient and revised the manuscript for important intellectual content, read, and approved the submitted version.

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CASE REPORT
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Case Report: Bow Hunter's Syndrome Caused by Compression of Extracranially Originated Posterior Inferior Cerebellar Artery

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Bow hunter's syndrome (BHS) is most commonly caused by compression of the vertebral artery (VA). It has not been known to occur due to an extracranially originated posterior inferior cerebellar artery (PICA), the first case of which we present herein. A 71-year-old man presented with reproducible dizziness on leftward head rotation, indicative of BHS. On radiographic examination, the bilateral VAs merged into the basilar artery, and the left VA was predominant. The right PICA originated extracranially from the right VA at the atlas–axis level and ran vertically into the spinal canal. During the head rotation that induced dizziness, the right PICA was occluded, and a VA stenosis was revealed. Occlusion of the PICA was considered to be the primary cause of the dizziness. The patient underwent surgery to decompress the right PICA and VA *via* a posterior cervical approach. Following surgery, the patient's dizziness disappeared, and the stenotic change at the right VA and PICA improved. The PICA could be a causative artery for BHS when it originates extracranially at the atlas–axis level, and posterior decompression is an effective way to treat it.

Keywords: posterior inferior cerebellar artery, Bow hunter's syndrome, persistent first intersegmental artery, posterior decompression, surgery

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INTRODUCTION

Bow hunter's syndrome (BHS) is a transient and symptomatic vertebrobasilar insufficiency that occurs during head rotation, resulting in dizziness and fainting (1). Compression of the dominant vertebral artery (VA) at the axis–atlas level of the cervical spine is commonly considered to be the cause when reduction of blood flow through the compressed VA is not compensated as expected by blood flow from the contralateral VA (2). Compression of the non-dominant VA may also cause BHS, but this situation is rare (3). BHS is not known to be caused by compression by any other artery except the VA.

The posterior inferior cerebellar artery (PICA) is the largest branch of the VA, and its position is highly variable. In some variations, it originates extracranially at the atlas–axis level, where it is associated with an embryonic remnant of the first intersegmental artery (FIA) (4). It enters the cervical dural sac in parallel with the C2 nerve root (5). This extracranial PICA could be compressed by head rotation and thereby cause BHS, but this situation has never been reported.

We herein present a rare case of BHS that was caused by compression of an extracranially originated PICA. To our knowledge, this is the first report of BHS in which compression was caused by another artery than the VA.

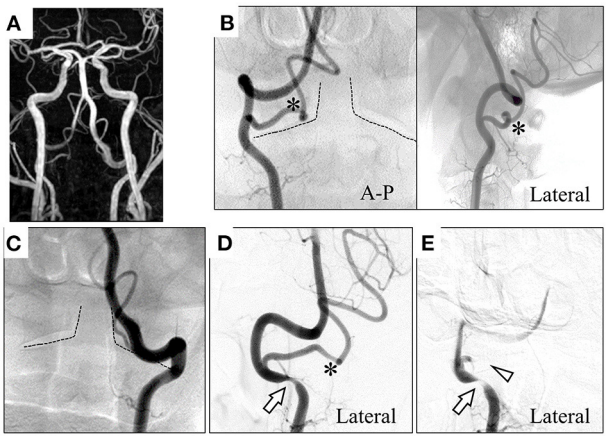

FIGURE 1 | Magnetic resonance angiography (MRA) shows the bilateral vertebral arteries (VAs) merging into the basilar artery, and the left VA is dominant **(A)**. Digital subtraction angiography (DSA) shows the right posterior inferior cerebellar artery (PICA) originating and coursing into the spinal canal between the atlas and the axis **(B)**. The left VA proceeds into the spinal canal at the atlas–axis level **(C)**. On dynamic DSA at 45° leftward head rotation **(D)**, the right VA was compressed at the V3 segment. At 60° leftward head rotation **(E)**, the right PICA becomes occluded in addition to severe compression of the right VA. Dotted line: trace of axis; *: right PICA; arrow: compressed right VA; arrowhead: occluded right PICA. A–P, anterior–posterior.

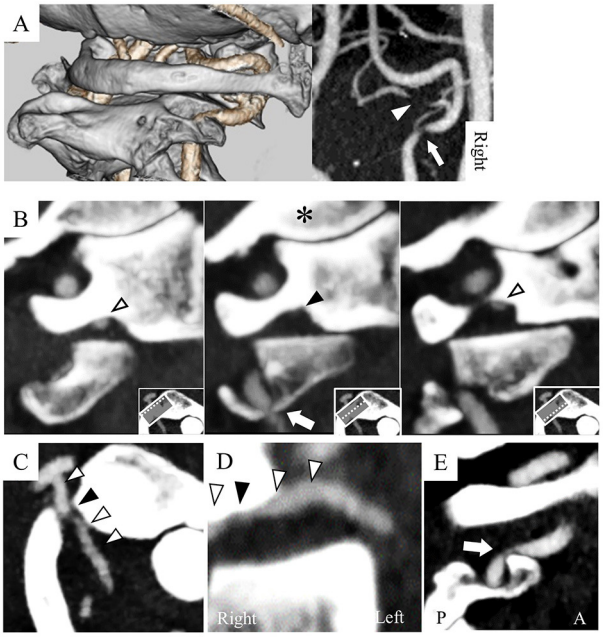

FIGURE 2 | Computed tomography angiography (CTA) with leftward head rotation shows the right PICA and VA as compressed **(A)**. The PICA was compressed in the narrow space surrounded by the posterior arch and lateral mass of the atlas and the superior articular facet of the axis (**B**: sagittal image of the atlas; **C**: axial; **D**: coronal). The right VA was compressed by the anterior wall of the transverse foramen at the axis (**E**: sagittal image of the axis). White arrowhead: PICA, black arrowhead: compressed PICA, arrow: compressed VA, *: occipital condyle, A: anterior, P: posterior.

CASE REPORT

A 71-year-old man presented with a several-month history of reproducible transient dizziness on leftward head rotation, with no neurological deficit, thus indicative of BHS. Magnetic resonance angiography (MRA) showed no pathological abnormality; he exhibited bilateral VAs merging into the basilar artery, and the left VA was dominant (**Figure 1A**). However, digital subtraction angiography (DSA) showed variants of the bilateral vertebral arteries; the right PICA originated from the right VA at the atlas–axis level and ran vertically into the spinal canal (**Figure 1B**), whereas the left VA ran into the spinal canal at the atlas–axis level without passing through the atlas' foramen transversarium (**Figure 1C**). Leftward head rotation at 45° did not induce dizziness, but dynamic DSA showed stenosis of the right VA at the level of the axis (**Figure 1D**). At 60° head rotation, which induced dizziness, occlusion of the right PICA was revealed (**Figure 1E**). Computed tomography angiography (CTA) on leftward head rotation showed that the PICA was severely compressed in the narrow space surrounded by the atlas and axis, and that the right VA was compressed at the axis level (**Figure 2**). Notably, the occipital articular facet did not shift during the head rotation, which was compensated by atlantoaxial hyper-rotation in the form of atlantoaxial rotary subluxation. Thereafter, the extracranial PICA, together with the C2 nerve root and perivascular venous plexus, ran through a narrow tunnel surrounded by bone components of atlas and axis during head rotation. The compression of the PICA was mainly considered responsible for causing the BHS in the patient.

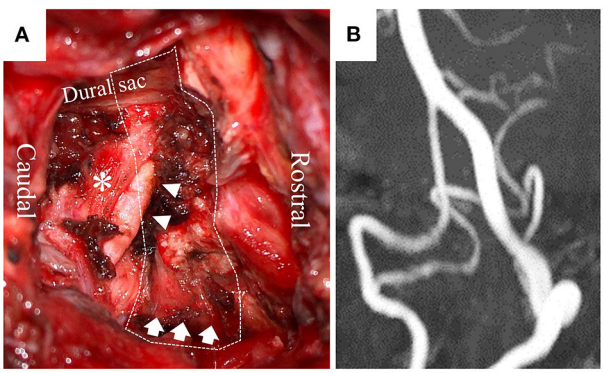

FIGURE 3 | Operative view **(A)** shows a dissected right PICA (arrowhead), C2 nerve root (*), and decompressed right VA (arrow) after resecting part of the atlas (dotted line: resected atlas). Postoperative MRA at 60° leftward head rotation **(B)** shows no compression of the right PICA and VA.

However, the concomitant VA stenosis may have resulted in poor blood supply into the PICA.

The dizziness was restrictive to the patient's daily activities; therefore, he underwent surgery to decompress the right PICA and VA *via* a posterior approach (**Figure 3A**). A 6-cm linear skin incision was made on the back of the neck, with 3 cm

TABLE 1 | PFIA-associated Bow hunter's syndrome/stroke.

	Case	Age	Sex	Type of disease	Pathology	Disposition of PFIA in vertebrobasilar system	Treatment	Outcome
1	Yamaguchi et al. (8)	45	M	Bow hunter's stroke	Embolic stroke due to dissected PFIA	VA fenestration	Atlas-axis fusion	Good
2	Buch et al. (9)	38	M	Bow hunter's syndrome	Transient poor blood flow due to PFIA stenosis	VA running into spinal canal at atlas-axis	Decompression of artery	Good
3	Our case	71	M	Bow hunter's syndrome	Transient poor blood flow due to PFIA occlusion	Extracranially originated PICA	Decompression of artery	Good

PFIA, persistent first intersegmental artery; VA, verterbral artery; PICA, posterior inferior cerebellar artery.

laterally to the right at the level of the axis–atlas. The posterior arch of the atlas was identified following dissection between the splenius capitis and semispinalis capitis muscles. Posterior cervical muscles were preserved, including the ones originating from the atlas and axis. The right VA was identified by Doppler on the cranial side of the atlas's arch. The posterior wall of the atlas transverse foramen was removed, and the VA was dissected from the canal of transverse foramen and surrounding connective tissues, enabling the VA to shift posteriorly. Bleeding from the venous plexus was controlled by bipolar coagulation with an oxidized cellulose-based hemostatic sheet. Following resection of the right posterior arch from the transverse foramen to the spinal canal, the PICA in the C2 root sheath was identified by Doppler. By opening the sheath, the intra-sheath PICA was identified running in parallel with the C2 nerve root, and it was dissected to be totally free between the VA and dural sac. There was no fibrous band compressing the PICA.

The postoperative course was uneventful. The patient had no dizziness during head rotation, thereby freeing him from the dizziness-associated life restriction. On postoperative MRA at 60° leftward head rotation, compression of the right VA and PICA had disappeared (**Figure 3B**). BHS did not recur without any thrombotic therapy for 3 months after the surgery.

