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The Impact of Cerebral Small Vessel Disease on Hemorrhagic Transformation After Mechanical Thrombectomy in Acute Large Vessel Occlusion Ischemic Stroke

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Abstract: With the intensification of population aging and the rapid development of neuroimaging, cerebral small vessel disease (CSVD) has garnered increasing attention. Endovascular thrombectomy (EVT) can significantly improve functional outcomes in patients with intracranial large vessel occlusion and has become the standard treatment for acute large vessel occlusion ischemic stroke. Numerous studies suggest that pre-existing CSVD before acute ischemic stroke may increase the risk of hemorrhagic transformation (HT) after EVT, yet results remain controversial. This article primarily discusses the impact of different subtypes of CSVD and the total burden on magnetic resonance imaging on HT after EVT in patients with acute large vessel occlusion ischemic stroke, aiming to provide a clinical reference.

Keywords: Cerebral small vessel disease; Acute large vessel occlusion ischemic stroke; After endovascular thrombectomy; Hemorrhagic transformation

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1. Introduction

Approximately 17 million people worldwide suffer from acute ischemic stroke (AIS) each year, leading to around 6 million deaths. It is projected that by 2030, the number of new ischemic stroke patients could reach 77 million [1]. Ischemic stroke is the most common type of stroke, accounting for 69.6%–70.8% of all strokes, with AIS caused by large vessel occlusion being the most critical, accounting for approximately 28% to 46% of all AIS cases [2]. Current effective treatments for AIS aim to rapidly open occluded vessels, restore blood flow perfusion to ischemic regions, and salvage viable brain tissue. Intravenous thrombolysis with alteplase within 4.5 hours of onset is recommended as the first-line treatment for AIS patients. However, for patients with concurrent large vessel occlusion (LVO), the recanalization rate with intravenous thrombolysis

is low (13%–18%), with suboptimal efficacy, and fewer than 3% of patients truly benefit [3]. A series of randomized clinical trials have demonstrated that EVT can significantly improve functional outcomes in patients with intracranial large vessel occlusion and has become the standard treatment for AIS-LVO patients [4–5]. However, complications such as HT, vascular embolism, vasospasm, and contrast-induced nephropathy may occur postoperatively, with HT being the most severe complication [6]. HT can exacerbate brain tissue damage and even increase the risk of death in patients, making it crucial to identify factors influencing HT after EVT to guide targeted clinical prevention and control measures [7].

Cerebral small vessel disease (CSVD) refers to a series of clinical, imaging, and pathological syndromes affecting intracranial small arteries, arterioles, capillaries, venules, and small veins, as well as the surrounding brain parenchyma, caused by various etiologies [8]. It may be a risk factor for intracranial hemorrhage [9]. Some studies speculate that the reasons for poor prognosis after EVT may be related to chronic ischemia and cerebral hypoperfusion caused by arteriole, venule, and capillary lesions [10]. With the rapid development of neuroimaging technology, an increasing number of AIS patients undergoing vascular recanalization treatment are being detected with concurrent CSVD signs in clinical practice. CSVD patients may have an impact on HT after vascular recanalization treatment due to factors such as blood-brain barrier disruption, cerebral microcirculation disorders, poor microvascular reperfusion, and reduced effective connectivity in neural networks [11]. In light of this, domestic and foreign scholars have conducted a series of studies, and this article will provide an overview of the current research status in this field.

2. Hemorrhagic transformation (HT) after endovascular therapy (EVT) in patients with acute ischemic stroke with large vessel occlusion (AIS-LVO)

Hemorrhagic transformation refers to bleeding within or at remote sites from the ischemic focus due to multiple potential mechanisms during ischemic stroke. Its diagnosis primarily relies on imaging findings. Before endovascular treatment, cranial imaging in patients with AIS-LVO does not show hemorrhage. However, when cranial imaging is repeated within 24–72 hours after mechanical thrombectomy, hemorrhage found within the infarct area or at remote sites is termed hemorrhagic transformation after mechanical thrombectomy for acute large vessel occlusion stroke [12]. Depending on whether it is accompanied by neurological deterioration (i.e., an increase of ≥4 points on the National Institutes of Health Stroke Scale (NIHSS) or an increase of ≥ 2 points in specific NIHSS items), hemorrhagic transformation can be classified as symptomatic intracranial hemorrhage (sICH) and asymptomatic intracranial hemorrhage. Among these, sICH is a more severe type of hemorrhage, often leading to poor patient prognosis or even death. The incidence of asymptomatic intracranial hemorrhage after mechanical thrombectomy performed within 8 hours of onset is 51.4%, while the incidence of sICH is 4.5% [13]. As the time from onset increases, the incidence of hemorrhagic transformation may be higher. According to the Endovascular Treatment of Acute Anterior Circulation Ischemic Stroke (ACTUAL) study in China, the incidence of postoperative hemorrhagic transformation in patients undergoing mechanical thrombectomy within 6 hours of onset is 46.7%, with an sICH incidence of 15.5% [14]. By analyzing the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN-NO IV and MR CLEAN-MED), among 1017 cases, 331 (33%) had asymptomatic intracranial hemorrhage, and 90 (9%) had sICH. Both asymptomatic intracranial hemorrhage and sICH were associated with poorer functional outcomes [15]. Overall, the incidence of HT after EVT ranges from 26.0% to 58.0%, while the incidence of sICH ranges

from 2.0% to 20.89% [16–17]. The mechanisms underlying HT may include oxidative stress, inflammatory responses, and blood-brain barrier disruption [18–20]. Exploring the risk factors for hemorrhagic transformation after mechanical thrombectomy helps in better preoperative patient selection and optimizing perioperative management, thereby reducing the incidence of hemorrhagic transformation and maximizing treatment benefits. In recent years, the correlation between cerebral small vessel disease (CSVD) and HT after EVT has gradually attracted attention.

3. Overview of cerebral small vessel disease (CSVD)

CSVD refers to degenerative brain diseases caused by lesions in cerebral small arteries and their distal branches, arterioles, capillaries, venules, and small veins [8]. Age-related and hypertension-associated cerebral small vessel disease and amyloid angiopathy are the most common types. Depending on the affected brain regions, CSVD patients may exhibit various clinical manifestations, including lacunar syndromes, gait disturbances, depression, cognitive impairment, and urinary incontinence [21]. Current examination methods cannot evaluate CSVD damage, and clinical diagnosis relies entirely on the detection of brain tissue damage associated with cerebral small vessel disease. Therefore, cranial imaging is crucial for diagnosing cerebral small vessel disease. According to the 2013 Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria, CSVD imaging manifestations mainly include the following six subtypes: recent small subcortical infarct (RSSI), presumed vascular origin lacunar infarction (LI), presumed vascular origin white matter hyperintensity (WMH), perivascular space (PVS), cerebral microbleed (CMB), and brain atrophy [22]. With the publication of the second edition of STRIVE (STRIVE-2) in 2023, new imaging features such as cortical superficial siderosis, cortical cerebral microinfarcts, and incidental DWI-positive lesions have been incorporated, and imaging characteristics have been defined and updated [23]. Multiple studies have shown that different CSVD subtypes can have additive effects on the brain and interact with each other [24–25]. However, not every degree of damage from each CSVD subtype can reflect the severity of brain damage. A comprehensive assessment of all existing lesions helps in reaching more accurate conclusions, leading to the concept of total CSVD burden. The total CSVD burden incorporates WMH, LI, CMB, and PVS imaging markers into a scoring scale to comprehensively evaluate their impact on clinical diagnosis and treatment [26]. Studies have confirmed that CSVD may increase the risk of stroke onset, treatment complications, and poor prognosis, as well as the risk of stroke recurrence [27].

4. Cerebral small vessel disease (CSVD) and acute ischemic stroke with large vessel occlusion (AIS-LVO)

The intracranial large and small vessels together form the cerebral vascular tree. Although there are certain differences in structure and function, their anatomical structures are continuous, and they are both influenced by hemodynamics and exposed to similar risk factors. Therefore, intracranial large vessel disease often coexists with CSVD, and large vessel disease can further aggravate CSVD, which in turn affects the prognosis of patients with AIS-LVO [28]. Intracranial large artery atherosclerosis (LAA) is the most common cause of intracranial large vessel disease [28]. Imaging analysis shows that the coexistence rate of LAA and CSVD can reach 49.5% [29]. LAA may lead to the development and progression of CSVD through the following mechanisms: (1) Thickening of the vessel wall, stenosis, or even occlusion in LAA patients causes

chronic ischemia and hypoperfusion; (2) Microemboli generated from LAA plaque rupture block distal arterioles with blood flow; (3) Abnormal matrix metalloproteinase activity in LAA patients damages the blood-brain barrier, promoting the occurrence of CSVD; (4) Hemodynamic changes in LAA cause functional and structural disorders in small vessels, leading to CSVD [30–33].