DISCUSSION

BHS has been known to be caused only by obstruction of the VA. This is the first case of BHS caused by compression of an extracranially originated PICA that was alleviated by vascular decompression.

An embryonic remnant of the FIA can be associated with VA variants at the atlas–axis level, and these are classified into three types: persistent FIA, VA fenestration, and atlas–axis originating PICA (as in the present case) (4). The frequency of atlas–axis originating PICA has been reported in up to 1.1% of the population; however, its association with BHS has not been previously reported (6, 7). Only two cases of BHS or bow hunter's stroke due to compression or injury of embryonic remnant FIA have been reported in the literature, and they affected the other two VA variations. One patient's BHS was attributed to compression of persistent FIA, and the other patient, with bow hunter's stroke, was caused by dissection of the fenestrated VA (8, 9) (**Table 1**).

In BHS, stenotic change of the VA is usually attributed to its compression by the transverse foramen, an osteophyte, a herniated disc, or a fibrous band (1). However, mechanisms by which an FIA-associated remnant artery can have stenotic change at head rotation are unknown. The FIA-associated remnant artery runs together with the C2 nerve root between the atlas and the axis between the posterior arch of the axis and the vertebral arch of the atlas (5). In our patient with the head rotation, the FIA-associated PICA went through an atlantoaxial rotary subluxation-forming narrow tunnel surrounded by bones (the posterior arch, the lateral mass of the atlas, and the superior articular facet of the axis) together with the C2 nerve root and the well-developed venous plexus. Hence, the atlantoaxial rotary subluxation might be one of the causes for BHS due to stenotic change at the FIA remnant. Cervical degenerative change and/or congenital abnormalities are believed to cause BHS (10). In our patient, degenerative spial change was suspected to have caused BHS by affecting the congenital vascular anomaly, given that BHS emerged at an older age.

BHS is normally caused by compression of the dominant VA where the ipsilateral decreased blood flow is not compensated by the collateral blood flow from the contralateral non-dominant VA (1). On the contrary, it is rare that compression of non-dominant VA causes BHS because of sufficient collateral flow from the contralateral dominant VA. However, a few cases have been reported to be associated with BHS because of insufficient compensatory collateral blood flow (3). In our patient, BHS was considered to be caused by compression of extracranially originated PICA. The VA stenosis at head rotation was also detected. However, the VA stenosis was not considered to be

the main cause of BHS because collateral blood flow from the contralateral dominant VA presumably compensated for the poor blood flow in the ipsilateral non-dominant VA. However, this may be indirectly associated with the BHS by decreasing perfusion pressure into the occluded PICA.

To identify the causative arterial stenosis in BHS with such a vascular anomaly, careful radiographic evaluation was needed, and head rotation to the degree inducing the symptom was necessary. In our patient, the PICA occlusion was able to be identified by the sufficient rotation of the head, leading to the effective treatment.

BHS impacts daily life by causing dizziness or syncope. In addition, it may cause life-threatening conditions such as cerebral infarction and VA dissection. Conservative management and surgical treatment have been performed. For conservative management, wearing a cervical collar, refraining from extreme neck rotations, and antiplatelet therapy are applied, but the effectiveness of these procedures is unclear and difficult to maintain. On the contrary, excellent results of surgical treatment with decompression of the VA or cervical fusion have also been reported; the success rates of treatment were 87% in VA decompression alone and 100% in fusion with/without decompressing the VA (1). Although cervical fusion may cure BHS more frequently than decompression alone, restriction of neck motion could occur postoperatively, resulting in limitations in the patient's daily activities. Therefore, decompression alone, which preserves neck motion, might be a first-line therapy (2). A standard surgical strategy for FIA remnant-associated BHS has not been established because only two cases have been reported (8, 9). One patient with persistent FIA-associated BHS was successfully treated by decompression alone *via* hemilaminectomy of the atlas; the other patient who had VA fenestration as FIA remnant and presented with dissection and stroke was treated by cervical fusion. In our patient, BHS was improved by vascular decompression alone. Atlantoaxial fusion could have led to severe motion restriction at the patient's neck, because poor movement of the atlanto-occipital joint was considered to be compensated by atlantoaxial hyper-rotation. The atlas hemilaminectomy was performed to decompress the FIA-associated PICA in concert with posterior transverse foraminotomy at the atlas. The hemilaminectomy might have directly improved the rotational compression of the FIA-associated PICA. The transverse foraminotomy indirectly improves impaired blood flow in the PICA by decompressing the VA.

CONCLUSION

BHS can be caused by compression of extracranially originated PICA, which can be alleviated by surgically decompressing it. In order to identify the exact causative arterial stenosis in BHS, such as the PICA, head rotation to the degree that induces the symptom might be needed during the radiographic evaluation, in order to determine the appropriate treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KY contributed to the conception and design of the manuscript. NE wrote the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Regulation of Blood Flow in the Cerebral Posterior Circulation by Parasympathetic Nerve Fibers: Physiological Background and Possible Clinical Implications in Patients With Vertebrobasilar Stroke

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Posterior circulation involves the vertebrobasilar arteries, which supply oxygen and glucose to vital human brainstem structures and other areas. This complex circulatory- perfusion system is not homogenous throughout the day; rather, its hemodynamic changes rely on physiological demands, ensuring brainstem perfusion. This dynamic autoregulatory pattern maintains cerebral perfusion during blood pressure changes. Accumulative evidence suggests that activity within the autonomic nervous system is involved in the regulation of cerebral blood flow. Neither the sympathetic nor parasympathetic nervous systems work independently. Functional studies have shown a tight and complicated cross talk between these systems. In pathological processes where sympathetic stimulation is present, systemic vasoconstriction is followed, representing the most important CNS parasympathetic trigger that will promote local vasodilation. Stroke is a clear example of this process. The posterior circulation is affected in 30% of strokes, causing high morbidity and mortality outcomes. Currently, the management of ischemic stroke is focused on thrombolytic treatment and endovascular thrombectomy within an overall tight 4.5 to 6 h ischemic time window. Therefore, the autonomic nervous system could represent a potential therapeutic target to modulate reperfusion after cerebral ischemia through vasodilation, which could potentially decrease infarct size and increase the thrombolytic therapeutic ischemic window. In addition, shifting the autonomic nervous system balance toward its parasympathetic branch has shown to enhance neurogenesis and decrease local inflammation. Regretfully, the vast majority of animal models and human research on neuromodulation during brain ischemia have been focused on anterior circulation with disappointing results. In addition, the source of parasympathetic inputs in the vertebrobasilar system in humans is poorly

understood, substantiating a gap and controversy in this area. Here, we reviewed current available literature regarding the parasympathetic vascular function and challenges of its stimulation in the vertebrobasilar system.

Keywords: vertebrobasilar system, ischemic stroke, autonomic system, parasympathetic system, sympathetic system, autoregulation, nitric oxide, neurovascular

INTRODUCTION

The importance of the vertebrobasilar system (VBS) relies on the structures that are supplied (such as cerebellum, occipital lobes, and brainstem). The latter is the most important of them from a biological point of view, as it is critical for life functions. The brainstem regulates respiratory and cardiac functions, consciousness, and sleep cycles. It also plays an important role in sensory and motor functions (1, 2). Therefore, its perfusion needs to be extremely well regulated. This hemodynamic success is achieved through an active autonomic and neural system composed of the sympathetic and parasympathetic system. During extreme physiological and pathological processes, these systems are activated with the aim to prioritize cerebral blood flow to the VBS to keep its functions intact (3). In recent years, molecular biology, complex animal models, and functional imaging techniques have shown the importance of the sympathetic/parasympathetic balance function and how vascular pathology can disturb normal perfusion.

Ischemic stroke affecting the posterior circulation can have devastating consequences with high morbidity and mortality. Therefore, under a hypersympathetic state, the role of parasympathetic regulation is critical in preserving posterior circulation function (1). Thus, parasympathetic modulation in ischemia could represent a promising target for neuroprotective strategies to improve the effects of acute treatments for vertebrobasilar stroke, such as endovascular therapy and thrombolysis. However, the vast majority of animal models and human research on neuromodulation during brain ischemia have focused on anterior circulation with disappointing results. In addition, the source of parasympathetic input in the VBS in humans is poorly understood, substantiating a gap and controversy in this area. Here, we reviewed current available literature regarding the parasympathetic vascular function, its stimulation challenges, and the potential effects in posterior circulation stroke.

METHODOLOGY

Due to the broad spectrum of topics reviewed, the authors searched medical reference databases (PubMed, EMBASE, Ovid, and Google scholar) according to assigned subtopics which, in our opinion, are critical for understanding the current topic. Anatomical references were obtained through medical textbooks as they have not changed.

Anatomy of the Posterior Circulation and Relationships With Autonomic Structures

From its origin, the posterior circulation has critical relationships with autonomic centers which play important roles in perfusion regulation through vasodilation and constriction.

The vertebral arteries (VAs) in their V1 portion (extraosseous or pre-foraminal segment), from their origin up to the entry into the initial foramen transversarium (C6-7), are related posteriorly with rami of spinal nerves C7 and C8 and the inferior cervical ganglion. Anteromedially, it is closely related to the middle cervical ganglion (2).

In their V2 segment (foraminal), considered from C6 to C1-2., they are accompanied by sympathetic nerves as well (2).

The V3 segment (extraspinal), from C2-1 to the foramen magnum, has had no clear autonomic relationships identified. The V4 segment enters the dura mater and it is the intracranial portion of the VAs. In this segment, the roots of the hypoglossal nerve (CN XII) ascend posteriorly (1, 2).

The posterior inferior cerebellar arteries (PICA) mostly originate from the vertebral arteries traveling just above hypoglossal nerve anteriorly and just inferior to the glossopharyngeal (IX), vagus (X), and XII cranial nerves along the posterolateral medullary surface. They also supply the caudal region of the IV ventricle where the "area postrema" is located, receiving input from the (X and XII CN), aortic depressor nerves, and carotid sinuses. The area postrema (AP) also has important efferences to the locus coeruleus and tractus solitarius. The role of AP in autonomic dysfunction is clear and is not only related to vomiting. Recent evidence suggests a vasopressive response via vasopressin and angiotensin II AP receptors with sympathetic response (4, 5).

Rostrally, the BA bifurcates into the posterior cerebral arteries (PCAs) (1, 2). At the mid portion of the BA, the anterior inferior cerebellar arteries (AICAs) arise. Proximal AICA's perforating arteries supply the brainstem through branches to the internal auditory canal and the labyrinth. The rostral trunk of AICA supplies the cerebellopontine fissure and the petrosal portion of the cerebellum. The inferior trunk supplies the more inferior aspect of the petrosal surface of the cerebellum, the flocculus, and forth-ventricular choroid plexus.

Distally, the SCAs arise from the BA (3). The SCA divides into the rostral trunk that supplies the vermis and adjacent paramedian upper cerebellar hemispheres and a caudal trunk that supplies the remaining superior cerebellar hemispheres, both superiorly (tentorial surface) and anteriorly (petrosal surface). Therefore, it perfuses the superior cerebellar hemisphere and vermis and deep cerebellar white matter (3). In the 1990's, prominent research in mid cerebellar lesioned rodents

demonstrated freezing motor posture abnormalities toward frightening stimuli with autonomic output dysfunction (blood pressure control and respiration rate). This has been documented in humans who have suffered medial cerebellar lesions and whose autonomic response is incomplete toward external stimulus, also called autonomic abnormalities of defensive response toward fear (6).

From the terminal BA, the PCAs are where the thalamoperforating, thalamogeniculate, and peduncular perforating arteries supply the mesencephalon, diencephalon, and the choroid plexus and walls of the lateral and third ventricles and cerebral branches to the cerebral cortex and callosal splenium. (3). Vas and common branches are shown in **Figure 1**.

Hemodynamics of the Posterior Circulation

The dynamics of blood flow in the posterior and anterior circulation are controlled by homeostatic mechanisms that continuously monitor and adjust to oxygen and glucose demands (7–9). The brain cannot store energetic substrates. Therefore, it requires a constant oxygen supply that can fulfill its actively changing requirements. The most important brain energy substrate is glucose. The brain oxygen requirements account for about 20% of the whole body demands in healthy adults. In children, during the first decade, the brain oxygen uptake can be as high as 50% (10). These demands are delivered at a rate of 800 ml/ min or 15–20% of the total cardiac output (CO) (9, 11).

Autoregulation plays a paramount role in modifying changes in cerebral blood flow (CBF) according to demands (9). Autoregulation, when functionally intact, allows the brain to accommodate varying levels of arterial perfusion changes within a wide range of systemic arterial pressures. When autoregulation becomes dysfunctional, the brain perfusion pressures become mostly dependent on systemic hemodynamic flow parameters (12).

Cerebral blood volume (CBV) correlates directly with CBF. Normally CBF is achieved by both cerebrovascular resistance (CVR) and cerebral perfusion pressure (CPP) (difference between systemic arterial pressure and venous back pressure).

CVR is the result or the intracranial diameter which also relies on blood viscosity. CBF and CBV will decrease as vessels constrict and vice versa (10).

The brain is a high flow low pressure with low resistance system (9, 10). This is not a new concept; in the 1800s, Monro-Kellie developed a hypothesis, describing the pressure dynamics in the relationship between brain tissue, blood and cerebrospinal fluid, and the skull. Any volume changes in any of the intracranial content will alter the intracranial pressure and dynamics with the others due to the skull's inflexibility. Normal intracranial pressures (ICP) range from 0–15 mmHg (9, 10).

CBF can be influenced by arterial blood, cerebral autoregulation, and metabolic rate through vasoneuronal coupling and nitric oxide (NO) which is an endothelium-derived relaxing factor. This is synthesized by endothelial cells from the amino acid L-arginine by the enzyme NO synthase. Among the three described NO isoforms (endothelial, neuronal, and inducible), the endothelial (eNOS) maintains blood flow by maintaining adequate vessel caliber. It has antiplatelet capabilities inhibiting platelet adhesion and aggregation, and therefore prevents thrombosis as well. Because of the antiplatelet and endothelial functions, it prevents atherosclerosis due to its vascular smooth muscle cell proliferation inhibition. In normal circumstances, there is a vasoconstriction (endothelium thromboxane and angiotensin II) - vasodilation (eNOS) intrinsic balance (13, 14).

Cerebral Autoregulation

Cerebral autoregulation refers to a natural phenomenon in which the brain receives the same CBF in spite of moderate variations in perfusion pressure. The aim of autoregulation is to protect the brain against hypoxia and brain edema as a result of decreased perfusion pressure, and critically high arterial blood pressures respectively (10, 15). In normotensive people, effectiveness of autoregulation is seen when mean arterial pressures are below 150 and above 60 mmHg (10). Below this range, hypoperfusion starts, promoting compensatory mechanisms such as incensement of oxygen extraction from arterial beds. On the contra side, above 150 mmHg, vasoconstriction is not efficiently sustained. Initially, in this process arteries exhibit an interesting phenomenon of autoregulation with dysregulation at the same time. This is exemplified with the "sausage stringing" sign characterized by an alternating pattern of dilation with constriction within the same vessel (which are regions with residual autoregulation) (16). If CPP continues to increase, "total" dilation is seen, permitting CBF to increase passively, disrupting vascular endothelium and producing blood-brain barrier disruption leading to plasma protein extravasation (examples of this dysfunction are seen in hypertensive encephalopathy, reversible vasoconstriction syndrome, and PRES) (16).

The limits of autoregulation mentioned above vary with some physiological stimuli and certain pathologies. The vasoconstrictor effect of sympathetic activation shifts the upper and lower limits of autoregulation (17). This response is considered "protective" in response to hypertension. These thresholds are changed in chronic hypertensive patients and partially explains massive vasoconstriction seen in hyper-stimulation of the sympathetic system in pathologies such as subarachnoid hemorrhage (10, 17).

Multiple factors physiologically modify autoregulation; Brain pH changes with systemicCO2 concentrations (18). Vasodilation induced by hypercapnia stimulates cerebral blood flow (CBF). Its precise vasodilatory mechanism is not fully understood. In animal models, hypercapnia stimulates endothelial potassium ATP channels enhancing vasodilation (19); another hypothesis suggests NO as a key player in vasodilation (20). In humans, this phenomenon has been corroborated with perfusion MRI and positron emission tomography, which have shown that hypercapnia increases CBF (21–23). This response can be slightly decreased but still prominent in older populations due to atherosclerotic changes that might interfere with full vasodilation. This effect is not ambiguous, and some acute neuropsychiatric phenomena have been associated with it (24).

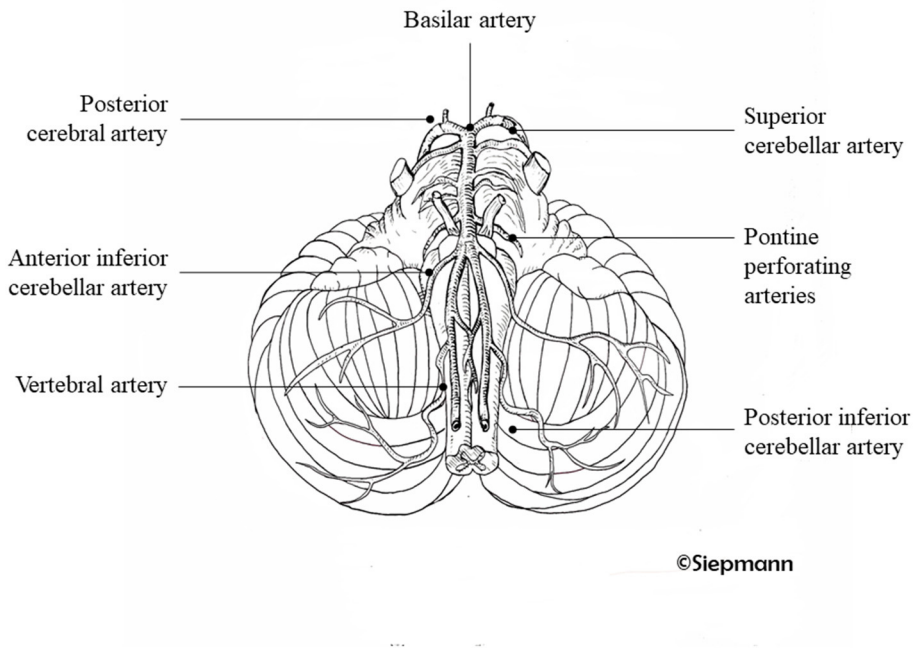

FIGURE 1 | Posterior arterial circulation system. Illustration of the branches of the vertebral arteries supplying the cerebral posterior circulation system. Drawing kindly provided by Antje Siepmann.

Hypoxia on the other hand promotes vasodilation due to hypoxic effect. Also, this response is mediated through nitric oxide and adenosine. This has been nicely investigated in climbers where rapid oxygen therapy modified vasodilation (25).

Parasympathetic Innervation of the Vertebrobasilar Arteries

The parasympathetic innervation of intracranial arteries (IA) possess two important differences in comparison to the extracranial arterial system: The IA parasympathetic innervation is 10–40 times higher, providing a powerful vasodilatory mechanism (26, 27). Another difference is that IA are minimally or not cholinergic dependent, that is, there is an inability to produce acetylcholine (ACh) as a transmitter (28), rather, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating peptide (PACAP), and most importantly NO are the main co-transmitters in parasympathetic neurons which, interestingly, are all very potent vasodilators, perhaps even more so than ACh (28–30). However, it seems that NO is the main vasodilator and the rest are mostly pre-synaptic modulators for NO release (29, 30).

Anterior Vs. Posterior Circulation Vascular Innervation

The origin of the parasympathetic innervation in posterior circulation is not fully understood and it differs from the anterior circulation. There is a common origin at the skull base and diffusely in the arachnoid space, identified as a diffuse collection of small cell groups.

In the anterior circulation the innervation is provided by fibers from the sphenopalatine ganglia (SPG), commonly known as pterygopalatine ganglia (PPG), the otic ganglia, the cavernous sinus, and the internal carotid mini-ganglia (CMG) (31, 32).

There is evidence of parasympathetic activity in the VBS but in humans the source and inputs are not fully known (33).

Animal models (34) have located preganglionic neurons projecting to the PPG, stimulating the ipsilateral superior salivatory nucleus (SSN) and specifically the greater petrosal nerve. This creates a stimulation cascade activating center in medulla oblongata (spinal trigeminal nucleus, the nucleus of the tractus solitarii or NTS, which plays an important processing role in autonomic response to hypoxia), pontine nucleus (parabrachial structures), and gigantocellular reticular nucleus and subcoeruleus region and A5 catecholaminergic cells (34, 35), paraventricular hypothalamic nuclei and the lateral pre-optic area. The bed nucleus of the stria terminalis, substantia innominate and the amygdalopiriform, the otic ganglia and CMG (33, 36) This nuclei-web enhances the importance of the SSN vasodilatory effect and the regions that may influence it (33).