For AIS patients with LAA complicated by CSVD, a high burden of WMH indicates a poorer neurological prognosis. Moreover, the correlation between WMH burden in different regions and post-stroke neurological status varies, with periventricular WMH burden appearing more relevant to poor post-stroke outcomes than deep WMH burden, possibly because periventricular white matter is more sensitive to decreases in cerebral blood flow [34]. In addition to WMH, LI and CMB also have potential impacts on the neurological prognosis of AIS. Due to aging and poor establishment of leptomeningeal collateral compensation, CSVD patients experience decreased cerebral metabolism and cerebrovascular reserve function, as well as reduced tolerance of local brain tissue to ischemia. When AIS occurs, the ischemic penumbra rapidly progresses to the core infarct area, leading to poor patient prognosis [35]. CSVD impairs the function of the neurovascular unit, increasing blood-brain barrier permeability. Vascular components leak into the perivascular space, causing local inflammatory responses and leading to poor prognosis in AIS patients [36]. CSVD patients have poor reperfusion of cerebral microvessels, and successful reperfusion of cerebral microvessels is a more effective predictor of functional outcomes than successful recanalization of occluded large vessels [37]. Additionally, patients with comorbid CSVD have an increased risk of postoperative complications after EVT, which also affects their prognosis [38]. With the widespread application of EVT in the treatment of AIS-LVO, the impact of CSVD on postoperative HT and clinical prognosis after EVT has become a research focus for scholars both domestically and internationally in recent years.

5. Different subtypes of CSVD and HT after EVT in AIS-LVO patients

Cerebral small vessel disease (CSVD) is a widely distributed cerebrovascular disease, primarily manifested as cerebral microbleeds (CMB), white matter hyperintensity (WMH), lacunar infarctions (LI), and perivascular spaces (PVS). Different subtypes of CSVD may have varying impacts on hemorrhagic transformation (HT) after endovascular therapy (EVT) in patients with acute ischemic stroke with large vessel occlusion (AIS-LVO), and different CSVD subtypes often coexist in the same AIS patient. Previous studies have suggested that CSVD may increase the risk of HT in EVT patients, but this has not been widely confirmed.

5.1. Relationship between WMH and HT after EVT

WMH is a parenchymal lesion caused by CSVD, commonly found in elderly patients who have a higher prevalence of stroke and transient ischemic attack (TIA) [39]. It is closely associated with an increased risk of stroke and vascular death [40]. As a marker of chronic hypoperfusion, WMH is strongly related to chronic endothelial dysfunction and disruption of the blood-brain barrier throughout the brain [41]. Cranial magnetic resonance imaging (MRI) indicates that as CSVD progresses, pathological changes in the white matter worsen, which is associated with early neurological deterioration and poor functional outcomes after AIS [42–43]. Studies have shown that severe WMH is associated with an increased risk of HT after vascular reperfusion in AIS. The incidence of symptomatic intracranial hemorrhage (sICH) is significantly higher in patients with moderate to severe leukoaraiosis in the deep white matter compared to those without or with mild leukoaraiosis [44]. Guo et al. conducted a multicenter retrospective analysis of 273 acute stroke patients

after EVT, evaluating early neurological improvement and deterioration based on the Van Swieten classification [45]. Multivariate analysis revealed that severe WMH was negatively correlated with early neurological improvement. Among patients with asymptomatic intracranial hemorrhage, severe WMH was an independent predictor of early neurological deterioration. A systematic review and meta-analysis of 1,296 patients after EVT across seven studies found unique differences in the risk factor profiles and clinical outcomes of ischemic stroke among patients with varying severities of WMH [46]. Patients with severe WMH may be associated with risk factors for cerebrovascular disease and have poorer outcomes. The severity of WMH is negatively correlated with the patency of collateral blood flow, indicating that chronic hypoperfusion associated with WMH may promote the development of cerebral collateral circulation [47]. Subjects with severe WMH also exhibit hypercoagulability, platelet activation, oxidative stress, and inflammation, which may facilitate the formation of microemboli leading to reperfusion failure [48]. Acute cerebral ischemia and reperfusion injury may exacerbate pre-existing blood-brain barrier disruption in patients with severe WMH [49]. Increased blood-brain barrier permeability will intensify the processes of edema, inflammation, and cytotoxicity, thereby promoting infarction and even HT [50]. Shi et al. retrospectively analyzed 105 patients with acute anterior circulation occlusion who underwent EVT and identified deep white matter and periventricular WMH on preoperative MRI images [51]. Patients were divided into a deep white matter (DWM) group and a non-DWM group. Comparison of the two groups revealed that moderate to severe WMH in the DWM group was an independent predictor of HT after EVT. Simone et al. graded the severity of WMH in 3,046 patients from the MR CLEAN study and found that more severe WMH was associated with poorer functional outcomes, a higher probability of ineffective recanalization, and a negative correlation with early neurological recovery, but not with the probability of successful reperfusion or sICH [42]. The results of the study by Kang-Ho Cho et al. also showed that WMH did not affect postoperative HT in AIS-LVO patients, which may be related to the use of a new stent retriever device in this study [52].