Neuromodulation of the Posterior Circulation

The most important vasodilator neurotransmitter is NO, mostly clustered in the basilar artery. NO possesses a half-life of 5–15 seconds and is produced through cholinergic neurons and VIPergic neurons (37). Endothelial cells, astrocytes, neurons, and immune cells are other sources of NO that contribute to VB dilation (33, 38–40).

Endothelial and smooth muscle cells express cholinergic receptors. However, the effectiveness of these receptors is not through acetylcholine, rather it is through muscarinic (M) and nicotinic (N) receptors (33, 41). There have been four muscarinic and one nicotinic type of receptors identified. NO-dependent vasodilation is achieved when Ach activates M and N receptors (42, 43). M1and 3 receptors mediate the NO-induced vasodilation in humans. M1 is mostly seen in the basilar artery (43). Their affinity for Ach is lower in comparison to M3 receptors that show high Ach affinity and requires high concentrations of Ach for activation. In the presence of functional endothelium M3 receptors, the activity of M1 is not minimal. This explains the dominance of M3 in intracranial circulation playing the major role in vasodilation (33, 44). In animals' M2 receptors, function is vasoconstrictive through inhibition of NO. These receptors have not been found in humans (43). The M5 receptor is also an M-type receptor the function of which is not well understood and some studies have proposed this to be similar to M3 in animals. This is, again, not confirmed in humans (45).

The vasodilator function of the vasoactive intestinal peptide (VIP) is not fully understood. VIP co-localizes with cholinergic acetyltransferase in some parasympathetic nerves and has been isolated mostly in the basilar artery (46, 47). The vasodilator effect of VIP could be through NO via the natriuretic peptide clearance receptors (NPRC) (47).

The final neuropeptides that play a role in vasodilation (but with weaker properties) are the human peptide histidine methionine and pituitary adenylate cyclase activating peptide (48, 49) which, due to poor vasodilatory function, will not be discussed further in this paper. The nicotinic receptors will be discussed shortly.

Parasympathetic and Sympathetic Inter-communication

It is not infrequently observed that parasympathetic and sympathetic nerves are interlaced in the same perineural sheath innervating cerebral arteries. Functional studies in animals' basilar arteries have shown poor vascular response to Ach and noradrenaline. This is not seen with adrenergic nerves which express nicotinic Ach receptors that once activated enhances intracellular calcium influx. Intracellular calcium then stimulates the release of noradrenaline, triggering vasodilation via β-2 adrenergic receptors. These receptors are located within the Ach-nitrergic fibers where NO is stored and released once NO and Ach are released. Modulating NO, pre-junctional M2 receptors are stimulated simultaneously with NO and Ach, inhibiting further NO synthesis (negative feedback phenomena). During β2 adrenergic stimulation, vasoconstrictions occur no more due to paucity of α-adrenoceptors (50, 51). In face of increased sympathetic drive, the expected response in the VB arteries would be dilation rather than constriction. This response guarantees, in normal circumstances, optimal CNS perfusion during systemic hypoperfusion due to adrenergic constriction (52).

Parasympathetic Pathophysiology of Stroke

Stroke is a neurovascular emergency secondary to intracranial ischemia or hemorrhage that leads to a specific neurological dysfunction related to the affected area. Unlike TIA (transient ischemic attack), the deficit in stroke usually persists >24 hours (53, 54). Approximately 30% of these strokes are located in the VBS (54, 55). Ischemia is secondary to a vascular occlusion. In the posterior circulation, etiological factors to consider are local thrombotic events in the VBA (30%), dissections or embolism, usually cardioembolic (40%) and small vessel related. In 30% of patients an etiological factor might not be found (54). Therefore, occlusive atherosclerosis is a major stroke risk factor supporting the role of hemodynamic insufficiency in the posterior circulation. This has been recently supported in the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke (VERiTAS) study, which monitored the hemodynamic status in posterior circulation with measurements of large cerebral vessel flow. This was achieved using phase-contrast quantitative magnetic resonance angiography (QMRA), which is considered a very reliable surrogate for vascular hemodynamic status (for further description of methodology, readers are encouraged to search for more specialized imaging literature). The VERiTAS study demonstrated with QMRA that hemodynamic compromised posterior circulation is a robust predictor for stroke, reaching a 4-fold higher risk over 24 months (56, 57) and the potential for both improvement and worsening relies on hemodynamic shifting over time. That is, if hypoperfusion continues, the stroke risk increases over two years and vice-versa. (58). In the acute setting, the aim of the parasympathetic vasodilatory function is to preserve cerebral blood flow, decrease ischemic core, and promote hemodynamic hypoperfusion which can lead to ischemic core extension and stroke recurrence (59, 60).

Therapeutic Activation of Parasympathetic System in Stroke Patients

Vagus Nerve Stimulation (VNS)

This can be summarized in four different mechanisms: effect on neurotransmitters, anti-inflammatory pathways, modulation of cerebral blood flow, and neurogenesis enhancement.

Neurotransmitters

Decreasing extracellular glutamate decreases the stimulation of N-methyl-D-aspartate receptors,VNS decreases cerebral ischemic penumbra and thus, infarct size, promoting less neurological deficit impairment (59, 61). Speculations regarding other mechanisms of action (59) suggest that VNS also stimulates norepinephrine and 5-HT which decreases extracellular glutamate as well (59). In humans, most studies have been focused on chronic stroke aiming to determine safety and improvement of rehabilitation outcomes. This strategy has shown to be promising in acute ischemic strokes (62).

Cholinergic Anti-inflammatory Pathway

After ischemic stroke, tissue inflammation worsens outcomes (63). Shortly after ischemia, resident microglia are activated and

accumulate at the lesion site and penumbra (peaks in 72 h). Upon activation, microglia undergoing proliferating factors are released, among them chemokines and cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and neurovascular proteases such as matrix metalloproteinase (MMP-9), are prominent, generating reactive oxygen and nitrogen species (ROS), via NADPH oxidase (nicotinamide adenine dinucleotide phosphate) (64, 65). The cholinergic anti-inflammatory pathway suppresses inflammation. This effect is through inhibition of cytokines expression and therefore inflammation (factorn-κB pathway) (66).

The vagus nerve represents the peripheral efferent output from a complex cortical cholinergic (Ach) system. The main properties are to reduce microglia inflammation through activation of the nAChRα7 receptors. These anti-inflammatory properties are activated through VNS (67). Parasympathetic stimulation also decreases the systemic inflammatory response (C-reactive protein among others) which can potentially worsen stroke outcomes. Pharmacologically, Ghrelin stimulates vagus-related nerve-mediated anti-inflammatory markers including cytokines and tumor necrosis α. (59).

CBF Modulation by Parasympathetic Stimuli

In this topic, complementing what we already discussed, SPG innervate intracranial vessels that express receptors to their nitroxidergic-cholinergic cells. Its stimulation increases cerebral blood flow through NO vasodilation, decreasing diffusion – perfusion mismatch in functional MRI studies. This effect is mostly seen in the penumbra area, avoiding further apoptosis and progression of infarct core size (68). Another important effect seen with SPG stimulation is the enhancement of the blood brain barrier permeability, which could be beneficial when using a neuroprotective agent, however, on the other hand, BBB permeability has shown risk of hemorrhage during thrombolytic therapy (69). In the authors' opinion, this lack of permeability and perfusion could explain why many neuroprotectant agents have failed to provide benefit. These findings could open new areas of interest in future neuroprotective research in stroke.

Parasympathetic Activation Enhances Neurogenesis

Stroke promotes neural stem proliferation conditions (70). Norepinephrine, brain derived neurotrophic factor, fibroblast grow factors, and 5-HT are promoted through VNS.

Norepinephrine and 5-HT regulate extensive cholinergic innervated hippocampal neurogenesis (survival, integration of newborn neurons, and maturation) through nAChRα7 (59, 71). Thus, neurogenesis enhancement could be achieved with VNS or with nAChRα7 agonists (59).

Therapeutic Perspectives

Parasympathetic stimulation through VNS is not a new concept. It has been used in other areas of neurology (epilepsy) and psychiatry (depression) (72). This is due to its ability to interfere with the ischemic stroke cascade pathophysiology through mechanisms such as norepinephrine and serotonin release. VNS has shown stroke size reduction in experimental animal models attenuating stroke volumes (72) and post stroke outcomes studied in rehabilitation only in anterior circulation strokes. **Figure 2** summarizes VNS effects during stroke.

Recently, the NOVIS trial (Non-invasive Vagus nerve stimulation in acute Ischemic Stroke) protocol was published (73) and is expected to start in 2021. This will be an open label clinical trial with blinded outcome assessment in 150 anterior circulation stroke patients at the Leiden University Medical Center. However, to date no VNS trial has focused on posterior circulation.

The parasympathetic effect of sphenopalatine ganglion stimulation has been recently studied in the ImpACT-24A trial (Sphenopalatine ganglion stimulation to augment cerebral blood flow. A randomized, sham-controlled trial) (74). They randomized 253 patients in the study where 153 were included in the study treatment and 100 in the control or sham. The primary outcome was improvement in disability beyond expectations after three months, which was shown to be 49.7 vs. 40%: odds ratio, 1.48 (95% CI, 0.89–2.47) $p = 0.13$. However, a significant treatment interaction with stroke location (cortical vs. non-cortical) was noticed. In 87 patients with confirmed cortical involvement, rates of improvement beyond expectations were 50.0 vs. 27.0% odds ratio, 2.70 (95% CI, 1.08-6.73);$P = 0.03$. The final results of the trial (75) did show a good safety profile but failed to reject the null hypothesis supporting SPG.

The use of α-7 nicotinic acetylcholine receptor agonist has shown in anterior circulation stroke-induced models in animals some neuroprotective effect reducing inflammation and oxidative stress. There is a need for further studies in this regard (76).

Facial Nerve System Stimulation

Stimulating the facial nerve directly stimulates SPG and the Otic ganglia. This produces further activation cascade only to VIP-expressing nerve fibers mostly found in the carotid arteries and anterior intracranial circulation. The final result is vasodilation. In the posterior circulation there is mild to non-VIP nerve expression and can only be found in the rostral portion of the basilar artery which is stimulated through the cavernous ganglia once the facial nerve is stimulated (77).