5.2. Relationship between CMB and HT after EVT

CMB is defined as the leakage of hemosiderin deposits (primarily macrophages) from cerebral small vessels around them, presenting as a hemorrhagic-prone pathological state, mainly attributed to cerebral amyloid angiopathy and hypertensive vasculopathy [53–54]. The prevalence of cerebral microbleeds increases with age, with a higher prevalence in males. Hypertension increases the risk of cerebral microbleeds, including those in deep and mixed locations [55]. Cerebral microbleeds have been confirmed to be associated with spontaneous cerebral hemorrhage and hemorrhagic recurrence [56]. The detection of cerebral microbleeds on susceptibility-weighted imaging (SWI) is a marker of hemorrhagic small vessel disease [57]. Study results indicate that an increased number of microbleeds is significantly associated with the risk of asymptomatic intracranial hemorrhage and sICH, introducing the concept of cerebral microvascular burden as a possible predictor of thrombolytic intracranial hemorrhage after AIS [58]. This risk is most pronounced in patients with >10 microbleeds, of whom 57% have experienced sICH. However, the impact of CMB on HT and clinical outcomes after EVT in AIS-LVO patients remains inconclusive. A subgroup analysis in the study by CHOI et al. showed that the presence of CMB has a greater impact on AIS-LVO patients, potentially increasing the risk of sICH and serving as an independent predictor of poor 3-month outcomes [52]. However, the study by Shi et al. suggested that a small number of CMBs do not increase the risk of HT and mortality after EVT, while the risk of HT in patients with extensive CMBs (≥ 5) requires further investigation [59].

5.3. Relationship between EPVS and HT after EVT

PVS are penetrating vessels surrounded by brain parenchyma. They are defined as round or tubular fluid-filled spaces that facilitate interstitial fluid drainage and the clearance of metabolites from the brain, with signal intensity similar to cerebrospinal fluid on all MRI sequences [60]. Typically, the diameter of PVS is less than 2 mm, while enlarged perivascular spaces (EPVS) can extend to a diameter range of 2–4 mm [61]. Initial pathological studies found that EPVS rarely cause damage to brain parenchyma and were therefore considered normal variants of limited clinical significance [62]. Recently, a study on elderly patients showed that EPVS are associated with an increased risk of stroke, dementia, and depression [27]. Furthermore, increasing evidence suggests that EPVS are more prevalent in stroke patients, and a high EPVS burden can predict poor outcomes after stroke [63–65]. However, there are few studies on the relationship between EPVS and HT after ischemic stroke. Whether EPVS play a role in HT remains uncertain. A study of 1,386 patients with AIS and TIA found that EPVS were associated with spontaneous intracranial hemorrhage during follow-up (mean follow-up period of 2.34 years) [66]. Evidence suggests that EPVS are more common in stroke patients and are associated with poor outcomes in AIS patients [67]. Increasing evidence indicates that EPVS are associated with intracerebral hemorrhage (ICH) [66, 68]. However, Song et al. found that EPVS are common in patients with ischemic stroke and are significantly correlated with other CSVD markers [69]. The presence or burden of EPVS is not associated with the risk of HT after ischemic stroke. In a population-based study, the presence of a large number of EPVS on MRI was significantly associated with an increased risk of subcortical infarction and CMBs, as well as more severe progression of WMH [70]. Whether EPVS increase the risk of HT after EVT and their role in HT remain uncertain. The sample sizes of the aforementioned studies are relatively small, and there are certain limitations in representing the stroke population. Therefore, the relationship between EPVS and HT after EVT requires further investigation.