Cavernous Ganglia Stimulation

Brilliant descriptions of its stimulation through the SPG have been done in animal models (78), demonstrating vasodilation in anterior and posterior circulation. The latest after stimulation follows the IV and VI CN backward to the basilar artery and tentorium cerebelli respectively. However, no clinical studies have been done in humans.

CONCLUSIONS

Our current knowledge of the autonomic vascular system innervation is still weak. The anatomical variants in different animal species have complicated this even further. The fact of not knowing the real parasympathetic origin in posterior circulation widens this gap, as no direct neuromodulation mechanism can stimulate the posterior circulation in isolation. However, one important feature learned is that this expected

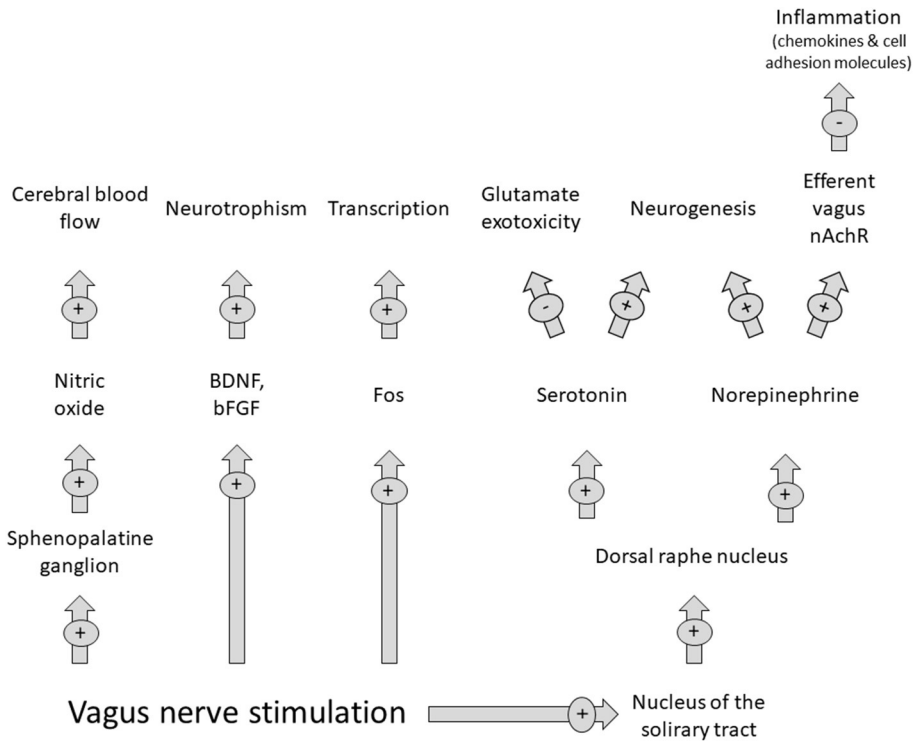

FIGURE 2 | Effects of vagus nerve stimulation on the parasympathetic nervous system. Abbreviations: BDNF: brain derived neurotrophic factor; bFGF, brain fibroblast growthfactor. Modified from Cai PY. (2014) Frontiers in Neurology doi: 10.3389/fneurol.2014.00107.

"isolated" system in anterior and posterior circulation seems non-existent. Therefore, functional imaging studies are needed to determine hemodynamics in posterior circulation during traditional parasympathetic stimulation in anterior circulation.

The protective role of the parasympathetic system in cerebral arteries (under hypersympathetic stimulation) in ischemic strokes is undoubtable. We believe that most research failures in humans could have been related to the long ischemic windows with no other intervention (IV thrombolytics or mechanical thrombectomy). This could represent another venue for future research. Furthermore, the lack of success with all neuroprotectant agents could have been related to the local hypoperfusion that ischemic stroke implies per se. Therefore, and speculating, the means of proper stimulation of this system might open the doors to more options in stroke patients.

While the stimulation of this complex system has been debated (78–82), in our opinion we believe the issue to be clear. We require more strict protocols with shorter ischemic windows, not forgetting that there is an approved management practice, as this could represent, in the future, ways to optimize our acute management in these critically ill patients.

AUTHOR CONTRIBUTIONS

AT contributed to conception and design of the article, reviewed literature and wrote content. TS contributed to conception and design of the article, reviewed and improved manuscript content. Both authors contributed to the article and approved the submitted version.

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REVIEW
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Posterior Fossa Venous Drainage

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This paper aims to make simple the evaluation of the main veins related to the brainstem and cerebellum. Posterior fossa venous drainage is best understood in context with its three main collectors: superior: toward the Vein of Galen; posterior: toward the torcular complex; and anterior: toward the superior petrosal sinus. A fourth possible drainage path, often harder to distinguish, is directed toward the inferior petrosal sinus. Veins of these four systems are frequently connected to one another. Despite traditionally being considered less regular than its arterial disposition, posterior fossa venous anatomy follows specific patterns that are easy to identify. The three more representative veins of each venous confluent have been selected, to help in recognizing them angiographically. Since pial large veins are primarily located over the surface of the encephalon, most related anatomical structures can be confidently identified. This is of special interest when angiographic 2D or 3D studies are evaluated and provide fundamental assistance in locating precise structures. To better aid in understanding venous disposition, an overview of embryologic and fetal development is also discussed.

Keywords: veins, vein of Galen, cerebellum, torcular, petrosal vein, stroke, cerebral vein thrombosis

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INTRODUCTION

Embryologic Overview

The brainstem and cerebellum, two main posterior fossa encephalic components, carry a different evolution during the fetal period. For instance, the brainstem already belongs to the neural tube, whereas from one lateral metencephalic plaque at each side, the cerebellum will expand in all directions and converge at the midline. This key distinction influences the subsequent venous disposition.

In general, neural development initially consists of a neural tube of neuroblasts containing a cerebrospinal fluid rich enough to cover the metabolic and energy needs of the surrounding tissue. Originally, cells (neuroblasts) come in contact with both the internal limiting membrane (ventricular or germinal) and the external limiting membrane of the neural tube. The ventricular layer of pluripotential neuroblasts divide rapidly, and subsequently, a ventricular zone, a subventricular zone, and a mantle zone can be differentiated. After a period of mitosis, cells stop dividing and lose contact with the ventricular wall, getting displaced to the mantle zone, where a superficial marginal layer harbors the prolongation with which cells anchor to the external boundary of the neural tube.

All cerebellar neurons are produced at the alar plate of the rhombomere 1 of the rhombencephalon (1). Progenitors in the cerebellar ventricular zone give rise to GABAergic neurons starting with those of the cerebellar nucleus and Purkinje cells (adult Purkinje cells are shown in **Figures 1c,d**). Cerebellar interneuron progenitors migrate into the developing cerebellar anlage. A secondary germinal zone, the rhombic lip,

is established at the junction of the cerebellar ventricular zone and the dorsal roof plate. It gives rise to glutamatergic neurons of the cerebellar nucleus which migrate over the top of the anlage to form the nuclear transition zone, which is a staging zone for cerebellar nuclei assembly. Later, from the rhombic lip (**Figure 1a**) emerge large numbers of granule neuron progenitors to migrate over the anlage to form the external granular layer, which resides on the pial surface (2).

Our observations of human embryos from three collections (Bellaterra, Blechschmidt and Hinrichsen Collections) confirm what can be seen in the mouse hindbrain development. In the first instance, the cerebrospinal fluid supplies most of the energy needs of developing neuroblasts, while arteries and veins develop and surround the neural tube (3). At the fetal stages, a plexal network of vessels cover the developing encephalic structures (**Figure 1b**).

At the embryonic and early fetal period, venous drainage is represented by multiple interconnected plexal venous structures located within the dural mesenchyme at the lateral aspect of the future posterior fossa. The young embryo shows the disposition of a large primary head sinus located laterally receiving three main venous stems: anterior plexus and stem (draining the prosencephalon), middle plexus and stem (for the metencephalon), and posterior plexus and stem (for the myelencephalon). The expansion of the craniofacial structures brings the interconnection of the anterior and middle stem components, forming the primitive lateral sinus, which connects to the remnant of the primary head sinus in the sigmoid sinus.

Brainstem veins maintain, more or less, the basic structural pattern of perpendicularly interconnected veins around the neural tissue. Cerebellar drainage, however, follow a particular course of action brought about by the vermian, hemispheric, and ventricular–choroidal tissue expansion.

There is little recent research dedicated to posterior fossa venous development. Old reports of Markowski, Steeter, and Padget (4–6) have been focused on the embryonic period, when the cerebellum is still very undeveloped. Okudera and cols. were interested in the fetal period, but their research in this area was centered aroundthe venous sinuses (7). Research done by the author highlights the important role of the choroid plexus as a directing structure related to further venous arrangement. At early stages, the fourth ventricle is represented by a very large cavity extending laterally and caudally. It is not yet covered by encephalon at its tectal (which will turn into posterior) aspect. With respect to the cerebellar drainage evolution, as Padget stated (7), the pioarachnoidal ventral metencephalic vein is the first to be in relationship with the alar plate of the metencephalon (which will develop into the future cerebellum). The embryonic ventral metencephalic vein becomes the superior petrosal sinus in the adult. This petrosal drainage plays an important role in draining the lateral aspect of the expanded choroid plexus of the fourth ventricle which initially looks like a lateral ribbon extending posterocaudally. Subsequently, the choroid plexus also gets developed at the midline and is drained by veins from the torcular region, foreseeing the development of the inferior vermian veins. The rhombic lip is anatomically connected to the choroid plexus.

It must be emphasized that in most of the embryological and fetal stages, the dura mater does not have the same appearance as in the adult. Instead of a thick fibrous membrane, the developing dura mater consists of large loose connective tissues (**Figure 1a**) around the neural tube. In embryos between the fifth and the seventh week of gestation only a layer, named "meninx primitiva," containing most vascular structures, is noted. No distinction can be made between the arachnoid and dural layers. In our specimens, 22 mm (7th week) embryos already show a differentiation between the arachnoid and dura. Vascular venous channels predominantly populate the dura mater, while most arteries are located in the arachnoid tissue. Along the embryologic period, lateral ventricles and the future fourth ventricle are very large cavities.

Most adult pial veins show a final intradural trajectory before entering the sinus, that is, between the dural lining and the corresponding sinus itself. For cerebellar veins draining into the torcula or transverse sinuses through the tentorium, the dural segment tends to be long, to the point that this group of veins of the cerebellar posterior aspect is referred to as the "tentorial sinuses."

The adult venous cerebellar configuration has been described in 1983 by Duvernoy et al. (8). Two categories of vessels (arterial and venous) were considered, pial and intracortical. About the intracortical veins, they recognized short veins, extremely numerous, related to the molecular layer, of around 10 μm in diameter; medium veins, scarce, originating in the vicinity of the Purkinje layer, and long, more related with the granular layer and white matter; these long veins may show a diameter of up to 90 μm.

On the surface of the cerebellum, they also distinguished between:

- deep pial veins, inside the cerebellar folia, forming venous arches toward larger veins (200 μm) located in the sulci, and
- superficial pial veins: some larger receiving the deep pial vein collectors, and other smaller veins located roughly at the center of the folia.

Some posterior fossa veins are helpful in localizing anatomical structures: the petrosal vein is located at the ponto-cerebellar angle, the precentral vein shows, in the lateral view the anterior margin of the central lobule and culmen, both tonsillar tributaries of the inferior vermian vein turn around the tonsil, sometimes an anterior venous channel shows in the lateral view, the

Abbreviations: Ch Pl, choroid plexus; DM, dura mater; IV, fourth ventricle; M, mesencephalon; OC, otic capsule; P, pons; Pu, Purkinje cell; RL, rhombic lip; Tent, tentorium; VZ, ventricular zone; Li, lingula; Ce, central; Cu, culmen; De, declive; Fo, folium; Tu, tuber; Py, pyramis; Uv, uvule; No, nodule; T, tonsil. Venous structures: Absv, anterior brainstem veins; Ahv, anterior hemispheric vein; Apmv, anterior pontomesencephalic vein; Apv, anterior pontine vein; Hv, hemispheric cerebellar vein(s); Ivv, inferior vermian vein; Lmv, lateromesencephalic vein; Lpmv, lateral pontomesencephalic vein; Mastv, mastoid emissary vein; Pcv, precentral vein; Psvv, posterosuperior vermian vein; PV, petrosal vein; SPS, superior petrosal sinus; StS, straight sinus; Svv, superior vermian vein; TS, tentorial sinus; VOG, Vein of Galen.

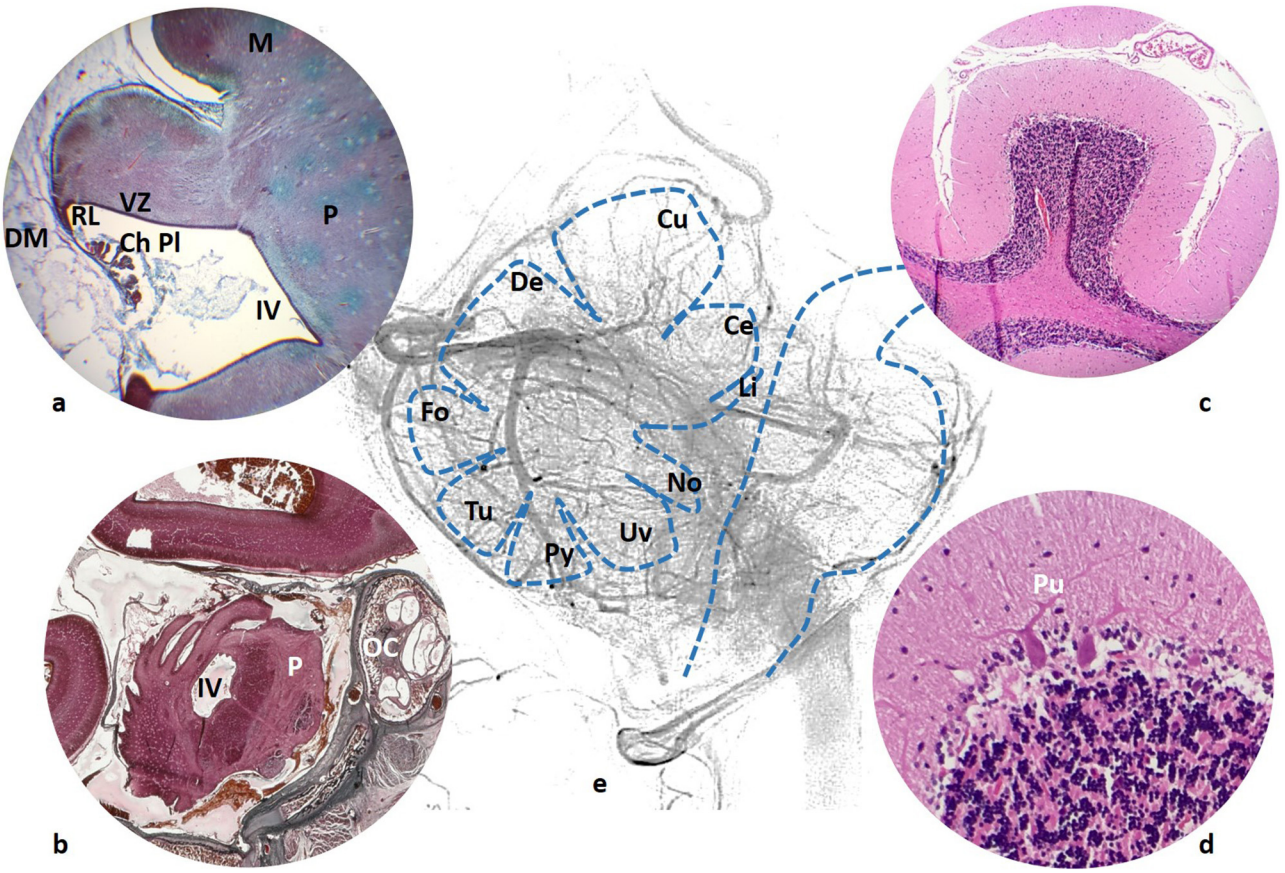

FIGURE 1 | (a) 59 mm fetus (10 weeks). Cerebellar ventricular zone (VZ) and rhombic lip (RL), continuous with the choroid plexus (ChPL) of the forth ventricle (IV). Duramater (DM) is still a large tissue surrounding the developing brain. **(b)** 160 mm fetus (20 weeks), cerebellar fissures are clearly seen just posterior to the forth ventricle (IV) and pons (P). A segment of the cochlea is also included in the section (OC). **(c)** Adult cerebellar folia with the typical appearance of the Purkinje cell (Pu) in **(d)**; **(e)** Schema of the vermian lobules (Li, Lingula; Ce, Central; Cu, Culmen; De, Declive; Fo, Folium; Tu, Tuber; Py, Pyramis; Uv, Uvule; No, Nodule) in relationship with the venous network.

mesencephalon at the interpeduncular cistern, the pons and the medulla (**Figure 1a**).

The straight sinus, receiving supra- and infratentorial Vein of Galen tributaries, the torcula, and both transverse-sigmoid (lateral) sinuses, represent the main drainage of the posterior fossa. The cavernous sinus, through the superior petrosal sinus and, in some instances, the inferior petrosal sinus, contributes as venous outlets. Additionally, veins of the lateral recess of the fourth ventricle, the restiform body, and anterior medullary veins may also connect with anterior and posterior spinal veins (see **Figure 3**).

The aim of this review of the venous anatomy of the posterior fossa is not to describe each brainstem or cerebellar vein in detail, but to give a general overview of the main veins normally seen in angiograms (**Figures 2a,b**) or multiplanar reconstructions of CT angiography (CTA) or MR angiography (MRA). Detailed descriptions of the veins of the brainstem and cerebellum are found elsewhere (9–13).

TENTORIAL OR POSTERIOR VENOUS CONFLUENT

This posterior drainage is represented by the cerebellar veins draining toward the torcular region. This also includes cerebellar veins draining to the posterior aspect of the straight sinus and those draining into the lateral sinuses. Pial veins drain through dural venous channels (tentorial sinuses) into the torcula, the lateral sinus, and the straight sinus. As stated by Shapiro et al. (14), these venous channels have been underappreciated in the supratentorial compartment, showing the same appearance as those in the tentorium cerebelli.

Veins of this posterior group include:

- Midline and paramedian veins: the posterosuperior vermian vein, and both inferior vermian veins, normally one on each side, and
- Hemispheric veins.

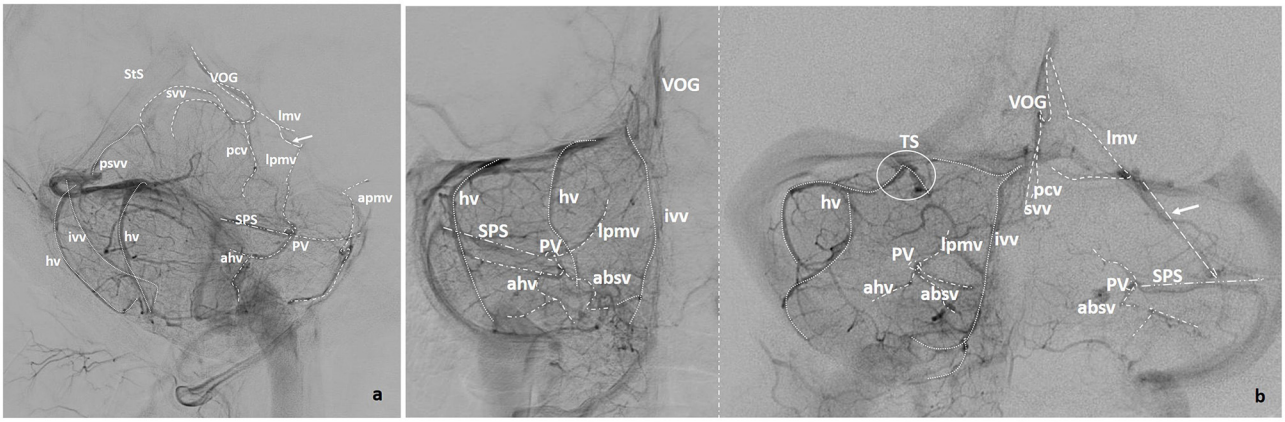

FIGURE 2 | (a) Lateral and **(b)** Anteroposterior projections of the veins of the posterior fossa (VOG, Vein of Galen; StS, Straight Sinus; pcv, Precentral Vein; svv, Superior Vermian Vein; lmv, Lateromesencephalic Vein; absv, Anterior Brainstem Veins; lpmv, Lateral Pontomesencephalic Vein; apmv, Anterior Pontomesencephalic Vein; ahv, Anterior Hemispheric Vein; Psvv, Posterosuperior Vermian Vein; hv, Hemispheric Cerebellar Vein(s); ivv, Inferior Vermian Vein; mastv, Mastoid Emissary Vein; PV, Petrosal Vein; SPS, Superior Petrosal Sinus; TS, Tentorial Sinus). Arrows point to bridging veins.