5.4. Relationship between LI and HT after EVT

LI is defined as a round or oval small cavity with a diameter of approximately 3–15 mm, mostly caused by ischemic stroke, but can also result from the outcome of hemorrhagic stroke. It is commonly found in the basal ganglia region and the centrum semiovale. LI often presents without clinical symptoms. On MRI, LI shows signal intensity similar to cerebrospinal fluid on T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI), with a central low signal and a peripheral high signal ring on fluid-attenuated inversion recovery (FLAIR) imaging. Studies on the relationship between LI and outcomes after EVT are extremely limited. An international multicenter large-scale randomized controlled trial indicated that lacunae have a predictive effect on sICH (OR=1.73) [71]. A study by Sillanpää et al. on the clinical outcomes of elderly AIS patients aged 60 and above who received EVT treatment showed that LI is correlated with poor prognosis after EVT [72]. That is, elderly AIS patients without LI lesions have a 3.7 times higher likelihood of achieving a good prognosis after EVT compared to those with LI lesions. However, Arba et al. argued that the presence and burden of LI are not associated with early or late clinical outcomes after EVT [73].

5.5. Relationship between total CSVD burden and HT after EVT

The academic community believes that CSVD is a dynamically progressive whole-brain disease, and it is difficult to comprehensively evaluate the impact on bodily functions using a single CSVD imaging marker. Therefore, the study of total CSVD burden has received increasing attention from the academic community. Studies have found that some pre-ischemic signs on cranial computed tomography (CT) in AIS

patients (tissue hypoattenuation, infarct size, swelling, and arterial hyperattenuation) and existing ischemic signs (old infarcts, WMHs, and atrophy) are associated with an increased risk of HT [71]. When multiple imaging markers are present simultaneously, the absolute risk of sICH increases. Wang et al. conducted a meta-analysis of 9,419 patients from 24 centers and found that CSVD is correlated with HT, sICH, and neurological outcomes at 3 months after intravenous thrombolysis [74]. Compared to patients without CSVD, the presence of CSVD is associated with an increased risk of HT (OR=1.81) and sICH (OR=2.42). Moreover, the heavier the total CSVD burden, the higher the risk of hemorrhage. SOHN et al. explored the association between CSVD burden and infarct growth rate in AIS-LVO patients receiving EVT treatment and conducted a retrospective analysis of 495 patients with anterior circulation stroke who received EVT [75]. After adjusting for confounding factors, a higher CSVD burden was significantly associated with a faster infarct growth rate. A high CSVD burden also independently predicted stroke progression and poor functional outcomes. Furthermore, the total CSVD burden reflects the decline in whole-brain reserve and compensatory capacity and may provide an overall reflection of the brain's functional reserve [76]. Poor brain reserve and compensatory capacity have adverse effects on stroke recovery [77]. Hooper et al. conducted a cohort analysis of AIS-LVO patients receiving EVT treatment and found that patients with severe CSVD burden had poorer functional outcomes and increased mortality at 90 days [10]. As an imaging marker of cerebral vascular reserve, CSVD burden, used alone or in combination with established quantitative imaging scores, can serve as an independent predictor of successful EVT. However, some studies have failed to find a correlation between the severity of CSVD and postoperative hemorrhagic transformation in AIS-LVO patients with poor EVT outcomes [78]. The impact of CSVD on HT after EVT in AIS-LVO patients may be influenced by multiple factors and exhibit individual differences. Therefore, the value of total CSVD burden in evaluating the prognosis of AIS-LVO patients still requires further verification.

6. Summary and outlook

In summary, assessing the severity of a single subtype of CSVD alone cannot accurately represent the overall brain damage caused by CSVD. The total CSVD burden score provides a more comprehensive and accurate evaluation of the impact of CSVD on the brain, offering a simple and practical approach. In clinical practice, it aids in further risk stratification for patients undergoing vascular recanalization therapy and assists in predicting HT and clinical outcomes. Although the relationship between CSVD and post-EVT HT in patients with AIS-LVO remains inconclusive, studies both domestically and internationally have indicated a certain correlation between the presence of severe WMH or CMB and HT following vascular recanalization therapy. Future research requires extensive multicenter prospective studies to validate the impact of CSVD on post-EVT HT in patients with AIS-LVO, providing a reference basis for clinical treatment decisions.

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Disclosure statement

The authors declare no conflict of interest.

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