A dominant *posterosuperior vermian vein* is infrequent and normally unique at the midline. This vein may be long (draining more than the declive), but usually, it is a short vein joining either the inferior vermian veins (**Figure 3a**) or draining into the straight sinus or into the torcula itself. In some instances, the posterosuperior vermian vein drains to the vein of Galen, or a superior vermian vein connects the posterior and superior confluent (**Figure 5a**).

Inferior vermian veins are usually lengthy, running along the paramedial aspect of the vermis on each side, in or close to the paravermian sulcus. In ∼80% of cases their full trajectory is noted in angiographic studies including the para-median PICA territory, draining the corresponding tonsillar region. The junction of a superior and an inferior retrotonsillar vein at what has been named the copular point gives rise to the inferior vermian vein (**Figure 3a**). The normal configuration is that of an inferior vermian vein either joining an ipsilateral hemispheric vein (**Figure 3b**) or running independently to drain in the torcular–paratorcular region (**Figure 2b**). Less frequently, the inferior vermian vein drains in the mid-transverse sinus (**Figure 4a**) or, exceptionally, in the transverse–sigmoid region. A short vein is uncommon and, in <5% of cases, no inferior vermian vein can be identified. Very uncommonly, the inferior vermian vein crosses the midline to join the torcula or the contralateral inferior vermian vein.

Hemispheric veins tend to be more than one in each cerebellar hemisphere, but frequently one is predominant in size. In each hemisphere, posterior draining veins may join in one larger collector with or without connecting to the inferior vermian vein. Drainage of these pial veins through their corresponding tentorial sinuses (**Figures 2b**, **4a**) tend to be directed toward the torcular–paratorcular region in more than 50% of cases, decreasing in frequency to the paramedian third of mid-transverse sinus, to the transverse–sigmoid region and to the straight sinus as points of confluence for those tentorial sinuses.

Clinical Pearl

The common difficulties that arise when assessing these veins are the following: The inferior vermian vein runs inside the posteroinferior vermian fissure. When seen in the lateral angiographic view, it lies, usually, slightly more anterior than hemispheric veins, but this should be checked in oblique views.

SUPERIOR OR GALENIC CONFLUENT

Veins of the brainstem (mainly midbrain–pontine region) and superior aspects of the cerebellum drain to the Vein of Galen and straight sinus representing the superior group. It may be more accurate to use the term "Vein of Galen Complex" since the vein of Galen may adopt different configurations. One of the most common appearances consists of a distinct anteroinferior joining area for the confluence of the internal cerebral vein, the Basal Vein of Rosenthal and/or the Lateromesencephalic vein (**Figures 4b**, **5a**). The junction with the straight sinus is variable, sometimes as a superior branch unrelated to the rest of the joining veins. The vein of Galen may also be a unique venous lake in direct connection to the straight sinus. On the other hand, this Galenic complex may, or may not, show an apparent stenosis at any point before the junction to the straight sinus (**Figure 5a**).

The main representatives of the superior drainage of the posterior fossa are located at the midline or paramedial venous channels:

- The precentral vein,
- The superior vermian vein, and
- The lateromesencephalic veins and tributaries.

The *precentral vein* is apposed to the anterior aspect of the central lobule of the cerebellum. In ∼60% of venograms, it is formed by the union of two paramedial brachial tributaries over the wing and central lobule, one at each side (**Figures 4b**, **5b**), while in some cases (<10%) two independent precentral veins can be found. Its angiographic interest lies

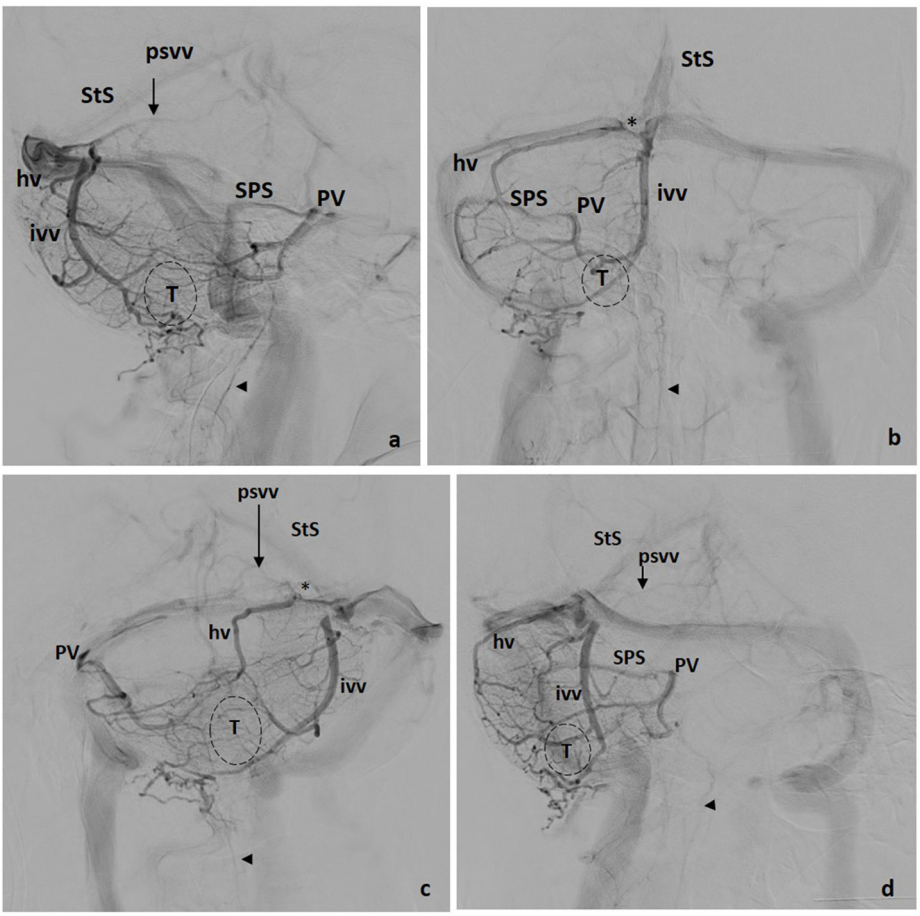

FIGURE 3 | Tentorial drainage. Four views: **(a)** lateral, **(b)** front, **(c)** left oblique, **(d)** right oblique. hv, Hemispheric Vein(s); ivv, Inferior Vermian Vein; psvv, Posterosuperior Vermian Vein; PV, Petrosal Vein; SPS, Superior Petrosal Sinus; StS, Straight Sinus; *, Tentorial Sinus; T, Tonsil; VOG, Vein of Galen; Arrowhead, Anterior Spinal Vein.

in the precentral vein delimits of the anterosuperior margin of the cerebellum, also depicting the collicular region and is almost constant. Huang and Wolf also note that the most caudal, first or fissural, segment of the vein runs behind and parallel to the roof of the upper portion of the fourth ventricle (9).

The *superior vermian vein* is located over the culmen, but its length is variable and may arrive anywhere up to and until the postclival fissure. It tends to be a midline unique vein, but the configuration is also variable, with more than one vein and/or extending mainly over the quadrangular lobe, as a superior hemispheric vein (**Figures 2a**, **5a**).

The most frequent configuration of the drainage of the superior cerebellar region is represented by a superior vermian vein joining the precentral vein (in nearly 80% of our cases) to lead into the vein of Galen complex. Sometimes a collicular vein from the quadrigeminal plate is also recognized.

For the brainstem superior drainage, a long vein turning around the midbrain pontine junction connects with the Vein of Galen Complex. This is referred to as the *lateromesencephalic vein* and runs inside the ambiens cistern (**Figures 2a**, **4a–c**). Huang and Wolf (18) name this vessel the posterior mesencephalic vein, and state that it originates in the interpeduncular fossa or on the lateral aspect of the mesencephalon to join the vein of Galen or the posterior portion of the internal cerebral vein.

In general, veins of the brainstem interconnect in an orthogonal fashion (**Figures 1**, **2a**). Their superior outlet is represented by this posterior or lateromesencephalic vein, which, in some instances, also serves as direct drainage for the basal vein of Rosenthal. In this case, a bridging point is established between supratentorial and infratentorial veins. Since a longitudinal vein frequently runs along the midbrain and the pons, it is more accurate to name it the lateral pontomesencephalic vein (**Figures 2a**, **3a**), which represents a bridging vein connecting the petrosal vein with the lateromesencephalic vein and/or the vein of Rosenthal.

Another interesting vein is the anterior pontomesencephalic vein. It is a longitudinal channel running caudally from the

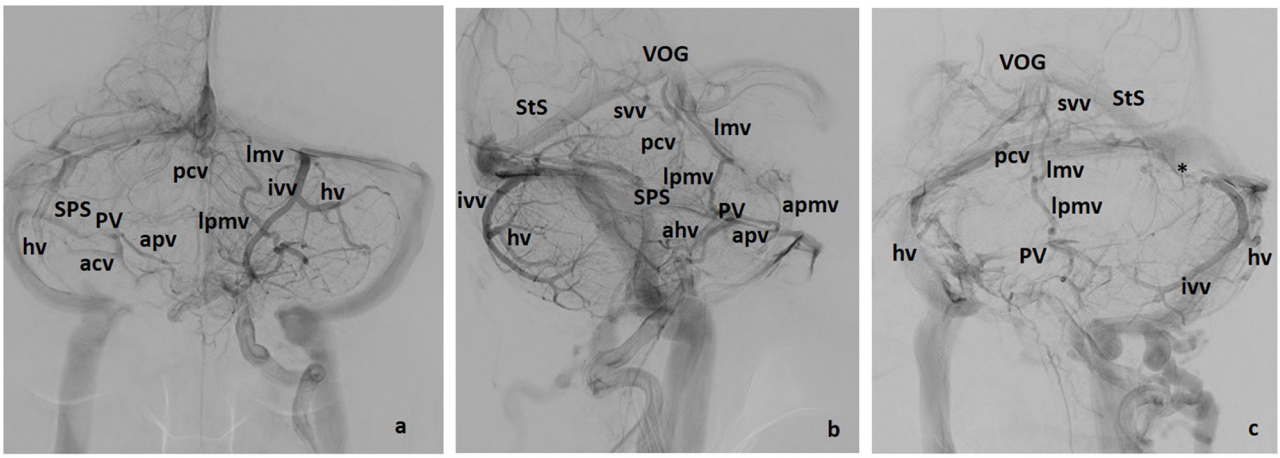

FIGURE 4 | Galenic and Petrosal drainage (including some posterior drainage veins). Three views: **(a)** lateral, **(b)** front, **(c)** left oblique. apmv, Anterior Pontomesencephalic Vein; ahv, Anterior Hemispheric Vein, apv, Anterior Pontine Vein; hv, Hemispheric Vein(s), ivv, Inferior Vermian Vein; lmv, Lateromesencephalic Vein; lpmv, Lateral Pontomesencephalic Vein; pcv, Precentral Vein; psvv, Posterosuperior Vermian Vein; PV, Petrosal Vein; SPS, Superior Petrosal Sinus; StS, Straht Sinus; svv, Superior Vermian Vein; *, Tentorial sinus; T, Tonsil; VOG, Vein of Galen.

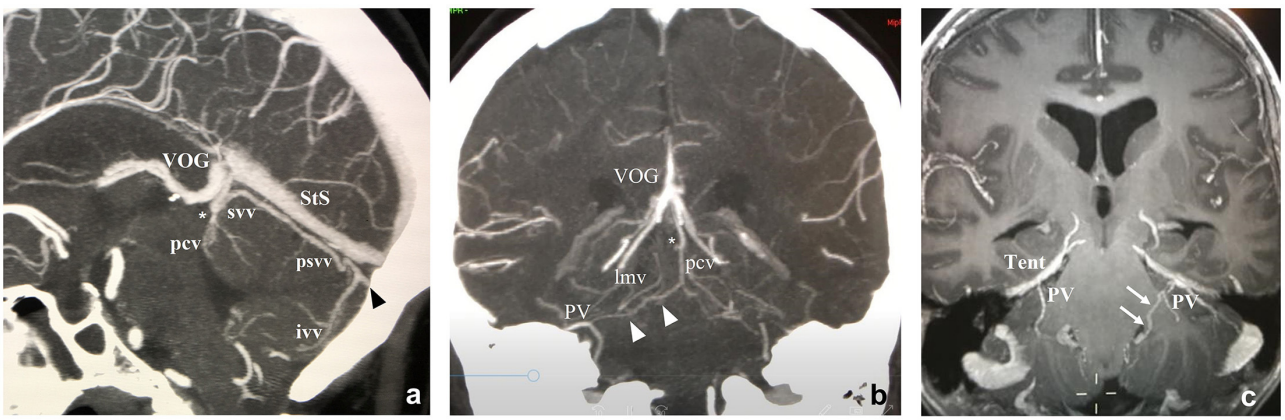

FIGURE 5 | Midline sagittal and retroquadrigeminal coronal CTAngio **(a,b)** and coronal MRAngio **(c)** reconstructions. ivv, Inferior Vermian Vein; lmv, Lateromesencephalic Vein; pcv, Precentral Vein; PV, Petrosal Vein; psvv, Posterosuperior Vermian Vein; StS, Straight Sinus; SPS, Superior Petrosal Sinus; svv, Superior Vermian Vein; Tent, Tentorium; TS, Tentorial Sinus; VOG, Vein of Galen. *Precentral vein and superior vermian vein unite to form a single vein draining into the Vein of Galen. White arrows: Connecting vein between the lateral recess of the IV ventricle and the petrosal vein on the left side. Black arrowhead: Tentorial sinus. White arrowheads: Connecting vein between the petrosal vein and the precentral vein on the right side.

interpeduncular fossa around the anterior aspect of the pons (**Figure 4b**). It is not constant, but again, when present, delineates, in the lateral angiographic view, the anteromedial aspect of the midbrain, and pons, and may also continue downward toward the medulla. Superiorly, it may connect with the basal vein of Rosenthal.

Clinical Pearl

The common difficulties that arise when assessing these veins are the following: The precentral vein is not a conspicuous vessel, but in the lateral view should be looked for, since it confidently delineates the anterosuperior margin of the vermis (**Figures 1e**, **2a,b**, **4**).

ANTERIOR OR PETROSAL DRAINAGE

The petrosal vein draining into the superior petrosal sinus represents a direct derivative of one of the initial pioarachnoidal drainages in the embryo: the ventral metencephalic vein. Being the main venous channel for the lateral pons and cerebellar primordium, it is maintained, essentially, as a constant vein in the adult. Each petrosal vein drains not only the brainstem and the anterior aspect of the cerebellum, but also the neighboring cranial nerves. Venous injection of the posterior fossa shows, at least, one drainage vein for each one of cranial nerves V, VI, VII, and VIII.

In a simplified way, three main venous branches usually converge in the petrous vein. This is a "convenient" landmark,

since it helps with roughly indicating the location of the internal auditory meatus and the pontocerebellar angle. These three veins, usually well-recognized in angiograms, meet at the large and short petrosal vein (**Figures 2a,b**). The petrosal vein is depicted as a "spot" not far from 2 mm in caliber in anteroposterior and lateral views. Then, it joins the superior petrosal sinus, which is a straight dural channel over the edge of the petrous pyramid and tentorium connecting with the transverse-sigmoid angle of the lateral sinus. The anterior connection of the superior petrosal sinus to the cavernous sinus is infrequently seen in angiograms. The main three confluents of the petrosal vein are:

- Lateral pontomesencephalic veins,
- Anterior brainstem veins, and
- Anterior cerebellar veins, superior and inferior.

As noted above, the most frequent lateral vein, running cranio-caudally and longitudinally at the lateral aspect of the mesencephalon and pons, corresponds to the *lateral pontomesencephalic vein* (**Figures 2a**, **5c**). It is an important bridging vein between the basal vein of Rosenthal (when present) or the lateromesencephalic vein, both transversal in direction, and the anterior or petrosal drainage. Additionally, veins coming from the wing of the precentral cerebellar region and superior cerebellar peduncle may join the petrosal vein posterocranially but are rarely well-distinguished in angiograms.

Anterior brainstem veins are variable. A transverse directed vein from the anterior aspect of the brainstem to the petrosal vein is usually recognized. The frequent configurations are:

- transverse anterior superior and inferior pontine veins, which run on either side of the emergence of the trigeminal nerve (**Figures 2a**, **4a,b**), or
- a longitudinal venous channel along the midline from the interpeduncular fossa to, sometimes, the anterior veins of the spinal cord, laterally connected perpendicularly with anterolateral veins toward the petrosal vein (**Figures 1**, **2a**), or
- a large anterolateral paramedian vein receiving the orthogonal connecting veins of the midbrain, pons, and medulla (in **Figure 4b**, these connect to the anterior spinal vein).

The veins of the brainstem also drain those veins of the cranial nerves—most of them toward the pestrosal vein—and are also frequently named based on their location, coursing transversely or longitudinally along the midbrain, pons, and medulla.

Anterior cerebellar veins include those of the anterior aspect of the cerebellum that may or may not join in one stem (**Figures 2a,b**, **4b**). The main described veins are the veins of the great horizontal fissure, which may or may not run in this fissure, and the vein of the lateral recess of the fourth ventricle which originates in the region of the dentate nucleus. From the lateral recess of the fourth ventricle, first turns laterally running caudal to the flocculus, and then shows an upward turn toward the petrosal vein. Other veins of the region as the medial tonsillar vein, or the vein of the flocculus are smaller. From a practical point of view, the largest inferior cerebellar vein joining radially those veins of the anterior, middle, and caudal aspect of the cerebellum and its peduncles helps to show the location of the flocculus and cerebellopontomedullary cistern.

Clinical Pearl

The common difficulties that arise when assessing these veins are the following: The superior petrosal sinus and the petrosal vein are the main anatomical markers of this anterior confluent. The superior petrosal sinus runs over the petrous ridge and its configuration is that of a quite straight venous structure connecting the petrosal vein with the transverse–sigmoid sinus. In consequence, the superior petrosal sinus is angiographically seen as a thin relatively linear venous channel (**Figures 2a,b**, **3a,b,d**, **4a,b**). In the frontal view, the location of the superior rim of the petrosal bone depends on the position of the head. In the lateral view, when both cerebellar hemispheres are angiographically depicted, two parallel channels from the petrosal vein to the lateral sinus are easy to find.

INFERIOR PETROSAL SINUS DRAINAGE

The *vein of the lateral recess of the fourth ventricle* after turning around the cerebellar peduncles, may also continue forward to join the caudal end of the inferior petrosal sinus. This configuration may be difficult to recognize angiographically, but in some instances, such as the dural fistulae can be objectivized.

CLINICAL IMPLICATIONS

Arterial ischemic stroke in the posterior fossa would, theoretically, affect infratentorial venous drainage as it does in the supratentorial compartment. Probably, a faster venous drainage of a large ischemic region can be present although underreported. For the venous sector, multiple connecting venous channels frequently prevent venous thrombosis when the occluded vein is secondary. Lesions of main trunks as the petrosal vein, tentorial sinuses, or the vein of Galen complex, however, would easily provoke venous ischemia. A review of isolated vein thrombosis of the posterior fossa presenting as localized cerebellar venous infarctions or hemorrhages found 9 cases among 230 intracranial venous thrombosis. Thrombosis was localized at the straight sinus, lateral sinuses, or the petrosal vein, meaning that in all cases a large venous drainage was affected (15). Anticoagulation remains the main treatment in these cases. Endovascular options as *in situ* venous fibrinolysis or even venous stenting remains, for the moment, as a compulsory treatment option.

On the other hand, postoperative cerebellar swelling (or stroke) may cause severe clinical problems, particularly when the superior petrosal veins are sacrificed during surgery of the posterior fossa (16). Knowledge of the anatomy of the draining patterns of the tentorial sinuses and their draining veins can also benefit the neurosurgeon carrying out repair near or on the cerebellar tentorium (17).

FINAL COMMENTS

The present review is based on the radiological approach of posterior fossa drainage. From a neurosurgical approach, Rothon (11) divides the posterior fossa veins into four groups: superficial, deep, brainstem, and bridging veins. The superficial veins are divided on the basis of the three surfaces they drain: (1) tentorial surface by the superior hemispheric and superior vermian vein, (2) the inferior or suboccipital surface is drained by inferior hemispheric and inferior vermian veins, and (3) the petrosal surface is drained by anterior hemispheric veins. The deep veins course in the three fissures between the cerebellum and the brainstem and on the three cerebellar peduncles: veins of the cerebellomesenchephalic, cerebellopontine, and cerebellomedullary fissures, and veins of the superior, middle, and inferior peduncles. In general, veins of the posterior fossa tend to terminate as bridging veins connecting the Galenic, petrosal, and tentorial confluents.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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